Paul Ellis Marik

Evidence-Based Critical Care

Third Edition

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Springer

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Learning without thinking is useless. Thinking without learning is dangerous.

—Confucius, Chinese Philosopher (551–479 BC)

To cure sometimes, to relieve often, to comfort always.

—Hippocrates, Greek Physician, Father of Western Medicine (460–370 BC)

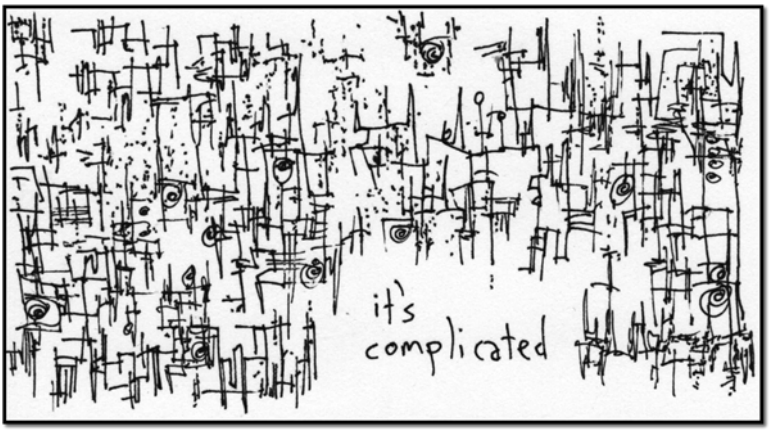
This book is dedicated to the memory of my father, Colin Sigmund Marik, a man of great intellect and wit.

Preface to Third Edition

After completing the Second Edition of *The Handbook of Evidence Based Critical Care* in 2009, I swore that I would rather stick needles in both my eyes than author another updated version of the book. But here we are in 2015 with the Third Edition of *Evidence-Based Critical Care* (no longer a handbook). So what made me change my mind? Most importantly, you, my dedicated readers, have implored me to update the book; I was told, "Medicine as we know it would be incomplete without an updated version." Your enthusiastic and positive feedback was the driving factors which led me to consider writing this revision. In addition, in the last 5 years we have witnessed a remarkable refinement in the management strategies of critically ill patients best characterized as "Less is More" (see Chap. 2). At the same time we have realized that while many of our patients survive their ICU stay, many have significant residual functional and cognitive disabilities. These changes in our approach and understanding of critical illness have necessitated the updated Third Edition of *Evidence-Based Critical Care*.

However, the basic guiding principles of Critical Care Medicine have not changed; compassionate, dedicated and thoughtful clinicians, who evaluate the functioning of the "whole" patient, ponder their disease processes and pathophysiology and provide the highest level of *Evidence-Based* interventions with the goal of restoring the patient to a quality of life which he/she values.

Due to the vast number of therapeutic interventions that ICU physicians make daily, the topics are presented as narrative summaries of the *best available evidence* rather than as systematic reviews of each and every intervention. In keeping with the goal of providing an evidence-based approach to critical care, references are provided to support the evidence presented. In writing this book my goal has been to take issues that appear complex and make them as simple as possible.



It appears to me that those who really don't have a good understanding of the complexities of physiology, pathophysiology and patient care make things so complicated that they themselves don't understand what they are trying to convey. This concept is exemplified by the following quotes:

> Make everything as simple as possible, but not simpler
> If you can't explain it simply, you don't understand it well enough
>
> Albert Einstein, Theoretical Physicist, 1879–1955

Evidence-Based Critical Care is not a reference text but presents a practical *evidence-based approach* to the management of critically ill ICU patients. The focus of this book is on issues that pertain specifically to the ICU. As such, the reader is referred to standard medical and surgical texts as well as online resources for more complete information on the wide spectrum of conditions and diseases from which ICU patients may suffer. While all attempts have been made to be current, due to the exponential growth of medical knowledge some of the information presented may already be outdated when this book comes to print. The reader should therefore keep up-to-date with the current medical literature.

The guidelines presented in the book are not meant to replace clinical judgment, but rather to provide a framework for patient management. Individual clinical situations can be highly complex and the judgment and wisdom of an experienced and knowledgeable intensivist with all available information about a specific patient is essential for optimal clinical management.

Norfolk, VA, USA Paul Ellis Marik

Acknowledgements

This book recognizes my mentors and students who have taught me everything I know and inspired me to learn even more.

A Note to the Reader

The author and publisher have made every attempt to check information and dosages for accuracy. Because information and the science of pharmacology is continually advancing, our knowledge base continues to expand. Therefore, we recommend that the reader check all information and all product information for changes, especially changes in dosages or administration before administering any medication.

Contents

Part I General ICU Topics

1 Evidence Based Critical Care 3
References 6

2 "Less Is More": The New Paradigm in Critical Care 7
References 8

3 "Classic" Papers 13

4 Critical Care Medicine 101 19
Factors to Consider When a Patient is Admitted to the ICU 20
Initial "Generic" Treatment Orders 20
Reference 21

5 House Officers Guidelines 1: Housekeeping 23
Admission History and Physical Examination 23
Daily Examination 24
General 24
Vital Signs (24 h Min and Max and Current) 24
Additional Observations 24
The Ventilator 25
Heart 25
Chest 25
Abdomen 25
CNS 26
Importance of the Daily Neurological Examination 26
Laboratory Tests 26
Imaging 27
Presenting on Daily Rounds 27
New Admissions 27

Follow Up Patients 28
Clinical Pearls 28
References 28

6 House Officers Guidelines 2: Procedures 29
Murphy's Laws of Procedures 29
Central Venous Access 30
Subclavian Vein Catheterization 31
Internal Jugular Vein Catheterization 32
Femoral Vein Catheterization 33
Complications of Central Venous Access 34
Arterial Catheters 34
Naso/Oro Gastric Tubes 35
Feeding Tubes 36
Thoracentesis and Paracentesis 36
Clinical Pearls 37
References 37

7 Admission-Discharge Criteria 39
ICU Admission Criteria 39
Prioritization of Potential ICU Admissions 40
Priority 1 40
Priority 2 40
Priority 3 40
Priority 4 41
Transfer from Another Hospital: Variable Priority 41
Disease Specific Indications for ICU Admission 41
Cardiovascular System 41
Pulmonary System 42
Neurological Disorders 42
Drug Ingestion and Drug Overdose 42
Gastrointestinal Disorders 43
Endocrine 43
Renal Disorders 43
Postoperative Care 44
Miscellaneous 44
Physiologic Indication for ICU Admission 44
Discharge Criteria 44
Reference 45

8 Chronic Critical Illness and the Long Term Sequela of Critical Care 47
Neuromuscular Abnormalities 49
Critical Illness Polyneuropathy 49
Critical Illness Myopathy (See also Chap. 32 on Nutrition) 49
Brain Dysfunction 51
"Prevention" of CCI 51

Management of CCI 52
Testing 52
General Management 53
Stress Hyperglycemia 53
Metabolic Bone Disease 53
Anabolic Steroids 54
Exercise Program 54
References 54

9 Fluid Responsiveness and Fluid Resuscitation 57
Echocardiographic Assessment of Fluid Responsiveness 66
Static Echocardiographic Parameters 66
Dynamic Echocardiographic Parameters 66
Passive Leg Raising (PLR) 67
The Fluid Challenge 69
Fluid Boluses in Volume Responsive Patients 71
What Type of Fluid? 72
Lactated Ringer's (Hartmann's Solution) vs. 0.9 % NaCl (Ab-Normal Saline) 72
Complications Associated with 0.9 % NaCl vs. Lactate Ringers Solution 73
Renal Failure 73
Hyperchloremic Metabolic Acidosis and DEATH 73
Lactate Generates HCO_3^- 73
Ringer's Lactate and Kidney Disease 74
Ringers Lactate and Liver Disease 75
Coagulopathy 75
Lactate as a Metabolic Fuel 75
Albumin 76
Hetastarches (HES) 77
So, Which Fluid? 78
Resuscitation in Specific Disease States 78
Hemorrhage 78
Traumatic Brain Injury 79
Dehydration 79
Sepsis (and SIRS) 80
Burns 80
Management of Oliguria 80
Management of Volume Overload/Acute Pulmonary Edema 81
References 81

10 Assessment of Cardiac Function and Cardiac Output 89
Echocardiographic Assessment of Cardiac Function 89
Methods of Measuring Cardiac Output 90
Pulmonary Artery Catheter 90
Transpulmonary Thermodilution 91

Pulse Contour Analysis 92
Esophageal Doppler 93
USCOM 93
Bioreactance 94
Utility of Cardiac Output monitoring 94
Determining Fluid and Inotrope Responsiveness 94
Driving up CI to Supranormal Values 94
References 95

11 Peri-operative Fluid Optimization 99
References 104

12 Sepsis 107
Bacteriology and Sites of Infection 108
Pathophysiology of Sepsis 109
Septic "Cardiomyopathy" 109
Complications Associated with Sepsis 111
Clinical Features and Diagnosis of Sepsis 112
Organ Dysfunction in Severe Sepsis/Septic Shock 112
Management of Sepsis 115
Antibiotic Therapy 118
Fluid Therapy (See also Chap. 9) 119
Vasopressors and Inotropic Agents 124
B-Blockers and Phenylephrine in Septic Shock 128
Resuscitation End-Points 129
The Dangers of a HIGH CVP 130
Does Tissue Hypoxia and Mitochondrial Dysfunction Exist in Sepsis? 133
Case Example 136
References 137

13 The Stress Response, Stress Hyperglycemia and Stress Hyperlactemia 149
The Stress Response 149
Cardiovascular Effects of the Stress Response 152
Immune Effects of the Stress Response 152
Metabolic Effects of the Stress Response 153
Stress Hyperglycemia 153
Treatment of "Stress Hyperglycemia" 155
So What to Do! 157
How to Achieve These Goals? 157
Glucose Control and Steroids 158
Stress Hyperlactemia 158
Lactate Metabolism 159
Lactate as a Marker of Illness Severity 160
Lactate as a Marker of Metabolic Stress 161

Lactate as a Metabolic Fuel 162
Heart Metabolism and Lactate 163
Brain Metabolism and Lactate 163
References 164

14 Understanding the Vital Signs: BP, HR, RR, TEMP, SaO_2 … and SV 169
Blood Pressure 169
The Brain-Heart Distance and the Giraffe Theory of Blood Pressure Determination in Humans 170
What's a Normal Blood Pressure? 171
BP Thresholds for the Intensivist/Anesthesiologist 172
Non-Invasive Blood Pressure (NIBP) vs Arterial Line Blood Pressure (IAP) and Systolic Blood Pressure (SBP) vs Mean Arterial Pressure (MAP) 172
Central vs Peripheral Blood Pressure Measurement 173
Blood Pressure Autoregulation 174
MAP, Organ Failure and Death 175
Circulatory Shock 176
Pulse Rate 177
Respiratory Rate (& Pattern) 178
Temperature 179
Pulse Oximetry 179
Too Much Oxygen Kills 184
Analysis of the Oximetric Waveform 188
Stroke Volume: The 6th Vital Sign 189
Putting the Vital Signs Together 190
Early Warning Scoring Systems and Rapid Response Teams 191
References 192

15 Management of Pain, Agitation and Delirium 197
Assessing the Level of Pain and Sedation 200
The Ramsey Sedation Scale 201
The Richmond Agitation-Sedation Scale (RASS) 201
Sedation Vacations 202
Non-pharmacologic Interventions 202
Delirium 202
Sedative and Analgesics Agents 205
Lorazepam 205
Midazolam 206
Propofol 206
Dexmedetomidine 207
Haloperidol 208
Fentanyl 208
Morphine 208
Meperidine 208

Neuromuscular Blockade 209
Neuromuscular Blocking Agents 209
References 210

16 Hospital Acquired Infections and Their Prevention 213
Colonization with Multidrug Resistant Organisms 215
Handwashing and Infection Control Measures 216
Handwashing 216
Chlorhexidine Bathing 216
Gloves and Gowns and Healthcare Provider Apparel 217
Universal Screening for MDR's and "Protective Isolation" 217
Oropharyngeal and Gastrointestinal Decolonization 218
Private Rooms and Environmental Control 219
Central Line Associated Blood Stream Infection 220
Management of CLABSI's 224
Antibiotics Lock Therapy 225
Prevention of CLABSI 225
Catheter Associated Urinary Tract Infection 227
Ventilator Associated Pneumonia 229
Pathogenesis of VAP 230
Diagnosis of VAP 232
Treatment 234
General Concepts for the Antimicrobial Treatment of VAP 234
Empiric Antibiotic Choices 235
"Specific" Interventions for Prevention of VAP 235
Clostridium difficile Infection 239
Laboratory Diagnosis 241
Sigmoidoscopy 242
Treatment 243
Fidaxomicin 244
Adjunctive Treatment Options 244
Probiotics 245
Surgical Intervention 245
Nosocomial Rhinosinusitus 246
References 248

Part II Pulmonary

17 The Bacterial Pneumonias: A New Treatment Paradigm 261
Unified Treatment Algorithm 263
No Risk Factors for a CAP-DRP 263
Risk Factors for CAP-DRPs 264
Influenza (Co-Existent or Influenza Pneumonia) 264
Diagnostic Testing of Hospitalized Patients with Pneumonia 265
Non-Infectious Diseases Masquerading as Pneumonia 265
Special Considerations 266
Severe CAP with no MDR Risk Factors 266

Community-Acquired MRSA Pneumonia (CA-MRSA) 266
Aspiration Pneumonia 267
Nursing Home-Acquired Pneumonia 269
Persistent Temperature/Failure to Respond to Rx 269
Unusual Pathogens 270
Complicated Pleural Effusion/Empyema 271
References 271

18 Fever 275
Common Misconception and Fables 275
Pathogenesis of Fever 276
Treatment of Fever 276
Causes of Fever in the ICU 278
Infectious Causes of Fever in the ICU 279
Non-Infections Causes of Fever in the ICU 279
Non-Infectious Causes of Fever 279
An Approach to the Febrile ICU Patient 286
Clinical Pearls 288
References 288

19 Mechanical Ventilation 101 291
Alveolar Overdistension Damages Normal Lungs 293
Ventilator Variables and Modes of Ventilation 293
Ventilator Variables (See Table 19.1) 297
Common Modes of Mechanical Ventilation 299
Positive End-Expiratory Pressure (PEEP) 303
Auto-PEEP 305
Monitoring Patients Undergoing Mechanical Ventilation 306
Sudden Increase in Airway Pressure and/or Fall in Arterial Saturation 307
When to Perform a Tracheostomy 307
Timing of Tracheostomy in the Critically Ill 308
References 308

20 Non-invasive Ventilation 311
Set Up 312
Initial Settings 312
Indications of NIV 313
COPD Exacerbations 313
Acute Cardiogenic Pulmonary Edema 313
Facilitating Extubation in COPD Patients 313
Immunocompromised Patients 314
Post-operative Patients 314
When to Use NIV 315
Hypercapnic Respiratory Failure 315
Hypoxemic Respiratory Failure 315

Contraindications to NIPPV 315
Success and Failure Criteria for NIPPV 316
References 316

21 Liberation (Weaning from Mechanical Ventilation) 319
General Concepts 319
Effect of Liberation on Oxygen Consumption and Cardiac Function .. 320
Fluid Overload and Liberation Failure 320
Vasopressors and Inotropic Agents and Weaning 321
Mechanical Ventilation Liberation Process 322
"Readiness" Testing 322
Spontaneous Breathing Trials 323
Causes of Liberation Failure 324
Early Extubation Followed by NIV in COPD 324
NIV for Persistent Liberation Failure 324
Extubation Failure 325
Patients at High Risk of Extubation Failure 325
The Cuff Leak Test 326
Corticosteroids for the Prevention of Post-extubation Stridor 326
References 326

22 Arterial Blood Gas Analysis 329
Indications for ABG Sampling 329
ABG Sampling 330
ABG Analysis 331
Alveolar Ventilation 332
Oxygenation 332
Acid-Base Balance 334
A Step Wise Approach to Acid-Base Disorders 335
Common Acid Base Disturbances in the ICU 338
Metabolic Acidosis 338
Metabolic Alkalosis 341
Venous Blood Gas Analysis (VBGs) 342
Mixed Venous/Central Venous Oxygen Saturation 343
References 344

23 ARDS 349
Definition, Causes and Assessment of Severity 349
Definition of ALI According the American European Consensus 349
Acute Lung Injury (ALI) 349
Acute Respiratory Distress Syndrome (ARDS) 350
Pathophysiological Definition of ARDS 350
Causes of ALI 351
Management of the Acute Phase of ARDS 351
Ventilatory Strategy 352
Pressure Controlled Ventilation 355

Airway Pressure Release Ventilation 357
Permissive Hypercapnia 359
Best PEEP 359
Recruitment Maneuvers 361
Non-Ventilatory Adjuncts to Gas Exchange 361
Prone Positioning 361
Neuromuscular Blocking Agents 362
ECMO 362
Corticosteroids 363
Inhaled Nitric Oxide 365
Nebulized Prostacyclin 365
β_2-Adrenergic Receptor Agonists 365
Surfactant 365
Omega-3 Enteral Nutrition 366
"Our" Approach to Refractory Hypoxemia 366
References 367

24 COPD Exacerbation 373
Common Precipitating Events 374
Indications for Hospitalization 375
Indications for ICU Admission 375
Treatment 375
Indications for NPPV 377
Indications for Endotracheal Intubation 377
Mechanical Ventilation in COPD 377
Suggested Initial Settings 378
References 378

25 Acute Severe Asthma 381
Indications for Admission to the ICU 382
Initial Treatment 382
Other Therapeutic Options 383
Complications of Acute Asthma 384
Noninvasive Positive-Pressure Ventilation in Status Asthmaticus 384
Indications for Intubation 385
Sedation Post-intubation 386
Mechanical Ventilation 386
Initial Ventilator Settings 387
References 388

26 Pleural Effusions and Atelectasis 391
Pleural Effusions 391
Pathophysiology 391
Drainage of Pleural Effusion 392
Hepatic Hydrothorax 393

Alelectasis 393
Respiratory Therapy 394
Mucolytics 394
Bronchoscopy 395
Bilevel/APRV 395
References 396

27 Venous Thromboembolic Disease: DVT and PE 399
Pregnancy, Venous Thromboembolism and Thrombophilias 399
Site of Venous Thrombosis 400
The Veins of the Lower Limb 401
Suggested DVT Prophylaxis Protocols 405
Diagnosis of DVT 405
Distal Lower Extremity DVT 406
Upper Extremity DVT 406
Superficial Phlebitis 407
Pulmonary Embolism 408
Diagnosis of Pulmonary Embolism 408
Treatment of Thromboembolic Disease 411
Thrombolytic Therapy 413
Catheter Directed Clot Fragmentation and Aspiration 418
Inhaled Nitric Oxide 418
Vena Caval Interruption 419
"Absolute Contraindications" for Anticoagulation with Heparin 419
References 419

Part III Cardiac

28 Hypertensive Crises 429
Definitions 429
Pathophysiology 430
Clinical Presentation 431
Initial Evaluation 432
Initial Management of Blood Pressure 433
Resident (or Hospitalist) Called to the Floor for High Blood Pressure: What to Do? 434
Drugs to AVOID 436
Recommended Antihypertensive Agents 437
Acute Postoperative Hypertension 439
Pre-operative Hypertension 440
Posterior Reversible Encephalopathy Syndrome (PRES) 441
Pregnancy-Induced PRES 441
Drugs Associated with PRES 442
References 442

29 Acute Decompensated Cardiac Failure 445
Confirm the Diagnosis of Cardiac Failure 446
Evaluation of the Patient with Cardiac Failure 447
B-Type Natriuretic Peptides 447
Echocardiography 448
Laboratory Testing 448
Hemodynamic Monitoring 448
Precipitating Factors 449
Treatment 449
Acute Phase of Treatment 449
Treatment of ADHF: Summary 456
Long-Term Management 456
Systolic Heart Failure 457
Management of Patients with Heart Failure with Preserved Ejection Fraction (HFpEF) 461
Takotsubo Cardiomyopathy 462
Stressors Reported to Trigger Takotsubo Cardiomyopathy 462
Mayo Clinic Criteria for Takotsubo Cardiomyopathy 464
References 465

30 Acute Coronary Syndromes 471
Unstable Angina/NSTEMI 471
Canadian Cardiovascular Classification of Angina 472
Types of Presentations of Unstable Angina 472
Differential Diagnosis 472
Electrocardiography 472
Tropinins 473
Management of UA/NSTEMI 473
Risk Stratification 473
Thrombolysis in Myocardial Infarction (TIMI) Risk Score 473
Global Registry of Acute Coronary Events (GRACE) Risk Model 474
Treatment Approach for UA and NSTEMI (PER AHA Guidelines) 474
Class I Recommendations 474
Class II Recommendations 475
Treatment Approach to STEMI (PER AHA Guidelines) 475
Class I Recommendations 475
Class II Recommendations 476
Complications Following STEMI 477
Recurrent Chest Pain Post-AMI 477
Mitral Regurgitation 477

Left Ventricular Failure and Low Output States 478
Right Ventricular Infarction 478
Atrial Fibrillation 478
References 479

31 Arrhythmias 481
Arrhythmias and Electrolyte Disturbances 481
Acute Atrial Fibrillation/Flutter 482
Urgent Cardioversion 483
Rate Control 483
Pharmacologic Cardioversion 484
Anticoagulation 484
Multifocal Atrial Tachycardia (MAT) 485
Paroxysmal Supraventricular Tachycardia (PSVT) 485
Management 486
SVT Mediated by Accessory Pathways 486
Sinus Bradycardia 487
Sick-Sinus Syndrome 487
Accelerated Idioventricular Rhythm 487
Ventricular Premature Complexes and Bigeminy 487
Nonsustained Ventricular Tachycardia 488
Sustained Ventricular Tachycardia 488
Polymorphic Ventricular Tachycardia (Torsades De Pointes) 489
Management 489
References 490

Part IV Gastrointestinal

32 Nutrition in the ICU: It's Whey Cool 493
Myths of Nutritional Support 494
Important Points to Digest 495
How Many Calories and How Much Protein to Give? 498
Muscle Wasting in Critical Illness 499
Factors That Activate Muscle Synthesis by the mTOR Pathway 502
Bolus vs. Continuous Feeding 504
So! What is the Best Way to Feed Critically Ill Patients? 506
The Obese Patient 507
The Refeeding Syndrome 507
References 508

33 Stress Ulcer Prophylaxis 513
Does SUP Reduce GI Bleeding? 514
Enteral Nutrition and Stress-ulcer Prophylaxis 515
Complications Associated with Acid Suppressive Therapy 516
So! What to Do? 517
Complications Associated with Specific Drugs 517

H2 Receptor Antagonists (H2RA) 517
Proton Pump Inhibitors (PPIs) 518
Sucralfate 518
References 519

34 Acute and Chronic Liver Disease 523
Chronic Liver Failure 523
Causes of Cirrhosis 524
Metabolic/Hematologic Derangements in Cirrhosis 525
Spontaneous Bacterial Peritonitis 525
Hepatic Encephalopathy 527
Grades of Hepatic Encephalopathy 528
Hepatorenal Syndrome 529
Hepatorenal Syndrome: Diagnostic Criteria 530
Diagnostic Approach 530
Treatment of HRS 531
Hepato-adrenal Syndrome 532
Pulmonary Consequences of Portal Hypertension 532
Infection and Cirrhosis 532
Supportive Care of the Hospitalized Cirrhotic 533
The Coagulopathy of Chronic Liver Disease 534
Portal Vein Thrombosis 535
Acute-on-chronic Liver Failure 537
Alcoholic Hepatitis 538
Differential Diagnosis 539
Management 539
Fulminant Hepatic Failure 540
Causes of Fulminant Hepatic Failure 541
Workup of Patients Presenting with FHF 541
Cerebral Edema in FHF 542
Management of Increased ICP 543
Supportive Measures 545
Indications for Liver Transplantation 545
Kings Criteria 546
References 546

35 GI Bleeding 551
Initial Assessment 551
Initial Resuscitation 553
Triage of Patients. Who to Admit to the ICU? 555
Upper GI Bleeding 555
The Major Causes of UGIB Include 556
Further Management of Upper GI Bleeding (See Fig. 35.1) 556
Further Management of Bleeding Peptic Ulcers 557
Recurrent Hemorrhage 559

Further Management of Esophageal Varices 559
Management of Patients with Lower GI Bleeding 560
References 562

36 Pancreatitis 565
Diagnosis 566
Risk Stratification 567
Complications 568
Management 569
References 571

37 Diarrhea & Constipation 575
Diarrhea 575
Infectious Diarrhea 575
"Non-Infectious" Diarrhea 576
Antibiotic Associated Diarrhea (AAD) 576
Enteral Feeding-Associated Diarrhoea 576
Management of "Non-Infectious" Diarrhoea 576
The Use of Probiotics and Prebiotics 577
Constipation 579
References 580

Part V Miscellaneous

38 Transfusion of Blood and Blood Products 585
Red Blood Cell Transfusions 585
Why Transfuse? 586
Risks Associated with Blood Transfusion (See Fig. 38.1) 586
Risks Associated with Blood Transfusion 587
Transfusion-Associated Immunomodulation 588
"Age" of Transfused Red Blood Cells 590
Tolerance to Anemia 596
Weighing the Risks and Benefits of Blood Transfusion 596
So, When Should Patients' Be Transfused? 597
Coagulation Disorders in the ICU 598
Fresh Frozen Plasma 600
FFP Prior to Invasive Bedside Procedures or Surgery 601
Paracentesis 604
Management of Non-therapeutic INRs With or Without Bleeding (Due to Coumadin Therapy) 604
Platelet Transfusion 606
Heparin Associated Thrombocytopenia 610
Thrombotic Thrombocytopenic Purpura (TTP) 612
Cryprecipitate 614
References 614

39 Adrenal Insufficiency 621
Causes of Adrenal Insufficient/Circi 622
Clinical Features of Adrenal Insufficiency/Circi 623
Diagnosis of Adrenal Insufficiency/Circi 624
Factors Affecting the Response to Corticosteroid Treatment 625
The Immune Status of the Host 625
Timing of Corticosteroids 626
Dose and Dosing Strategy 626
Acute Rebound After Discontinuation of Corticosteroids 627
Genetic Polymorphisms 627
Abnormalities of the Glucocorticoid Receptor 628
Treatment of Adrenal Insufficiency/CIRCI 628
Who to Treat with Steroids? 628
Adverse Effects of Corticosteroids 630
References 631

40 Electrolyte Disturbances 635
Sodium and Water 635
Rules of the Game 635
Hyponatremia 635
Hypernatremia 640
Hypokalemia 641
Hyperkalemia 641
Hypophosphatemia 642
Management 643
Hypomagnesemia 643
Management of Hypomagnesemia 644
Disorders of Calcium Homeostasis 645
Hypocalcemia 646
Should Hypocalcemia Be Corrected in Critically Ill Patients? 647
Treatment 647
Hypercalcemia 648
Treatment 649
Second Line 649
Additional Therapies 650
References 650

41 Acute Kidney Injury 653
Pre-Renal Azotemia 654
Contrast Agents and the Kidney 655
Prevention of Contrast Induced AKI 655
“Common” Nephrotoxic Agents 656
Management of Established Acute Renal Failure 657
When to Initiate Renal Replacement Therapy (RRT) 657

Mode of Renal Replacement Therapy 658
Advantages of CRRT Therapy Include 658
Dosing of RRT 659
Summary of Recommendations for RRT in Patients with AKI 659
Rhabdomyolysis 659
Epidemiology 660
Etiology 660
Pathophysiology 663
Mechanisms of Acute Renal Failure in Rhabdomyolysis Patients 663
Clinical Manifestations 663
Laboratory Findings 664
Management 664
Dialysis 665
References 666

42 Acute Ischemic Stroke 669
Stroke ICU's, Medical ICU's or Stroke Units 670
Profiles Predictive of Futility After Devastating Stroke 670
Acute Ischemic Stroke (AIS) 671
Imaging 671
Thrombolytic Therapy 672
Treatment of Acute Ischemic Stroke With Intravenous rtPA 674
Endovascular Interventions 675
Antiplatelet Therapy and Anti-Coagulation 676
Anticoagulation in Cardio-Embolic Stroke 676
Raised ICP and Decompressive Surgery 677
Treatment of Hyperglycemia 678
Treatment of Fever 678
Treatment of Post Stroke Hypertension 678
Supportive Medical Therapy 680
References 681

43 Intracerebral and Subarachnoid Hemorrhage 685
Intracerebral Hemorrhage 685
Medical Management 687
Blood Pressure Control 689
Surgical Interventions 690
Subarachnoid Hemorrhage 692
Diagnosis and Evaluation 693
Initial Management 693
Specific Therapeutic Issues 698
Antifibrinolytic Therapy 698
Surgical and Endovascular Methods of Treatment 698
Management of Cerebral Vasospasm 698
Transpulmonary Thermodilution (TPTD) Hemodynamic Assessment 701

Subdural Hematoma 702
Epidural Hematoma 703
Increased Intracranial Pressure (ICP) 703
Measurement of ICP 704
Indications for ICP Monitoring 704
Management of Raised ICP 705
References 708

44 Seizures & Status Epilepticus 717
Seizures in the ICU 717
Seizures Occurring as a Complication of Critical Illness 718
Seizures from Primary Neurological Disease 719
Management 719
Seizure Therapy 719
Status Epilepticus 720
Etiology 721
Common Causes of Status Epilepticus Include 721
Pathophysiology 722
Complications of Generalized Status Epilepticus 722
Diagnosis 722
Treatment 723
General Measures 723
Pharmacotherapy 724
Management of Refractory Status Epilepticus 726
The Management of Nonconvulsive Status Epilepticus 727
Prevention of Seizure Recurrence Once Status Epilepticus is Terminated 728
References 728

45 Toxicology 731
General Measures 731
Technique for Performing Gastric Lavage 732
Activated Charcoal 732
Hemodialysis/Hemoperfusion 733
Common Agents Responsible for 734
Common Intoxications 735
Acetaminophen 735
Salicylates 738
Tricyclic Antidepressants 738
Acute Ethanol Intoxication 739
Ethylene Glycol and Methanol Poisoning 740
Ethylene Glycol 740
Methanol 741
Isopropyl Alcohol 742
Digitalis 743
Phenytoin 743
Lithium 744

Opiates 745
Cocaine 745
Carbon Monoxide Poisoning 748
References 750

46 Alcohol Withdrawal Syndrome 751
The Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar) 753
Differential Diagnosis 753
Treatment 754
Other Treatment Considerations 755
Prevention of Post-operative DT's 756
References 756

47 Pregnancy Related Disorders 759
Obstetrical Hemorrhage 760
Antepartum Hemorrhage 760
Postpartum Hemorrhage 760
Management 760
Hypertension 761
Pre-eclampsia 761
Diagnosis of Pre-eclampsia 762
HELLP Syndrome 764
Posterior Reversible Encephalopathy Syndrome (PRES) 765
Treatment of Pre-eclampsia 765
Anti-hypertensive Agents for the Treatment of Pre-eclampsia 766
Corticosteroids and Plasmapheresis as Adjunctive Treatment of HELLP 767
Acute Fatty Liver of Pregnancy 768
Amniotic Fluid Embolus Syndrome 768
Sepsis in Pregnancy 768
Respiratory Failure in Pregnancy 769
References 770

48 The Geriatric ICU Patient 773
The Physiology of Aging 773
Cardiovascular Changes 774
Changes in Respiratory Function 775
Changes in Renal Function 775
Immune System Changes 776
Body Composition and Muscle Mass 776
The Outcome of Elderly Patients Admitted to the ICU 776
Trauma and the Elderly Patient 778
Surgery and the Elderly 778
Delirium in the Elderly 779
Drug Dosing and Polypharmacy in the Elderly 780

American Geriatric Society Beers Criteria 781
Drugs to Avoid in the Elderly 781
References 782

49 Obesity in the ICU 787
Effect of Obesity on Critical Care Outcomes 787
Respiratory Effects of Obesity 788
Ideal Body Weight 789
Cardiovascular Effects of Obesity 789
Hepatic and Renal Effects of Obesity 790
Drug Dosing in Obese Patients 790
Nutritional Requirements 790
Gaining Vascular Access 791
Radiological Procedures 791
Malignant Obesity Hypoventilation Syndrome (MOHS) 791
Major Criteria 792
Minor Criteria 792
Treatment of MOHS 792
References 793

50 Radiology 797
The Chest Radiograph 797
Position of Tubes and Catheters 798
Lung Parenchyma, Pleura and Mediastinum 798
Plain Abdominal Radiography 801
Computed Tomography (CT) 801
Indium Labeled Leukocye Scans 802
References 803

51 End-of-Life Issues 805
Palliative Care 806
"Principles" of Palliative Care 807
References 809

52 Words of Wisdom 811
References 812

Index 813

Part I
General ICU Topics

Chapter 1
Evidence Based Critical Care

There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance.

—Hippocrates (c460–c377 BCE), Greek physician

Before medicine developed its scientific basis of pathophysiology, clinical practice was learned empirically from the events of daily experience in diagnosing and treating the maladies patients presented. Students learned as apprentices to clinicians, observing the phenomena of disease, the skill of diagnosis and treatment, and the outcomes of different remedies. Sir William Osler's classic textbook of medicine was based almost entirely on his "*personal experience correlated with the general experience of others*" [1]. With advances in our understanding of human physiology and the pathophysiologic basis of disease, these remedies fell by the wayside and treatment became based on modalities of treatment that were shown to interrupt or otherwise modify the disease process. Until recently, it was considered sufficient to understand the disease process in order to prescribe a drug or other form of treatment. However, when these treatment modalities were subjected to randomized, controlled clinical trials (RCTs) examining clinical outcomes and not physiological processes, the outcome was not always favorable. The RCT has become the reference in medicine by which to judge the effect of an intervention on patient outcome, because it provides the greatest justification for conclusion of causality, is subject to the least bias, and provides the most valid data on which to base all measures of the benefits and risk of particular therapies [2]. Numerous ineffective and harmful therapies have been abandoned as a consequence of RCTs, while others have become integral to the care of patients and have become regarded as the standard of care.

Many RCT's are, however, inconclusive or provide conflicting results. In this situation systematic reviews that are based on meta-analysis of published (and unpublished) RCTs are clearly the best strategy for appraising the available evidence. While meta-analyses have many limitations, they provide the best means of determining the significance of the *treatment effect* from inconclusive or conflicting RCTs (as well as trials that demonstrate a similar treatment effect). Furthermore, as a result of publication bias positive studies are more likely to be published and usually in more prestigious journals than negative studies. A clinician may base his/her therapeutic decisions on these select RCTs which may then lead to inappropriate patient care. It is therefore important that common medical interventions be systematically

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reviewed and the strength of the evidence (either positive or negative) be evaluated. Although over 250,000 RCTs have been performed, for many clinical problems, there are no RCT's to which we can refer to answer our questions. In these circumstances, we need to base our clinical decisions on the *best evidence* available from experimental studies, cohort studies, case series and systematic reviews.

Alert
Be cautious in the interpretation of retrospective "before-after" studies and small single-center unblinded RCT's [3, 4]. The investigators of these studies may have a vested interest in the outcome of the study resulting in "misrepresentation" of the true data. Generally blinded studies show less of a treatment effect than unblinded studies evaluating the same intervention; both subconscious and conscious bias influence unblinded studies Before-after studies are particularly of questionable scientific value particularly if the variables and end-points are not defined prior to commencing the study, the data is collected retrospectively and there is no control arm (as other factors may influence the outcome). Prospective cluster controlled trials take these factors into account [5]. If a finding is true and valid it can be reproduced; that's the amazing thing about scientific exploration. So be very wary of invalidated single studies no matter how robust they appear [6].

And lastly, If a study seem too good to be true, it is likely too good to be true [3, 7].

Every decision that the clinician makes must be based on sound scientific evidence (a collection of anecdotes is not scientific evidence). Science is the continuing effort to discover and increase human knowledge and understanding through disciplined research. Using controlled methods, scientists collect observable evidence, record measurable data relating to the observations, and analyze this information to construct explanations of how things work [8]. Intuition, anecdotes, common sense, personal biases, and clinical experience is not considered "science" and cannot be used to justify clinical decision making or therapeutic policies.

Evidence is not static; both the strength and direction of evidence change as new evidence becomes available. It is therefore important to keep an open mind and reevaluate the scientific basis and strength of what we think we know and how we practice. Furthermore, there is a hierarchy of evidence from anecdotes and "clinical experience" to strong irrefutable evidence (see Fig. 1.1).

Science progresses best when observations force us to alter our preconceptions

—Vera Rubin, Astronomer, 1928

As critical care medicine has evolved into a discreet specialty that crosses anatomical and other artificial boundaries and deals with an enormous array of human

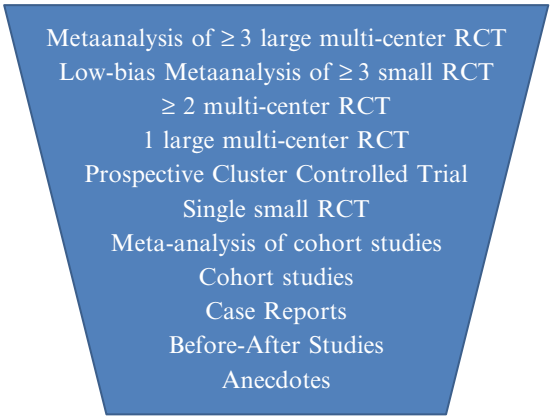

Fig. 1.1 The hierarchy of scientific evidence

conditions, it has become evident that to achieve the best outcomes for our very complex patients, all our clinical decisions should be based on the *best available evidence.* The complexity of the critically ill patient together with the vast armamentarium of therapeutic options available makes it essential that we critically evaluate established and emerging clinical practices. It is important that we challenge established dogma through thoughtful scientific enquiry. Many of our current practices are based on anecdotes which have been passed down from teacher to student and assumed to be the undeniable truth. It is important to realize that nothing stays the same, that knowledge and understanding march forward with no end in sight. Those who hang on to the past will get lost in the dark:

Life (and Medicine) is like riding a bicycle; you need to move forward to keep your balance

—Albert Einstein, Theoretical physicist, 1879–1955

While Evidence Based Medicine (EBM) is frequently criticized as "cook-book" medicine, this is most certainly not the case. Rather, the best scientific evidence should be applied to the unique characteristics of each patient [2]. Each patient is unique, and the "art" of medicine is the ability to integrate and apply the best scientific knowledge to each patient. Checklists may be fine if you are flying a plane, however, patients are not planes and doctors are not pilots [9, 10]. Clinical Practice Guidelines (CPG's), which are evidence-based and up-to-date, are useful in providing the clinician with direction, but should never be followed blindly. Rigid protocols and policies, have little place in clinical medicine.

Lastly, it is important to realize that Critical Care Medicine can only be practiced by close observation of the patient (at the bedside), by contemplation, and by the integration of a large data base of evidence-based medicine together with a good deal of humility.

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Chapter 2
"Less Is More": The New Paradigm in Critical Care

The art of medicine consists of amusing the patient while nature cures the disease

Voltaire, French writer and historian (1694–1778).

What appears to be the world's first ICU was established at the Municipal Hospital of Copenhagen in December of 1953 by the Danish anesthesiologist Bjorn Ibsen during the polio epidemic of 1952–1953 [1]. The first patient admitted to the unit was a 43 year old man who had unsuccessfully attempted to hang himself. The patient had a tracheotomy performed and received manual positive pressure ventilation with 60 % oxygen in N_2O [2]. The first physician staffed ICU's in the US were developed in 1958 by Max Harry Weil and Herbert Shubin at the Los Angles County General Hospital and by Peter Safar in Baltimore [3, 4]. The introduction of the pulmonary artery catheter (PAC) in the early 1970s by Swan and colleagues became the monitoring tool that defined critical care medicine for the next four decades [5, 6]. The PAC became synonymous with critical care medicine. The era of the PAC resulted in a style of medicine that can best be characterized as aggressive. If some care is good, more care is even better. However almost all medical interventions be they invasive procedures, diagnostic tests, imaging studies, mechanical ventilation, surgery or drugs have some risk of adverse effects [7]. In some cases, these harms outweigh the benefits. This may be particularly so in ICU patients who are highly vulnerable and at an increased risk of iatrogenic complications [8]. Beginning in 1996 the safety and effectiveness of the PAC came into question [9]. Subsequent studies demonstrated that the PAC provided misleading ("physiologic variables") that could lead to inappropriate therapeutic interventions and that the use of the PAC did not improve patient outcome [10–12]. The PAC has now all but been abandoned [13]. In 2000 the ARDSnet group published their now landmark study which demonstrated that mechanical ventilation with low tidal volume of 6 mL/kg/IBW improved patient outcome as compared to the standard approach (12 mL/kg/IBW) [14]. The last decade has witnessed a slew of studies that have challenged conventional wisdom and which have led to a gentler, less invasive approach to the critically ill patient… this has led to the paradigm that "*Less may be More*" (*see list below*) [7, 8]. We now realize that our goal as intensivists is too be supportive and allow the body to heal itself while at the same time limiting the harm we cause with are arsenal of therapeutic and diagnostic weapons.

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Interventions for which less has been shown to be associated with better outcomes:

- Lower tidal volume and lower plateau pressures [14]
- Less blood [15, 16]
- Less invasive hemodynamic monitoring [13, 17]
- Lees fluids [18–20]
- Less insulin and less intensive glycemic control [21]
- Less antibiotics; de-escalation of empiric therapy and shorter course [22–24]
- Less sedation and less benzodiazepines [25–27]
- Less corticosteroids; 200 mg hydrocortisone (equ) daily for sepsis and COPD [28–31]
- Less CXR; no daily CXR [32, 33]
- Less oxygen; hyperoxia kills (COPD) and damages the brain and lungs [34–43]
- Less calories and protein; trophic feeds may be safe; less protein = less muscle breakdown [44, 45]
- Less antiarrhythmics; no prophylactic lidocaine in AMI [46]
- Less stress ulcer prophylaxis (=less *C. diff.* and less HAP) [47, 48]
- Less intense renal replacement therapy [49–52]
- Less blood pressure control (in ischemic stroke) [53, 54]
- NO dopamine [55–57]
- NO "supranormal" hemodynamic targets [58, 59]
- NO TPN [60, 61]
- NO diuretics for acute renal failure [62]
- NO hetastarch [63, 64]
- NO Activated Protein C [65]
- NO MRSA/MDRO screening and protective isolation [66–68]
- NO therapeutic hypothermia [69, 70]

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Chapter 3
"Classic" Papers

If we knew what it was we were doing, it would not be called research, would it?

Albert Einstein, Theoretical Physicist (1879–1955)

A limited number of publications have had a dramatic impact on the practice of Critical Care Medicine. These publications are regarded as "compulsory" reading for residents, fellows and other practitioners of Critical Care Medicine. Surprisingly, although not unexpectedly, those publications with the potential to have the most dramatic positive impact on patient care have been slow to be adopted, while publications of questionable scientific rigor are frequently adopted with an unexplained religious fervor. This chapter reviews those papers which have dramatically altered the practice of Critical Care Medicine (for good or bad) as well as those "classic" papers that have shaped the history of Critical Care Medicine.

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.

Perhaps the most important publication in the history of Critical Care Medicine is that of the ARDSnet low vs. standard tidal volume study. This study demonstrated a significant reduction in 28-day mortality in patients randomized to the low tidal volume group (6 mL/kg PBW) as compared to the traditional tidal volume (12 mL/kg PBW) group. The results of this study are supported by extensive experimental and clinical studies. Furthermore, high tidal volumes are associated with progressive lung injury in patients who initially do not have acute lung injury. A tidal volume of 6–8 mL/kg is therefore considered the standard of care for ALL ICU patients.

Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369:428–37.

These authors randomized 400 patients undergoing abdominal surgery to an intraoperative ventilatory strategy of either 8–10 or 6–8 mL/kg. The risk of major pulmonary and extrapulmonary complications occurring within the first 7 days after surgery was significantly higher in the patients receiving the non-protective ventilation strategy.

Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471–7.

P.E. Marik, *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-11020-2_3

This study demonstrated that in patients who are receiving mechanical ventilation, daily interruption of sedative drug infusions decreases the duration of mechanical ventilation and the length of stay in the intensive care.

Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. Lancet. 2008;371:126–34.

This study demonstrated that "a wake up and breathe protocol" that pairs daily spontaneous awakening trials (ie, interruption of sedatives) with daily spontaneous breathing trials results in better outcomes for mechanically ventilated patients than the "standard approaches." This approach should be considered the standard of care in all ICU patients.

Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian critical care trials group. N Engl J Med. 1999;340:409–17.

In a landmark study, Herbert and colleagues compared a conservative (transfusion for Hb < 7 g/dL) vs. liberal (transfusion for Hb < 10 g/dL) blood transfusion protocol. In this study the complication rate and 28-day mortality tended to be lower in the conservative group. This results of this study are supported by additional RCT's and cohort studies.

Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA. 1996;276: 889–97.

The "classic" study by Conners et al. in 1996 raised the possibility that the PAC may be harmful in critically ill patients. Subsequent studies have been unable to demonstrated any benefit associated with the use of the PAC. Additional studies have demonstrated that physicians are unable to interpret the data obtained from the PAC. The PAC is now considered a relic from the past

Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359;7–20.

The optimal dosing of intermittent hemodialysis (IHD) and continuous renal replacement therapy in the ICU had been unclear with data suggesting that more aggressive renal replacement therapy (RRT) was associated with improved renal recovery. The VA/NIH Acute Renal Failure Trial Network randomized 1,124 patients with ARF to receive intensive or less intensive RRT. Hemodynamically stable patients underwent IHD (6 vs. 3 times per week) and hemodynamically unstable patients underwent CVVHD (35 vs. 20 mL/kg/h). There was no difference in clinical outcomes between the two groups of patients.

November the 8th was a dark day in the history of Critical Care. On that day two "studies" were published in the *New England Journal of Medicine* which changed (overnight) the way critical care was practiced around the world (EGDT and the Leuven Trial). The external validity of both of these trials have come into question.

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.

Rivers and colleagues randomized 288 patients with severe sepsis and septic shock to "Early goal Directed Therapy (EGDT)" or standard care. EGDT was reported to be associated with a 16 % absolute reduction of hospital death (35 % relative reduction in death). Based on this single study EGDT become adopted as the "standard of care" around the world and has become the cornerstone of the recommendations of the "*Surviving Sepsis Campaign*". It is however important to recognize that this was an unblinded, small, single center study with investigators who were highly "invested" in the outcome of the study. None of the components of EGDT have a solid scientific foundation and by any stretch of the imagination the results of this study were "*to good to be true"*. Three ongoing, international, multicenter, randomized controlled trials are attempting to replicate the findings of EGDT, so stay tuned. [Protocolized Care for Early Septic Shock (ProCESS); NCT00510835; Australian Resuscitation in Sepsis Evaluation Randomized Controlled Trial (ARISE) and Protocolised Management in Sepsis (ProMISe)].

van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.

The "*Leuven Intensive Insulin Therapy Trial #1*" compared the outcome of patients randomized to an insulin infusion protocol that achieved "tight glycemic control" (blood glucose 70–110 mg/dL) as compared to "standard glycemic control" (blood glucose 180–200 mg/dL). This study demonstrated a significant reduction in morbidity and mortality in the patients randomized to the "tight glycemic group". Similar to EGDT, based on this single center, unblinded study performed by highly "invested" investigators, "tight glycemic control" became adopted overnight as the standard of care throughout the world. Subsequent studies have failed to reproduce the findings of Van den Berghe et al. and "tight glycemic control" should now be abandoned.

Intensive versus conventional glucose control in critically ill patients: the NICE-sugar study investigators. N Engl J Med. 2009;360:1283–97.

In this study performed by the ANZICS group 6,104 patients were randomized to undergo either intensive glucose control, with a target blood glucose range of 81–108 mg/dL or conventional glucose control, with a target of 180 mg/dL. In this large study the authors found that intensive glucose control increased mortality; a blood glucose target of 180 mg/dL or less resulted in lower mortality than did a target of 81–108 mg/dL.

ProCESS investigators. A Randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014.

ProCESS enrolled 1,341 patients, of whom 439 were randomly assigned to protocol-based EGDT (Rivers EGDT), 446 to protocol-based standard therapy, and 456 to usual care. There was no significant difference in 90-day and 1 year mortality between groups. This pivotal study essentially invalidated the EGDT study by Rivers et al.

Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014.

These authors randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80–85 or 65–70 mmHg.

There was no difference in 28 day mortality (the primary end point) between the two groups.

Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862–71.

In this study 300 patients with septic shock were randomized within 6 h of presentation to receive either hydrocortisone (50 mg IV q6 h) and fludrocortisone (50 μg/daily) or placebo for 7 days. The hospital mortality was 69 % in the placebo group as compared to 63 % in the treatment group (NS). However in those patients with adrenal; insufficiency (ACTH non-responders) the hospital mortality was 72 % in the placebo group and 61 % in the steroid group ($P = 0.04$). This study is confounded by the fact that about a third of patients had received etomidate which is known to impair cortisol synthesis.

Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111–24.

In this multicenter, randomized, placebo-controlled trial, 500 patients were randomized to receive 50 mg of intravenous hydrocortisone or placebo every 6 h for 5 days; the dose was then tapered during a 6-day period. Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. This study is limited by a severe selection bias; only about 5 % of eligible patients were enrolled into the study.

Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364:2483–95

This is a landmark study of enormous clinical significance. These authors randomly assigned 3,141 children with severe febrile illness and impaired perfusion to receive boluses of 20–40 mL/kg of 5 % albumin or 0.9 % saline solution or no bolus (control group) at the time of admission to a hospital. The 48-h mortality was 10.6 %, 10.5 % and 7.3 % in the albumin-bolus, saline-bolus, and control groups, respectively. This study suggests that paradigm of fluid boluses in patients with sepsis and severe sepsis may be harmful.

Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013:368:2159–68.

In this multicenter, prospective, randomized, controlled trial, the authors randomized 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 h or to be left in the supine position. Severe ARDS was defined as a $FiO_2/PaO_2 < 150$ with a FiO_2 of at least 0.6. The 28-day mortality was 16.0 % in the prone group and 32.8 % in the supine group ($P < 0.001$).

Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early respiratory distress syndrome. N Engl J Med. 2010;363:1107–16.

In this multicenter, double-blind trial, 340 patients with severe ARDS ($FiO_2/PaO_2 < 150$) were randomly assigned to receive, for 48 h, either cisatracurium besylate or placebo. Mortality at 28 days was 23.7 % with cisatracurium and 33.3 % with placebo ($P = 0.05$).

Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33C versus 36C after cardiac arrest. N Engl J Med. 2013;369: 2197–206.

In this international trial, 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause were randomized to targeted temperature management at either 33 or 36 °C. At the end of the trial, 50 % of the patients in the 33 °C group had died, as compared with 48 % of the patients in the 36 °C group. Follow-up at 180 days demonstrated no difference in survival or neurological status amongst survivors.

Chapter 4
Critical Care Medicine 101

An ICU is a geographically distinct area of a hospital where critically ill and injured patients undergo continuous monitoring and support of failing organ systems. The critical care team applies physiologically based interventions, monitor the response to these interventions, which then serves as the basis for further interventions. It is therefore clear that critical care medicine can only be practiced at the bedside; office based and remote "intensivists" have no place looking after critically ill patients. While a number of ICU organizational models exist the optimal model requires the frequent presence of intensivists at the patient's bedside supported by a multidisciplinary team of health care professionals.

Patients in the ICU need to be managed by doctors who can see the "big picture", be able to integrate and understand the patients' complex mufti-system disease and formulate an integrative plan that is evidence-based, systematic and is in keeping with the patients' treatment goals and values while be consistent with reality. This chapter reviews the concepts and basic interventions which should be addressed when admitting the "generic patient" to the ICU. A number of issues need to be addressed regardless of the type of ICU to which the patient is being admitted and the patient's diagnosis.

It is important to note that no two patients are ever the same and that patients' don't read medical textbooks or "policies and procedures". Furthermore, patients respond differently to the same intervention. Each patient's care must therefore be individualized based on the patient's unique demographics, co-morbidities, acute disease processes, response to physiological based interventions' and their values and goals. "Policies and procedures" and "bundles of care" have a limited place in the ICU. Parallels are often drawn between the airline industry and the practice of medicine. In general, this is a dangerous position to take; patients are not airplanes and doctors are not pilots [1]. Each patient is different and will not respond to the same intervention in a stereotypical manner.

P.E. Marik, *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-11020-2_4

Factors to Consider When a Patient is Admitted to the ICU

- The patients age (chronological not physiological) (see Chap. 48)
- Co-morbidities particularly
  - Cardiac disease and ventricular function
  - Underlying lung disease
  - Baseline renal function (and estimated GFR[1])
  - Use of immunosuppressive drugs
- The diagnoses and differential diagnoses
- Is this patient septic?
- Does this patient have acute lung injury (ALI)
- What is the status of this patients' intravascular volume? (see Chap. 9)
  - Normal
  - Increased
  - Decreased
- Does this patient have evidence of impaired tissue/organ perfusion
- Decreased urine output
  - Cold/clammy skin
  - Mottled peripheries
  - Hypotension
- The patients code status, preferences for life supportive therapy and goals/expectations of treatment MUST be determined when the patient s admitted to the ICU
- Determine the adequacy of venous access
- Communicate with the patients' nurse and respiratory therapist
- Keep the family informed
- Measure the patients height and weight on admission

Initial "Generic" Treatment Orders

- Fluids
  - Sate the type of fluid and the infusion rate
- Oxygenation or
  - Nasal canula or face mask or BiPAP
- Initial ventilator settings
  - AC rate 6–8 mL/kg IBW#
  - Flow rate 60 L/min
  - FiO_2 100 %
  - PEEP 5–10 cm H_2O

[1] Estimated GFR (Cockcroft-Gault equation): (140 − age) × (Weight in kg) × (0.85 if female)/(Creatinine × 72).

- ICU patients are at a high risk for deep venous thrombosis (DVT) and therefore **ALL** ICU patients require DVT prophylaxis. This should be individualized based on the patients risk of DVT, risk of bleeding, risk of HIT and renal function (see Chap. 27)
  - subcutaneous heparin (5,000 U BID, TID)
  - subcutaneous low-molecular weight heparin (Enoxaparin 40 mg daily or equivalent)
  - subcutaneous fondaparinux (2.5 mg daily)
  - sequential compression devices
  - combination of SCD and anticoagulant
- Routine stress ulcer prophylaxis is not required
- Nutrition (see Chap. 32)
  - Unless specifically contraindicated or the patients length of stay in the ICU is expected to be less than 24 h all patients should be fed enterally once they have been resuscitated. If the patient cannot take orally enteral nutrition should be started within 12 h of ICU admission. While a general polymeric formula is acceptable, we prefer a semi-elemental diet high in omega-3 FFA. Bolus enteral feeding is preferred over continuous tube feeds (see Chap. 32).
- All patients require antiseptic mouth wash and body bathing.
- Patients should be nursed head up at an angle of 15–30° (higher than 30° is not feasible and patients slip down)
- Ocular lubricant to prevent exposure keratopathy
- Treat pain with a fentanyl infusion
- Sedation should be minimized and benzodiazepines avoided
- All ICU patients should be regularly screened for the presence of delirium
- While screening lower extremity venous Doppler's are not cost effective in all patients these should be considered in high risk patients.

Reference

1. Rissmiller R. Patients are not airplanes and doctors are not pilots[Letter]. Crit Care Med. 2006; 34(11):2869.

Chapter 5
House Officers Guidelines 1: Housekeeping

Intensive care units embody the miraculous advances of modern medicine. An ICU provides an environment where high-quality, compassionate, physiologically orientated, and evidence-based medicine can be practiced. The ICU is an exciting and challenging place to work and provides a remarkable learning environment. The keys to a successful rotation in the ICU are (1) teamwork and (2) a systematic, disciplined, and organized approach to patient care.

Admission History and Physical Examination

It is essential that a detailed and systematic history and physical examination be performed on all patients admitted to the ICU. This should include past medical and surgical history, current mediations as well as details of the current illness. The patient's *code status* and the presence of advance directives should be established on admission to the ICU. The initial physical examination frequently serves as the baseline reference, and it should include a basic neurological examination (including reflexes, motor power, evaluation of mental status, and funduscopic examination). Following the history and physical examination, and review of the available laboratory data and chest radiograph, a differential diagnosis and a management plan should be formulated.

The patients' weight and height should be measured (directly, with a scale and tape measure on admission to the ICU). These values should not be estimated as they are frequently WRONG [1]; the height and weight are used in dosing calculations as well as estimation of GFR and Predicted Body Weight (PBW); so the correct data should be used.

P.E. Marik, *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-11020-2_5

Daily Examination

It is essential that the patients' flow sheet (paper or electronic) over the last day be thoroughly reviewed and the major events of the last 24 h be documented. Most ICU's use a 24-h flow sheet which runs from midnight to midnight. Hence when reviewing and documenting the patients' progress over the "last day" the last 24-h period (midnight–midnight) as well as the progress since midnight should be reviewed. The following serves as a guideline for the daily progress note.

It is important to be systematic and develop a consistent template for your daily progress notes.

General

Primary and secondary diagnoses. Overall condition of patient. Events of the last 24 h.

Vital Signs (24 h Min and Max and Current)

- temperature
- blood pressure, including MAP
- pulse (rate and rhythm)
- respiratory rate
- arterial saturations

Fluid balance and urine output are VITALLY important in the daily and ongoing evaluation of the ICU patient. The following should be recorded:

- 24 h in
- 24 h out
- 24 h urine
- Output of each drain should be noted
- *Cumulative fluid balance*

Additional Observations

- The doses of all pressors should be documented
- The presence of all pulses and the adequacy of peripheral perfusion
- Limb symmetry and swelling (?DVT)
- Presence of rashes and decubitus ulcers
- The presence of all invasive lines, tubes, and devices should be noted including the duration of each central line

The Ventilator

The ventilator is an extension of the patient and it is therefore essential that the following features be recorded

- Mode
  - assist control (volume or pressure)
  - pressure support
  - APRV
  - SIMV
- Rate (set)
- Tidal volume (Vt)
  - Total
  - mL/PBW(kg)[1] (*THIS IS VERY NB*)
- Minute ventilation
- FiO_2
- PEEP
- Most recent blood gas analysis (if within past 24 h)

Heart

Heart sounds and murmurs

Chest

Symmetry of air entry (i.e. presence of breath sounds) and presence of rhonchi or crackles

Abdomen

The presence of distention and tenderness (especially right upper quadrant). The type of enteral feeds, evidence of reflux, gastric residual volumes and the presence of diarrhea (see Chap. 37).

[1] Lung volume is indexed to predicted body weight (PBW) which is dependent on sex and height:
Male = 50 + 0.91(Ht in cm—152.4)
Female = 45.5 + 0.91(Ht in cm—152.4)
Patients require a daily spontaneous breathing trial if criteria met (see Chap. 21).

CNS

A focused neurological examination is essential, particularly in patients receiving hypnotic/sedative agents, and should include the following:

- Level of consciousness and response to commands
- Presence of agitation confusion or delirium
- Pupillary size and response
- Eye movements
- Limb movements; spontaneous and in response to noxious stimuli (pain)
- Presence of deep tendon reflexes

Importance of the Daily Neurological Examination

Critically ill patients in the ICU are at risk of developing serious neurological complications including ICU psychosis, septic encephalopathy, critical illness polyneuropathy, entrapment neuropathies, compartment syndromes, cerebral edema, intracerebral hemorrhages (related to coagulopathies), cerebral ischemia (related to hemodynamic instability), and cerebral embolism. These conditions can be detected and diagnosed only by physical examination. Furthermore, these conditions may frequently be masked in patients who are sedated. If the patient does not respond to noxious stimuli, the sedation must immediately be stopped, to facilitate further neurological evaluation.

Laboratory Tests

All ICU patients require the following tests daily (if a patient does not require these tests, he/she probably does not need to be in the ICU!):

- Complete blood count
  - hemoglobin
  - white cell count (differential and number bands)
  - platelet count
- Urea and electrolytes
- Oxygenation should be assessed in all patients (usually by pulse oximetry and blood gasses when appropriate)
- Ca^{2+}, Mg and Phosphorus should be measured every 2–3 days or more frequently if clinical circumstances dictate
- All other laboratory tests should be ordered on merit; standing laboratory tests are not cost-effective

- It is not cost effective to perform a complete blood count and urea and electrolyte tests more frequently than every 24 h unless special circumstances dictate, such as
  - Diabetic ketoacidosis, hypernatremia, hyponatremia where Na^+ and K^+ should be tested every 2–4 h
  - In patients who are bleeding, a hematocrit should be followed no more frequently than every 6 h (it takes 72 h for the hematocrit to stabilize following blood loss).
- Pay special attention to a falling platelet count (see Chap. 38)
  - HIT
  - Drug induced thrombocytopenia
- Patients with hypernatremia receiving 3 % NaCl should have electrolytes followed 1–2 hourly

Imaging

- Daily chest X-rays are not cost effective (see Chap. 50).
- Chest-rays should only be performed on demand (as clinical circumstances dictate).

Presenting on Daily Rounds

Producing a succinct and complete summary of a patient's status is an important skill that all clinicians must master. Due to the large volume of data, together with the rapid turnover of high acuity patients, clear, succinct, and logical presentation are essential in the ICU.

New Admissions

The Classic "medical-student" presentation is highly structured and begins with a detailed history of the main complaint followed by a historical review of the major organ systems, followed by past medical and surgical history, social history, family history, drug history, physical examination and lastly the results of laboratory and special tests. Such an approach is a useful exercise for medial students leaning how to do a comprehensive H&P but is insanity in the ICU; in the ICU the presentation should be brief and to the point. A suggested presentation outline is listed in Table 5.1 together with the traditional approach [2].

Table 5.1 Comparison of the traditional H&P and proposed ICU presentation format

Presentation element	Traditional	ICU format
Total time	10–20 min	5 min
Opening line	Chief complaint	Working diagnosis
History of present illness	Thorough chronology	Brief summary
Past medical history	Complete	Only major medical problems that pertain to working diagnoses
Social history	Complete	Brief
Family history	Complete	Only if highly relevant
Physical examination	Complete	Pertinent abnormalities only
Laboratory and radiologic data	Complete	Pertinent abnormalities and normal values
Assessment	Complete list of problems. Differential diagnosis for each problem	Only major problems
		Explain reasoning
Plan	Diagnostic and therapeutic plan for each problem	Plan for major problems

Follow Up Patients

The following schema for follow-up patients is suggested:

- Events over last 24 h
- Daily exam (as outlined above)
- Relevant Laboratory results
- Review of medications (all)
- Assessment
- Plan

Clinical Pearls

- If you don't understand something, Ask!
- If unsure … don't do it!
- Ask the primary ICU nurse … she (he) knows best

References

1. Bloomfield R, Steel E, MacLennan G, et al. Accuracy of weight and height estimation in an intensive care unit: implications for clinical practice and research. Crit Care Med. 2006;34: 2153–7.
2. Dhaliwal G, Hauer KE. The oral patient presentation in the era of night float admissions: credit and critique. JAMA. 2013;310:2247–8.

Chapter 6
House Officers Guidelines 2: Procedures

- The tradition of "*See one, Do one, Teach one*" can no longer be condoned. The safety and well being on the patient is one's overriding concern.
- If you don't know how to do it, don't do it!
- Before doing a procedure make sure you have all the equipment required.
- Make sure you know how to get out of trouble should the procedure "go wrong"
- If you fail after two to three attempts at the procedure STOP. Ask a more experienced operator for help
- Check the platelet count, PTT and INR before any invasive procedure (see Chap. 38)
  - As a general rule the risk of bleeding is related to the skill of the operator rather the ability of the blood to clot (however this helps)
  - Patients receiving therapeutic anticoagulants tend to bleed; stop anticoagulants prior to the procedure
  - Generally it is safe to do a procedure with a platelet count >50,000 and an INR <2.0. However the risk depends on the type of procedure.
  - Evaluate the risk/benefit ratio in coagulopathic patients and the urgency of the procedure.
- Obtain informed consent from the patient (or surrogate), unless an emergency. Explain the benefits and risks (including death).

Murphy's Laws of Procedures

- Murphy's First Law of Procedures
  - Nature sides with the hidden flaw
- Murphy's Second Law of Procedures
  - If a procedure can go wrong it will go wrong usually at the most inopportune time

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- Murphy's Third Law of Procedures
  - If a patient can bleed he/she will bleed
- Murphy's Fourth Law of Procedures
  - Never "force" a patient into a procedure they decline or are hesitant about; these are the patients that will suffer a complication
- Murphy's Fifth Law of Procedures
  - Never "force" a device into a patient; if it does not "go in easily" it will go into the wrong place

Central Venous Access

- Many ICU patients require a central line. Indications include:
  - High doses of vasopressor agents. In select circumstances low dose vasopressors may be given via a well secured and flowing peripheral catheter (see Chap. 12)
  - Multiple mediations, infusions, antibiotics, etc
  - Patient requiring volume/blood resuscitation with inadequate peripheral venous access
- Placement
  - A fully stocked procedure cart is highly recommended
  - ICU nurse should be at bed-side to assist (and observe) the operator
  - The operator should be fully gowned and gloved
  - Full body drape
  - Clean skin with chlorhexidine
  - Don't shave skin with razor, can use hair clipper
  - An antibiotic/antimicrobial coated catheter is recommended in units which have a high baseline incidence of catheter related blood stream infection (>3/1,000 catheter days)
  - Clean up your mess after you are completed; don't leave it up to the nurse. Dispose of all sharps
  - Document procedure in patients chart (with date and time)
- Site of placement
  - Site of choice should depend on patient's body habitus, existing and previous lines and your degree of comfort with each site
  - Ultrasound guidance is highly recommended for placement of internal jugular lines (IJ) and visualization of the inguinal anatomy in obese patients
  - The femoral site is suggested in highly coagulopathic patients, in emergency situations, in patients with severe bullous lung disease, etc.
  - The femoral site is compressible should the artery be accidentally stuck (as apposed to the IJ or subclavian).

  - It is also nearly impossible to cause a pneumothorax or hemothorax when placing a femoral line. Caution should be used when placing an IJ or subclavian line in patients with ALI/ARDS or severe COPD. A pneumothorax can be fatal
  - Despite a common misconception femoral lines are not associated with a greater risk of infection [1]. However the risk of infection may be higher at the femoral site in morbidly obese patients.
  - Femoral catheters have a significantly higher risk of thrombosis. "Aggressive" DVT prophylaxis is indicated in these patients.
  - Do not replace old lines over a guidewire. This is an outdated practice
  - A CXR is required after a IJ/subclavian to confirm correct placement and to exclude a pneumothorax.
- ? Arterial placement of venous catheter
  - Transduce the line
  - Check a blood gas
  - If you think the line is in an artery, don't remove. Call a vascular surgeon stat to evaluate the situation. The line may need to be removed surgically and a tear repaired.

The Do NOT'S
- DO NOT PLACE A FEMORAL LINE IN A KIDNEY TRANSPLANT PATIENT
- DO NOT PLACE A CENTRAL LINE ON THE SAME SIDE AS A DIALYSIS FISTULA (femoral or subclavian CVC)
- DO NOT remove a CVC (subclavian or IJ) in an upright patient (may cause air embolism)

Subclavian Vein Catheterization

- ADVANTAGES—consistent identifiable landmarks, easier long term catheter maintenance, relatively high patient comfort
- DISADVANTAGES
  - pneumothorax (1–2 %)
  - subclavian artery puncture (1 %)
  - difficult to perform under ultrasound guidance
- CONTRAINDICATIONS
  - Subclavian puncture is a relative contraindication in patients with a coagulopathy and/or pulmonary compromise (dependent on the expertise of the operator).
- ANATOMY—It is continuation of axillary vein, beginning the at outer border of first rib, extending 3–4 cm along the undersurface of clavicle and joining ipsilateral internal jugular vein behind the sternoclavicular joint

- POSITION (Most Important)—The patient is placed supine with arms at the side and head turned to opposite side. 15–30° Trendelenburg position, with a small bedroll placed between the shoulder blades.
- INFRACLAVICULAR APPROACH (Blind)
  - Identify the clavicle, the suprasternal notch, and the acromioclavicular junction
  - The operator's position is next to patient's ipsilateral shoulder. Feel along the inferior border of the clavicle moving from medial to lateral, until you feel a "give" in the tissue resistance. This point is approximately at the junction between the medial and middle thirds of the clavicle and at the point of the first "S bend" in the clavicle.
  - The skin and subcutaneous tissue should now be infiltrated with 1 % lidocaine. The thumb of the left hand is now placed "in" the suprasternal notch, to serve as a landmark.
  - A two 3/4 in., 14 gauge needle is mounted on a syringe and directed cephalad from the "point" until the tip abuts under the clavicle. With the needle hugging the inferior edge of clavicle the needle is now advanced toward the suprasternal notch (the thumb of your left hand). The needle is advanced until the subclavian vein is entered.

Internal Jugular Vein Catheterization

ADVANTAGES—MINIMAL RISK FOR PNEUMOTHORAX, PREFERRED IN PATIENTS WITH HYPERINFLATION AND THOSE RECEIVING MECHANICAL VENTILATION.

- DISADVANTAGES—Carotid artery puncture (2–10 %) with blind technique
- ANATOMY—It emerges from the base of the skull through jugular foramen and courses posterolateral to the internal carotid artery in the carotid sheath and runs beneath the sternocleidomastoid muscle
- POSITION is supine with 15° Trendelenburg and the head turned gently to the opposite side
- CENTRAL APPROACH (Blind)
  - The skin is punctured at the apex of the triangle formed by the two muscle bellies of sternocleidomastoid muscle and the clavicle, at a 30–45° angle with the frontal plane and directed at the nipple on the same side.
- ULTRASOUND APPROACH
  - The IJ vein is typically anterior and lateral to the artery
  - The IJ vein can be distinguished by the fact that the vein is compressible, non-pulsatile and distensible by the Trendelenberg position
  - Screening US to assess the degree of overlap of carotid artery by the IJ vein, the compressibility of the vein and the presence of internal echos that may signify clot

- Color Doppler can be used to visualize distinct arterial and venous pulsations (color dependent on direction of the probes in relations to flow and not the "color" of the blood)
- Once the appropriate site is selected, the site is sterilized and draped with full barrier precautions
- Using US to mark the skin and proceed without real-time guidance is not recommended
- The US probe is placed in a sterile sheath; this step requires an assistant. Sterile gel must be placed on the probe and the outside of the sheath
- As the procedure is performed in real time a "finder" needle is not required
- In the "one handed" method the operator control the ultrasound probe with the non-dominant hand and the needle with the dominant hand
- Passage of the introducer needle into the IJ vein can be performed either with a transverse (short axis) view or a longitudinal (long axis) view
- The primary advantage of the longitudinal view is that allows better visualization of the advancing needle tip
- Once the IJ vein is entered with the introducer the US probe is placed on the field and the typical Seldinger technique used to place the central venous catheter

Femoral Vein Catheterization

- ADVANTAGES—SAFE, easily accessible, don't need Trendelenburg. Safe to perform in patients with a coagulopathy.
- DISADVANTAGES—Limits flexion of leg at hip, ? increased risk of thrombosis.
- ANATOMY It is continuation of popliteal vein and becomes external iliac vein at inguinal ligament. It lies medial to femoral nerve and femoral artery in the femoral sheath at the inguinal ligament.
- TECHNIQUE
  - Clean the area well. The patient is placed supine with the leg extended and slightly abducted at hip
  - Palpate for the femoral arterial pulsation; the site of puncture is 1–1.5 cm medial to the femoral arterial pulsation below the inguinal ligament. In a patient with no palpable femoral pulse, it is 1–1.5 cm medial to the junction of medial third and lateral two-thirds of a line joining the anterior superior iliac spine and pubic tubercle
  - A 14 gauge needle is placed at the site of puncture and advanced at a 45–60° angle to the frontal plane with the tip pointed cephalad.
  - After obtaining return of venous blood, the syringe and needle are depressed to skin level and free aspiration of blood reconfirmed.

Complications of Central Venous Access

- Catheter related blood stream infection
- Local infection
- Local bleeding
- Venous air embolism
  - Entry of air into the central venous system through the catheter can be fatal
  - It is best prevented by positioning patient in 15° Trendelenburg position during catheter insertion
  - It will manifest as tachypnea, wheezing, hypotension and "mill wheel" murmur over precordium
  - The patient should be immediately turned onto his/her left side, in the Trendelenburg position and air aspirated after advancing the catheter into the right ventricle.
- Venous thrombosis
- Pneumothorax and/or hemothorax
  - occurs due to injury to pleura and underlying lung
  - small pneumothorax can be observed, but medium to large pneumothoraces will require chest tube insertion
  - As a general rule, all intubated patients with a pneumothorax require a chest tube
- Arterial puncture
  - if occurs, apply sufficient pressure for at least 10 min
  - arterial puncture may be confirmed by pulsatile flow and high hydrostatic pressure.
- Catheter tip migration and perforation of free wall of cardiac chamber
  Vascular erosions
  - Uncommon
  - typically occur 1–7 days after catheter insertion
  - causes sudden dyspnea with new pleural effusion or hydromediastinum on chest radiograph
  - more common with left sided catheter placement
- Occlusion of catheter—common. Best treated by replacement of catheter.
- Retained catheter fragment—catheter tips may get sheared off by traction on beveled tip of inserting needle, or by fracture of catheter due to improper fixation and excessive movement
- Inadvertent venous catheter placement—into internal jugular vein or opposite subclavian vein from subclavian vein approach is not uncommon.

Arterial Catheters

- In most patients blood pressure can be monitored using the traditional time honored technique used by Florence Nighingale, RN; namely, using an adequately sized blood pressure cuff and a mercury or automated manometer

- Indication for arterial lines include:
  - Ongoing shock and hemodynamic instability
  - Very frequent requirement for arterial blood gas analysis
  - Patients' requiring frequent titration of vasoactive agents
- Preferred site
  - My preference is the femoral artery unless the patient has severe peripheral arterial disease. The femoral artery was placed superficially in the groin to make the intensivists life easier! The femoral artery provides the measurement of the central arterial pressure
  - The radial artery is okay… however check for the patency of the ulnar artery and monitor perfusion of the thumb

Naso/Oro Gastric Tubes

- As a general rule an orogastric tube is preferred over a nasogastric tube to limit the risk of sinusitis
- In patients who require endotracheal intubation it is preferable to place the ET tube before the NG/OG tube
- Patients with previous trans-sphenoidal surgery, maxilla-facial and/or facial fractures placement should always be performed under direct vision (not blind) by an operator experienced in this technique (e.g. ENT surgeon)
- All intubated patients should have an OG tube placed after intubation
  - Decompresses the stomach (air and gastric contents)
  - Allows early enteral feeding
  - Allows PO medication
- Placement
  - Tell the patient what you are doing (if awake)
  - Ask them to swallow as the tube "goes in"
  - Lubricate the end of the tube with "surgi-lube"
  - Flex the neck
  - Gently push the tube past the naso/oropharynx and into the esophagus.
  - NEVER FORCE the tube
  - If the patient coughs, remove and attempt again
  - If you are having difficulty it may help to soften the tube with warm water
  - In those difficult cases, placement may be achieved under direct vision either using a standard or fiber-optic laryngoscope. An experienced intensivist, surgeon or ENT is required for this maneuver.
- Confirming placement in the "stomach"
  - Inject air and auscultate over the epigastrium (Whoosh test)
  - Aspirate; stomach contents or bile confirms placement
  - An abdominal (or half-half) X ray is required in all patients to confirm placement

Feeding Tubes

- Small bore feeding tubes may be indicated in patients who do not tolerate gastric feeds as well as non-intubated patients who require enteral nutrition
- Small bore feeding tubes are "designed" to go into the lung; This is a BAD thing.
- Feeding tubes should NOT be placed by those inexperienced in the technique
- Devices are currently available that allow accurate placement using electromagnetic guidance technology (GPS for the feeding tube). This method is highly recommended [2].
- In patients with lesions of the upper airway and those with previous transsphenoidal surgery placement should be performed under direct vision using a portable fiber-optic laryngoscope (by ENT surgeon, general surgeon or intensivist)
- When placed by under direct vision and when using the GPS device a confirmatory X-ray may not be required unless uncertain about position of tube

Thoracentesis and Paracentesis

- The old dictum that "*any body cavity can be needled with a strong arm and a 14 gauge needle*" can no longer be supported
- Ultrasound guidance is recommend for ALL thoracentesis and paracentesis regardless of the perceived size of the fluid collection; the lung and bowel have a funny habit of being where they should not be. The literature has clearly demonstrated that the complication rate (including DEATH) is significantly less when these procedures are done using ultrasound [3–6].
  - The procedure is best performed at the bedside using a portable ultrasound device
  - Use the cardiac or curvilinear probe and NOT the vascular probe.
  - For thoracentesis you need to locate the diaphragm, liver or spleen and effusion in both longitudinal and short axis view. The depth of the effusion must be at least 1.5 cm in order to attempt a thoracentesis.
  - Ultrasound not only confirms the presence of ascites, but also is used to locate the best site to perform a successful paracentesis, especially when dealing with smaller volumes of fluid
  - Alternatively this procedure can be performed by the radiologist, however the radiologist should not mark the spot with an "X" for needling at a later time (the fluid moves)

Clinical Pearls

- If you don't know how to do a procedure, don't do it.
- Most ICU patients require a central line and a oro/nasogastric tube
- Only those with "experience" should place a thin bore feeding tube
- When doing a procedure make sure you have all the necessary equipment
- AND clean up once you are done

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Chapter 7
Admission-Discharge Criteria

ICU Admission Criteria [1]

The advanced life support technology which can be provided in the ICU is intended to provide temporary physiologic support for patients with potentially reversible organ failure or dysfunction. In general, only patients who have a reasonable prospect of recovery should be treated in the ICU. The current guidelines of the Society of Critical Care Medicine state that "*in general ICU's should be reserved for those patients with reversible medical conditions who have a reasonable prospect of substantial recovery*." [1] The merits of each potential ICU admission should be assessed on an individual basis, and taking the following factors into account:

- the patients wishes or advance directives regarding life-support treatment
- the patients underlying disease(s) and physiologic function
- the severity and reversibility of the patients acute condition
- the patients baseline function and level of independence

When the reversibility and prognosis of a patient's condition is uncertain, a "*time-limited therapeutic trial*" in the ICU may be justified. A DNR order does not preclude a patient from being admitted to the ICU; this is a specific instruction not to perform advanced cardiac life support (ACLS) once the patient's heart has stopped (i.e. once the patient has died). Patients with advanced chronic disease, patients with terminal illnesses, and patients who have suffered a catastrophic insult should only be admitted to the ICU if there is a reasonable chance that the patient may benefit from aggressive management in the ICU *and* the patient or surrogate is prepared to accept the burden (i.e. pain, suffering) that such therapy may incur. It should be appreciated that death is the only certainty of life, and that the ICU is not a halfway station between life on earth and the hereafter; this implies that not all dying patients need to (or will benefit from) admission to an ICU.

Once a patient is admitted to the ICU the appropriateness of continuing care in the ICU should be evaluated in an ongoing fashion; the fact that aggressive life supportive therapy has been provided to a patient does not imply that it cannot be

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withdrawn. Patients should only remain in the ICU as long as they continue to derive benefit from the physiological support provided in the ICU. When all the ICU beds are filled the ICU/Critical Care Director or his designee will have the responsibility to admit/discharge patients from these units. Triage decisions should be made explicitly, fairly and justly. Ethnic origin, race, sex, social status, sexual preference or financial status should not be considered in triage decisions. Triage decisions may be made without patient, surrogate or attending physician consent.

In evaluating the appropriateness of an admission to the ICU, the priority of the admission should be determined as well as the disease specific or physiologic indications for admission (as outlined below).

Prioritization of Potential ICU Admissions

This system defines those patients that will benefit most (Priority 1) to those that will not benefit at all (priority 4) from admission to an ICU.

Priority 1

These are critically ill, unstable patients in need of *intensive treatments and monitoring* that cannot usually be provided outside of the ICU. Examples of such treatments include ventilator support, continuous titration of vasoactive drug infusion, etc. These patients have no limits placed on the extent of therapy they are to receive. Illustrative case types include post-operative or acute respiratory failure patients requiring mechanical ventilatory support, and patients with hemodynamic instability/failure requiring advanced hemodynamic monitoring and titration of vasoactive drugs.

Priority 2

These are patients that require the *intensive monitoring* services of an ICU and are at risk to require immediate intensive treatment. No limits are placed on the extent of therapy these patients are to receive. Examples of these patients include patients with underlying heart, lung, renal or central nervous system disease who have an acute severe medical illness or have undergone major surgery.

Priority 3

These are critically ill, unstable patients whose previous state of health, underlying disease, or acute illness reduces the likelihood of recovery and therefore benefit from ICU treatment. These patients may receive intensive treatment to relieve acute illness but therapeutic efforts may stop short of measures such as intubation or

cardiopulmonary resuscitation. Examples include patients with metastatic malignancy complicated by infection, pericardial tamponade or airway obstruction, or patients with end-stage heart or lung disease complicated by a severe acute illness.

Priority 4

These are patients who are generally not appropriate for ICU admission. Admission of these patients should be on an individual basis, under unusual circumstances and at the discretion of the ICU attending/ICU director. These patients can be placed in the following categories:

- Little or no additional benefit from ICU care (compared to non-ICU care) based on low risk of active intervention that could not safely be administered in a non-ICU setting (i.e. too well to benefit from ICU care). These include patients with peripheral vascular surgery, hemodynamically stable diabetic ketoacidosis, conscious drug overdose, mild congestive heart failure, etc.
- Patients with terminal, irreversible illness who face imminent death (i.e. too sick to benefit from ICU care). This includes patients with severe irreversible brain damage, irreversible multiorgan system failure, metastatic cancer unresponsive to chemotherapy and/or radiation therapy (unless the patient is on a specific treatment protocol), brain dead non-organ donors, patients in a persistent vegetative state, patients who are permanently unconscious, etc.

This group includes patients with decision-making capacity who decline intensive care and/or invasive monitoring and who elect too receive comfort care only. This group excludes brain-dead patients who are organ donors or potential organ donors (these patients require intensive monitoring and/or treatment in an ICU).

Transfer from Another Hospital: Variable Priority

The priority of transfers from other hospitals should be based on the current ICU census as well as the nature of the patient's acute condition and the risks of inter-hospital transfer. Consent for transfer must be obtained from the patient or his/her surrogate by the transferring attending physician prior to transfer.

Disease Specific Indications for ICU Admission

Cardiovascular System

- Acute myocardial infarction (AMI) complicated by ongoing pain, arrhythmias, CHF, or hemodynamic instability.
- Patients suffering an AMI who are candidates for, or have received reperfusion therapy

- Unstable angina
- Cardiogenic shock
- Acute congestive heart failure with respiratory failure
- Hypertensive emergencies; i.e. accelerated hypertension with encephalopathy, chest pain, pulmonary edema, aortic dissection or eclampsia.

Pulmonary System

- Acute respiratory failure requiring emergent ventilatory support, including non-invasive positive pressure ventilation
- Severe asthma, with FEV1 or Peak flow <40 % predicted, pulsus paradoxus >18 mmHg, pneumothorax or pneumomediastinum, $PaCO_2 > 40$ mmHg, or an "exhausted" patient.
- Hemodynamically unstable patients with pulmonary emboli and/or patients who are candidates for thrombolytic therapy

Neurological Disorders

- Patients suffering a CVA who are candidates for or have received thrombolytic therapy (i.e. within a 3 (4.5 h??) hour window following the onset of the CVA) and patients with cerebellar or brain-stem CVA's.
- Patients with a large MCA ischemic stroke at risk of midline shift and herniation.
- Central nervous system or neuromuscular disorders with deteriorating neurologic or ventilatory function
- Patients with subarachnoid hemorrhage (Hunt & Hess Grades I–IV)
- Status epilepticus
- Patients with an intracerebral bleed with ventricular extension that require placement of a ventriculostomy. Patients with both small and massive intracerebral bleeds are unlikely to benefit from admission to an ICU.

Drug Ingestion and Drug Overdose

- Hemodynamically unstable drug ingestion
- Drug ingestion with significantly altered mental status with inadequate airway protection
- Seizures following drug ingestion
- Drug ingestion requiring mechanical ventilation
- Drug ingestion requiring acute hemodialysis/hemoperfusion

Gastrointestinal Disorders

- Gastrointestinal bleeding from any source with:
  - Hemodynamic instability:
    - systolic arterial pressure <100 mmHg
    - pulse rate >120/min
    - postural hypotension after 1,000 mL of fluid resuscitation (but excluding postural hypotension on presentation alone)
    - hypotension requiring pressors
  - Ongoing bleeding (bright red blood on NG aspirate; red or maroon blood per rectum)
  - Rebleeding
  - Erratic mental status
  - "Unstable" comorbid disease
  - Coagulopathy (INR > 1.6 and/or PTT > 40 s)
- Fulminant hepatic failure
- Chronic liver failure with
  - Grade III/IV encephalopathy
  - Oliguria
  - sepsis
- Acute hemorrhagic pancreatitis (three or more Ranson criteria)

Endocrine

- Diabetic ketoacidosis with severe acidosis, hemodynamic instability or altered mental status
- Hyperosmolar state with coma and/or hemodynamic instability
- Thyroid storm or myxedema coma
- Severe hyponatremia, hypernatremia or hypercalcemia with altered mental status
- Hyperkalemia, severe and acute
- Adrenal crisis

Renal Disorders

- Patients who require acute emergent dialysis
  - severe hypertension
  - pulmonary edema
  - hyperkalemia

Postoperative Care

- Post operative patients requiring hemodynamic monitoring, ventilatory support, treatment of hemodynamic instability or airway monitoring
- Neurosurgical patients requiring hemodynamic monitoring or aggressive, titrated treatment of intracranial hypertension and vasospasm etc.

Miscellaneous

- Septic shock or sepsis syndrome requiring hemodynamic monitoring or hemodynamic or respiratory support.

Physiologic Indication for ICU Admission

- Apical pulse <40 or >140 beats/min (>130 beats/min if age >60 years)
- Mean arterial pressure (MAP) < 60 mmHg after adequate fluid resuscitation (2,000 mL) or the need for vasoactive agents to maintain a MAP > 60 mmHg
- Diastolic blood pressure >110 mmHg **AND** one of the following:
  - pulmonary edema
  - encephalopathy
  - myocardial ischemia
  - dissecting aortic aneurysm
  - eclampsia or preeclampsia (diastolic >100 mmHg)
  - Subarachnoid hemorrhage (diastolic >100 mmHg).
- Respiratory rate >35/min (sustained) and respiratory distress
- $PaO_2 < 55$ mmHg with $FiO_2 \geq 0.4$ (acute)
- Serum potassium >6.5 mEq/L (acute)
- pHa < 7.2 or >7.6 (diabetic ketoacidosis pHa < 7.0)
- Serum glucose >800 mg/dL
- Serum calcium >15 mg/dL
- Temperature (core) <32 °C

Discharge Criteria

In order to maximize the efficient use of ICU resources, the discharge process should be ongoing and continuous. Once admitted, it may be possible to determine that a patients is too well to benefit or too sick to benefit from continued intensive care. Patients should be discharged from the ICU when it can be determined that the

patient is no longer benefitting from being in the ICU. The discharge process should be a collaborative one between the intensivist, the primary care physician or surgeon and the nursing staff to assure that the needs of the patients can be met by the receiving unit. General criteria for ICU discharge have been met when the need for intensive care is no longer present because:

- The indication for initial or continued treatment has reverted spontaneously or with therapy
- Therapy provided has not reversed the reason for admission and little benefit will be attained from continued intensive therapy.
- The need for intensive monitoring is no longer present
- The patient has responded to treatment but the long-term prognosis is such that continuing further care is unacceptable to the patient or his surrogate

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Chapter 8
Chronic Critical Illness and the Long Term Sequela of Critical Care

Although advances in intensive care have enabled more patients to survive an acute illness they have also created a large and growing population of patients with prolonged dependence on mechanical ventilation and other intensive care therapies. The term "chronically critically ill" was coined for this group of patients by Girard and Rafin in a 1985 article that asked in its title "to save or let die?" [1] They focused on patients who survived an initial episode of critical illness but remained dependent on intensive care, neither dying in the acute period of intensive care unit treatment nor recovering. Chronic critical illness (CCI) usually defined as an icu patient who requires more than 21 days of assisted ventilation. The placement of a tracheostomy for long term ventilation is used by many to identify CCI patients [2]. Although prolonged dependence on mechanical ventilation is a hallmark of CCI, CCI is not simply an extended period of acute critical illness but a discreet syndrome including profound weakness attributed to myopathy, neuropathy, alteration in body composition, anasarca, neuroendocrine changes, brain dysfunction manifesting as coma or delirium, increased vulnerability to infections and skin breakdown leading to decubital ulceration [3–6].

Depending on the setting, CCI patients account for between 5 and 10 % of adult ICU admissions. It is estimated that there are currently approximately 100,000 CCI in the United States [2, 6]. This increasing number of CCI patients led to an 8.8 % increase in the number of long term acute care (LTAC) hospital beds between 1997 and 2006 [2]. Mechanically ventilated patients with a history of prior pulmonary disease and who require renal replacement therapy are at the greatest risk of CCI [3, 7–9]. These patients are usually elderly with a slight male predominance. Patients suffering postoperative complications make up a large percentage of CCI patients. These are usually patients with underlying cardio—pulmonary disease who have undergone cardiac or abdominal surgery. Trauma and burn patients as well as those with acute lung injury (ARDS) and patients with chronic respiratory failure (usually COPD) make up the majority of the remaining patients. CCI occurs in the setting of

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multiple episodes of sepsis with SIRS, multiorgan dysfunction syndrome (MODS) and respiratory failure. The prognosis of patients with CCI is generally poor, surprisingly the hospital survival is about 50 % with a 1 year survival of approximately 25 %. Nearly all patients with chronic critical illness leave the hospital with profound impairments of physical function, cognitive status or both, and most therefore require institutional care. Hospital readmission during the year after hospital discharge exceeds 40 % [6]. Only about 10 % of CCI patients are alive at home and functionally independent at 1 year [2].

In addition to the CCI patients who remain ventilator dependent and are managed in long term acute care facilities (LTAC) is an even larger group of patients who recover from their acute illness but suffer from long term disabilities, most notably neuromuscular dysfunction. These patients are distinguished from CCI in that they are not ventilator dependent. The chronic sequela of critical illness represent an extension of many of the characteristic morbidities of CCI. The number of patients with persistent cognitive dysfunction after CCI may be as high as 65 % [6]. In survivors of ARDS, Herridge and colleagues demonstrated muscle weakness and functional impairment up to 5 years after hospital discharge [10]. In this study only 48 % of survivors had returned to work at 1 year, with only 78 % of these returning to their previous employment.

The pathophysiology of CCI is complex and incompletely understood. The need for chronic respiratory support is due to the complex interplay between critical illness polyneuropathy, critical ill myopathy, recurrent chest infections, delerium and immobility. Chronic elevations in cortisol, catecholamines and cytokines, resulting from recurrent infection and inflammation, act in concert to depress hypothalamic-pituitary growth hormone, gonadal and thyroid axes, as well as modulate renal, bone and energy metabolism. These derangements lead to clinical manifestations, such as altered body composition (increased fat and decreased lean mass), hyperglycemia, osteoporosis and immune dysfunction [4, 5]. In patients with CCI the pulsatile secretion of GH is suppressed with very low mean nocturnal concentration of GH. These findings are suggestive of relative GH deficiency, which is postulated to play a role in the wasting syndrome of CCI. These changes appear to be more severe in men. The acute phase of critical illness is characterized by low levels of T3 with normal levels of TSH and T4. This contrasts with the pattern in CCI, in which the TSH is low (or low-normal), with low T4 and T3 levels. The pulsatility in the TSH secretory pattern is dramatically diminished and like the GH axis, the loss of TSH pulse amplitude, is related to low levels of thyroid hormone.

Metabolic bone disease is prevalent in the CCI patient population. Prolonged immobilization and cytokine-mediated events increase the risk of bone hyperresorption. Vitamin D deficiency is extremely common resulting from lack of exposure to sun, malnutrition, malabsorption and impaired renal or hepatic function [11]. Nierman and Mechanick demonstrated that 92 % of CCI patients had bone hyperresorption due to either vitamin D deficiency and/or immobilization [12]. These authors have used the combination of pamidronate and calcitriol [1, 25 (OH)2 vitamin D] to control bone hyper-resorption [13].

Neuromuscular Abnormalities

Neuromuscular problems are an extremely common in CCI patients. These include critical illness polyneuropathy, delirium, metabolic encephalopathy (with coma) and myopathy. The problems further delay weaning from mechanical ventilation and increase the morbidity and mortality of this syndrome. In addition, the persistence of neuromuscular dysfunction is largely responsible for the long term disabilities following acute critical illness.

Critical Illness Polyneuropathy

Critical illness polyneuropathy (CIP) first described by Bolton in 1983, is defined as a predominantly motor, axonal dysfunction of peripheral nerves in the setting of SIRS, MODS and respiratory insufficiency [14–16]. Postmortem examination of peripheral nerve specimens from patients with CIP has shown primary degeneration of motor and sensory nerves that supply the limbs and respiratory system. Although this denervation is more widespread and severe in the distal muscle groups, the phrenic nerve, diaphragm, and intercostals muscles are also involved.

Classically CIP is associated with a symmetric predominantly distal paresis, with legs involved worse than arms, along with impaired sensory testing in the feet and hyporeflexia. CIP is difficult to diagnose clinically and is often suspected when critically ill patients are otherwise improving yet continue to have difficulty in weaning from mechanical ventilation. In most patients the initial neurologic symptom of CIP is failure to wean. The definitive diagnosis of CIP is made by EMG and nerve conduction studies. EMG is characterized by:

- Widespread fibrillations and positive sharp waves
- Reduced amplitude of compound muscles and sensory nerve action potentials
- Relatively normal conduction studies

There are no proven treatments that will speed the recovery of peripheral nerve function in patients who have developed CIP. CIP is associated with prolonged weaning difficulties, a long convalescence and a high mortality. Both the time to liberation from mechanical ventilation and the mortality are directly related to the severity of the polyneuropathy.

Critical Illness Myopathy (See also Chap. 32 on Nutrition)

Multiple studies have shown an accelerated loss of muscle mass in patients admitted to the ICU and this play a major role in terms of post-ICU functional disability. This disorder is known as Critical illness myopathy (CIM). CIM is characterized by

a diffuse non-necrotizing myopathy accompanied by fiber atrophy, fatty degeneration of muscle fibers and fibrosis. Loss of muscle mass results from an imbalance between muscle proteolysis and protein synthesis, with proteolysis overwhelming an inadequate synthetic response. Proteolysis is achieved by several cellular signaling networks, but the predominant proteolytic pathway activated in animal models of muscle atrophy is the ubiquitin–proteasome system. In the critically ill patient multiple factors are likely to play a role in inducing muscle atrophy including muscle inactivity, inflammation, cellular energy stress and inadequate provision of amino acids (low quality and continuous rather than bolus feeding). Clinically, patients with CIM may demonstrate weakness, failure to wean or paresis. Creatinine phosphokinase (CPK) levels are relatively normal, consistent with a myopathy and not a myositis. CIM remains difficult to distinguish clinically from CIP because they share similar clinical characteristics and may occur in the same patient. Although the presence of normal sensory nerve action potentials with small compound muscle action potentials on electrodiagnostic studies may suggest a component of CIM, muscle biopsy remains the gold standard for diagnosis. However, because there is no effective treatment for CIM, the indications for invasive biopsies are unclear.

Puthucheary and colleagues demonstrated a 17 % reduction in the rectus femoris cross sectional area in critically ill patients after 10 days of mechanical ventilation [17]. Casaer and colleagues demonstrated a 6.9 % loss of femoral muscle volume over 7 days of mechanical ventilation [18]. The loss of muscle mass in these studies occurred despite provision of adequate dietary protein. Indeed, the provision of high concentrations of amino acids parenterally or as continuous enteral feeding may inhibit protein synthesis [17]. CIM may persist for years after discharge from the ICU.

The diaphragm is the principle muscle of respiration. Respiration is essentially an endurance effort, and the structure of the normal human diaphragm reflects its major contribution to sustaining ventilation. In addition to loss of skeletal muscle mass, loss of diaphragmatic mass occurs in mechanically ventilated patients. Grosu and colleagues demonstrated the loss of diaphragm thickness at a rate of 6 % per day of mechanical ventilation [19]. Levine and colleagues obtained biopsy specimens from the diaphragms of 14 brain-dead organ donors who had undergone mechanical ventilation for between 18 and 69 h before organ harvest and compared them with intraoperative biopsy specimens from the diaphragms of control patients [20]. As compared with diaphragm-biopsy specimens from controls, specimens from case subjects showed decreased cross-sectional areas of slow-twitch and fast-twitch fibers of 57 % and 53 %, and a marked upregulation of the mRNA transcripts of those proteins involved in the ubiquitin–proteasome muscle breakdown system. Difficulties in discontinuing ventilatory support are encountered in 20–25 % of mechanically ventilated patients, with a staggering 40 % of time spent in the ICU being devoted to weaning [21]. Because the respiratory muscles play a pivotal role in determining the weaning outcome, diaphragmatic dysfunction plays a major role in patients who fail weaning from mechanical ventilation. Patients with diaphragmatic dysfunction demonstrated frequent early and delayed weaning failures. CIM

has profound implications in the elderly. Body composition changes dramatically with aging. There is an increase in body fat and a decrease in lean muscle mass by up to 40 % at age 80 years [22]. Furthermore, the acute loss of muscle mass (CIM) is most severe in the elderly [17]. This suggests that critically ill elderly patients who have been ventilated for over 7–10 days may develop severe diaphragmatic atrophy to the point that they are unable to breathe without mechanical assistance. This progresses into a vicious cycle in which ongoing mechanical ventilation results in further diaphragmatic atrophy which further compromises attempts at weaning. These patient remain ventilator dependent frequently develop multiple complications including pneumonia, delirium, bed-sores and ultimately succumb to multi-organ system failure.

Brain Dysfunction

Cognitive dysfunction is reported to occur in up to 65 % of CCI patients [23]. Unlike the delirium of acutely ill patients which usually lasts about 48 h, the delirium occurring in CCI patients may persist for a prolonged period of time. Followup studies reveal that most of the hospital survivors including those living at home remain profoundly cognitively impaired [23]. Pandharipande and colleagues evaluated the long-term cognitive impairment of 821 patients who were admitted to an ICU with respiratory failure or shock [24]. Delirium developed in 74 % of patients during their hospital stay. At 3 months, 40 % of the patients had global cognition scores that were 1.5 SD below the population means (similar to scores for patients with moderate traumatic brain injury). Deficits occurred in both older and younger patients and persisted, with 34 % and 24 % of all patients with assessments at 12 months that were similar to scores for patients with moderate traumatic brain injury and scores for patients with mild Alzheimer's disease, respectively. A longer duration of delirium was independently associated with worse global cognition and worse executive function at 12 months.

"Prevention" of CCI

CCI is essentially an iatrogenic disease resulting from the aggressive management of acute critical illness. This may not be a preventable state but reflects advances in acute resuscitation and support of critical illness. However there are important strategies that may decrease the incidence of CCI and reduce the burden of CCI for patients who are affected. Most importantly, only "functional" patients who have a reasonable chance of surviving their ICU stay and returning to their previous level of functioning should be admitted to the ICU. For bed-ridden frail patients and those with advanced end-stage organ failures admission to the ICU is unlikely to be curative and is likely create a population of CCI patients who are destined to die;

with advanced life support serving only to prolong death. These patients should not be admitted to the ICU.

All attempts should be made reduce the length of time patients remain on mechanical ventilation, as this is a major factor leading to neuromuscular and cognitive dysfunction. Evidence-based management strategies including lung protective ventilation [25], conservative fluid management [26] and spontaneous breathing trials [27] not only improve survival but result in fewer ventilator days for survivors. Limiting the use of sedatives and avoiding benzodiazepines reduces duration of ventilation and likely reduces the risk of delirium and post ICU cognitive dysfunction [28]. Strategies to prevent ventilator associated pneumonia are likely to reduce the length of mechanical ventilation. Strategies to limit loss of lean body mass (muscle) may expedite liberation from ventilation and limit long term functional disabilities. Early mobility programs, coupled with less sedation and high quality protein may limit the loss of muscle mass [29]. Why protein which is high in leucine and other branch chain amino acids is more effective in stimulating protein synthesis than soy or casein protein [30, 31]. Furthermore, bolus as opposed to continuous tube feeds may be more effective in promoting muscle synthesis [32] (see Chap. 32). Parenteral nutrition does not support muscle synthesis and should be avoided [18]. Interventions such as preservation of the Day-Night cycle, improvement in the quality and duration of sleep, control of noise pollution, music therapy and orientation therapy may limit acute delirium and long term cognitive dysfunction. Medications such as benzodiazepines, H2-antagoists, anticholinergics, tricyclic antidepressants, fluoroquinolone antibiotics, clozapine, thioridazine and clonidine, etc have been linked with delirium particularly in elderly patients and should be avoided [33]. Opiates (especially meperidine) are associated with delirium and the lowest doses should be used to treat pain; avoid if no pain. Dexmedetomidine appears to be a useful sedative agent that may limit delirium [34, 35].

Management of CCI

The management of CCI patients is essentially supportive with meticulous attention being paid to prevent infections, to minimize further muscle breakdown and to promote recovery with successful weaning. The management plan should include:

Testing

- T4, T3 and TSH to exclude hypothyroidism
- PTH and vitamin D to evaluate for metabolic bone disease
- ACTH stimulation test if not on steroids
- EMG—to diagnose CIP (important for prognosis)
- EEG if comatose or poorly responsive (important for prognosis)

General Management

- All ventilator dependent patient should have a tracheotomy performed
- A small bore feeding tube should be placed in stomach; consider a PEG tube
- Air mattress or kinetic bed to prevent bed sores
- VAP precaution measure
- Immuno-enhancing enteral nutrition; high arginine, omega-3 and leucine. Six hour bolus feeding is highly recommended. AVOID TPN
- AVOID blood transfusion. Blood t/f increases the risk of further organ dysfunction and death [36]
- Although EPO (erythropoietin) has not been shown to improve the outcome of general ICU patients [37], high dose EPO (40,000 u once or twice weekly) should be considered to minimize the requirement for blood transfusion. Check ferritin levels and supplement with iron as required.
- PICC line for venous access
- Monitor volume status; prevent volume overload
- Daily physiotherapy; mobilize out of bed if possible and early exercise program
- DVT prophylaxis
- Replete magnesium and phosphorus as required
- Limit use of corticosteroids
- Avoid benzodiazepines
- Use opiates sparingly for pain
- Consider daily olanzapine if delirium and/or haloperidol PRN [38, 39]
- Consider night-time dosing with melatonin [40]
- Maintain day/night sleep cycle with natural light during day
- Consider music therapy

Stress Hyperglycemia

- Use intermediate acting insulin (lente or NPH) every 12 h or long acting insulin for basal inulin dosing
- If bolus feeding use basal-bolus technique
- If continuous feeding use insulin sliding scale 4–6 h
- Aim for blood glucose of between 140 and 180 mg/dl
- Avoid oral hypoglycemic agents

Metabolic Bone Disease

- Pamidronate 30 mg × 3 days
- Calcitriol 0.25 μg day 4

Anabolic Steroids

Oxandrolone is an oral anabolic steroid with enhanced anabolic activity and minimal androgenic activity when compared with testosterone. In burn patients as well as chronically malnourished renal dialysis patients, as well as malnourished patients with COPD and HIV anabolic steroids in combination with enhanced calorie and protein diet has been shown to improve body mass and muscle strength. On the basis of these observations the role of oxandrolone in critically ill patients has been examined in two RCT [41, 42]. Both of these studies failed to demonstrate a benefit, with the study in CCI patients demonstrating an increase in the duration of mechanical ventilation as well as ICU length of stay. Based on the results of these studies anabolic steroids cannot be recommended in CCI patients.

Exercise Program

A number of studies have demonstrated that early mobilization and physical activity is feasible and safe in respiratory failure patients requiring mechanical ventilation [43, 44]. Burtin and colleagues initiated an individually tailored exercise training protocol during the early ICU stay of patients requiring mechanical ventilation [45]. The results of this study suggested that exercise training may enhance recovery of exercise capacity, self-perceived functional status and muscle strength. Similarly, Schweickert and colleagues performed a RCT in which patients who remained ventilator dependant for more than 3 days were randomized to early physical and occupational therapy which was coupled with daily awakenings [46]. Patients in the intervention group had shorter duration of delirium and more ventilator-free days with significantly more patients returning to an independent functional status.

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Chapter 9
Fluid Responsiveness and Fluid Resuscitation

The illiterate of the 21st Century will not be those who cannot read and write, but those who cannot learn, unlearn and relearn

Alvin Toffler, Writer and futurist (1928–)

THIS IS THE MOST IMPORTANT CHAPTER OF THIS BOOK. IT IS COMPULSORY READING.

Current "wisdom" suggests that aggressive fluid resuscitation is the best initial approach to the patient with hemodynamic instability. The source of this wisdom is difficult to discern, however, "Early Goal Directed therapy" (EGDT) as championed by River's et al. [1] appears to have established this as the irrefutable truth. However, over the last decade it has become clear that aggressive fluid resuscitation is associated with increased morbidity and mortality across a diverse group of patients, including patients with severe sepsis (see Chap. 12), ARDS [2], as well as surgical and trauma patients and those with pancreatitis.

Alert
Excess fluid leads to iatrogenic salt water drowning.

Multiple RCT's and cohort studies have demonstrated that a conservative fluid strategy in patients undergoing elective non-cardiac surgery is associated with significantly fewer complications with a lower mortality (in the high risk patients) than patients managed with the traditional liberal fluid strategy in which fluids are administered to fill the non-existent "third space" [3–5]. For patients with traumatic injuries, high volume fluid resuscitation as promoted by the early Advanced Trauma Life Support (ATLS) strategy [6], has given way to a "damage control" resuscitation strategy [7]. This approach has seen a fall in the volume of crystalloid delivered in the emergency department and an associated fall in mortality. In a prospective analysis of 3,137 trauma patients' treated in the Emergency Department, fluid volumes of 1.5 l or more were significantly associated with mortality [8]. This observation is supported by a meta-analysis which demonstrated in both RCT's and cohort studies

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that a conservative fluid strategy was associated with a lower mortality in trauma patients [9]. Similarly, an aggressive fluid strategy in the resuscitation of patients with acute pancreatitis has been associated with an increased risk of complications [10]. The results of multiple studies across diverse patient populations have clearly demonstrated that aggressive fluid "loading" is associated with an increased risk of complications and death. The only published study conducted in humans that has demonstrated that early aggressive fluid resuscitation "improves" outcome is the EGDT study by Rivers et al. [1]. However the results of this study are implausible and likely not true. These observations have resulted in a major paradigm shift in the techniques used to assess volume status and the approach to fluid resuscitation; fluid resuscitation serves as the prime example of the "less is more" paradigm. While hypovolemia will result in decreased cardiac output (and blood pressure) with inadequate organ perfusion leading to organ dysfunction, overzealous fluid resuscitation and hypervolemia induces a cascade of events that similarly results in organ dysfunction. From an evolutionary point of view we have evolved to deal with hypovolemia and not hypervolemia. The argument is no longer "wet or dry" but "***just the right amount of fluid***". This is not an easy determination and requires an evaluation of the patient's hemodynamics, organ perfusion, cardiac function and an assessment of "fluid responsiveness" in addition to understanding the patients' clinical condition. It is no longer acceptable to pour in liters of fluid and "see what happens". In addition to understanding that we need to precisely titrate fluid volumes we have also gained much better insight into which fluid to give. It is also import to note that at 3 h only 15 % of a crystalloid bolus remains intravascular in normal health volunteers, while in experimental sepsis models almost 100 % of the fluid bolus filters into the interstitium [11–13]. This can't be a good thing. It would therefore appear that clinicians are required to unlearn the traditional methods of fluid resuscitation and embrace the new approach.

The first step in the hemodynamic management of critically ill patients is to determine the adequacy of tissue/organ perfusion. While the signs of shock may be obvious, those of sub-clinical hypoperfusion may be more subtle. The signs of hypoperfusion include:

- Mean arterial pressure (MAP) <65 mmHg
- Tachycardia with narrow pulse pressure
- Decreased urine output
- Altered mentation

- Poor capillary refill
- Skin perfusion/mottling
- Cold extremities (and cold knees)

It should be noted that hypotension and tachycardia reflect significant volume depletion. A blood loss of about 1 l is required before a patient develops a tachycardia and about 1.5 l before the blood pressure begins to drop. In those patients with hypotension or evidence inadequate tissue perfusion, fluid resuscitation is generally regarded as the first step in resuscitation. Clinical studies have, however, demonstrated that only about 50 % of hemodynamically unstable critically ill patients (In ER, ICU or OR) are volume responsive [14].

Alert
Fluid responsiveness is generally defined as a significant increase (>10–15 %) in stroke volume in response to a fluid challenge (usually 500 cm^3). Fluid responsiveness occurs only in patients with biventricular preload responsiveness.

Fundamentally, the only reason to give a patient a fluid challenge is to increase stroke volume (volume responsiveness). If the fluid challenge *does not* increase stroke volume, volume loading serves the patient no useful benefit (and is likely harmful). According to the Frank-Starling principle as the preload increases left ventricular (LV) stroke volume increases until the optimal preload is achieved at which point the stroke volume remains relatively constant (Fig. 9.1). This optimal preload is related to the maximal overlap of the actin-myosin myofibrils. It is important to note that in an intact heart the actin-myosin links cannot be disengaged and hence there is *no descending limb* of the Frank-Starling curve. Once the left ventricle is functioning near the "flat" part of the Frank-Starling curve fluid loading has little effect on the stroke volume. In normal physiologic conditions, both ventricles operate on the ascending portion of the Frank-Starling curve [15]. This mechanism provides a functional reserve to the heart in situations of acute stress. In normal individuals, an increase in preload (with volume challenge) results in a significant increase in stroke volume [16].

An analysis of the overlapping Frank-Starling and extra-vascular lung water (EVLW) curves demonstrate that as patients' become less fluid responsive EVLW (and tissue edema) increase markedly (see Fig. 9.1) due to increased cardiac filling pressures and transmitted hydrostatic pressures [17]. This process is accentuated in patients with endothelial damage (sepsis, ARDS, pancreatitis, burns) [18]. It should be noted that as "one" climbs up the Frank-Starling Curve "one" get diminishing returns; a smaller increase in SV with greater propensity to develop tissue edema. Increased cardiac filling pressures trigger the release of natriuretic peptides, presumably to assist in fluid removal. What is most disturbing about this sequence of events is that natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins

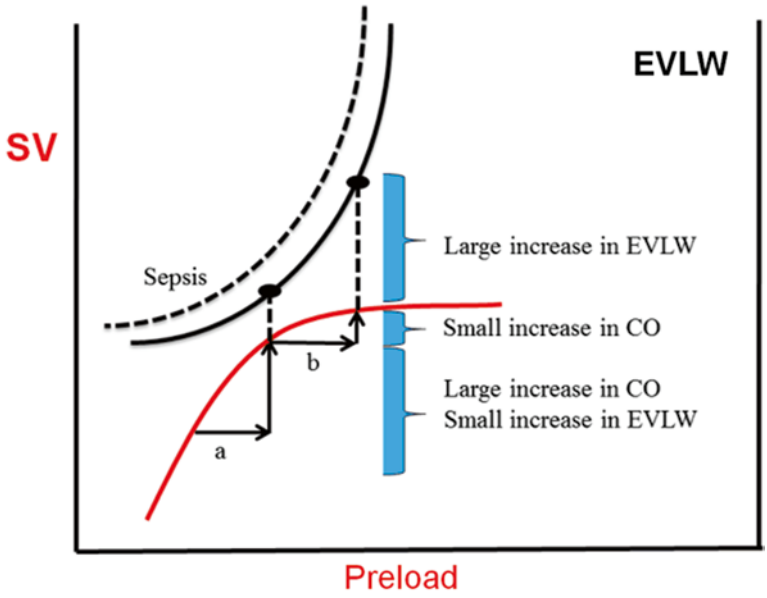

Fig. 9.1 Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume and lung water in a patient who is pre-load responsive (**a**) and non-responsive (**b**). With sepsis the EVLW curve is shifted to the left. *EVLW* extravascular lung water, *CO* cardiac output, *SV* stroke volume

(most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx (see below) [19, 20]. The endothelial glycocalyx plays a major role in regulating endothelial permeability [21]. Therefore, excessive volume expansion increases the release of natriuretic peptides which in turn damages the endothelial glycocalyx and this is followed by a rapid shift of intravascular fluid into the interstitial space leading to a marked increase in EVLW and tissue edema [19, 20]. To make matters even worse, natriuretic peptides inhibit the lymphatic propulsive mechanism and the return of lymph into the vascular system further aggravating tissue edema [22, 23].

The Endothelial Glycocalyx

The vascular endothelium is coated on the luminal side by the endothelial glycocalyx [25–27]. The glycocalyx is a web of membrane-bound glycoproteins and proteoglycans associated with various glycosaminoglycans which contribute to the volume of the layer (see Fig. 9.2). These membrane-bound proteoglycans and glycoproteins, together with bound plasma constituents, build up to the physiologically active endothelial surface layer with a functional thickness of over 1 mm. The glycocalyx has a major role in the vascular barrier function and in preventing large macromolecules moving across the endothelium, preventing leucocyte adhesion and platelet aggregation, mitigating

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inflammation and limiting tissue edema (see Fig. 9.3a, b). A non-circulating part of plasma volume of about 700–1,000 ml in humans is fixed within the endothelial glycocalyx but in dynamic equilibrium with the circulating plasma. A certain plasma concentration of albumin seems to be a required to maintain the functional integrity of the endothelial surface layer. The glycocalyx is semi-permeable with respect to anionic macromolecules such as albumin and other plasma proteins, whose size and structure appear to determine their ability to penetrate the layer. Red blood cells are excluded from the glycocalyx. **The glycocalyx is compromised in systemic inflammatory** states such as diabetes, hyperglycemia, surgery, trauma, and sepsis. Inflammatory mediators which have been implicated so far include C-reactive protein, A3 adenosine receptor stimulation, tumour necrosis factor, bradykinin, and mast cell tryptase. In addition, hypervolemia, through the release of natriuretic peptides damages the glycocalyx.

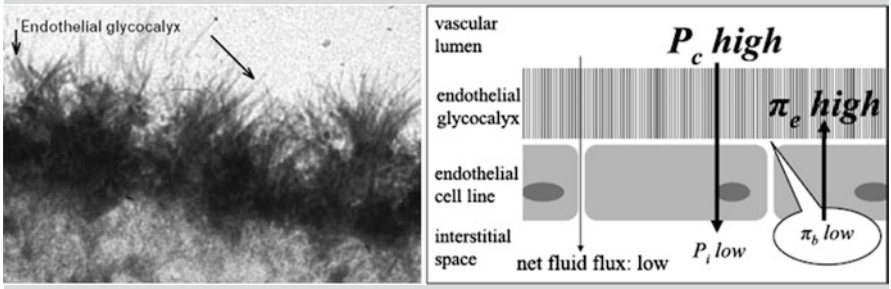

Fig. 9.2 Endothelial glycocalyx [5, 24]. Reproduced with permission from Elsevier, Best Practice & Research Clinical. Anaesthesiology 2009; 23:145-157

In clear contrast to the traditional assumption, transcapillary fluid loss actually seems to be limited by an oncotic pressure gradient across the endothelial glycocalyx, a structure that was unknown to Ernest Starling (see Fig. 9.2) [5]. Therefore, his classical principle needs to be updated, taking into consideration the current knowledge indicating a strong dependency of vascular integrity on the integrity of the endothelial glycocalyx. An intact endothelial glycocalyx is obviously a prerequisite of a functioning vascular barrier. Furthermore, fluid moves in a unidirectional manner, from the vasculature (leaking from the capillaries or post-capillary venules) into the interstitium and then retuning into the vascular system via the lymphatics. The Starling concept that fluids moves into the interstitium at the arterial side of the vasculature and is then absorbed by oncotic forces on the venous end, does not occur. Interstitial fluid does not move directly back into the vasculature. Therefore, the concept of giving a colloid to "suck" fluid back into the vasculature is a MYTH. However, unlike crystalloids and hetastarch, albumin increases the ESL (glycocalyx) thereby limiting but not preventing the transcapillary fluid flux.

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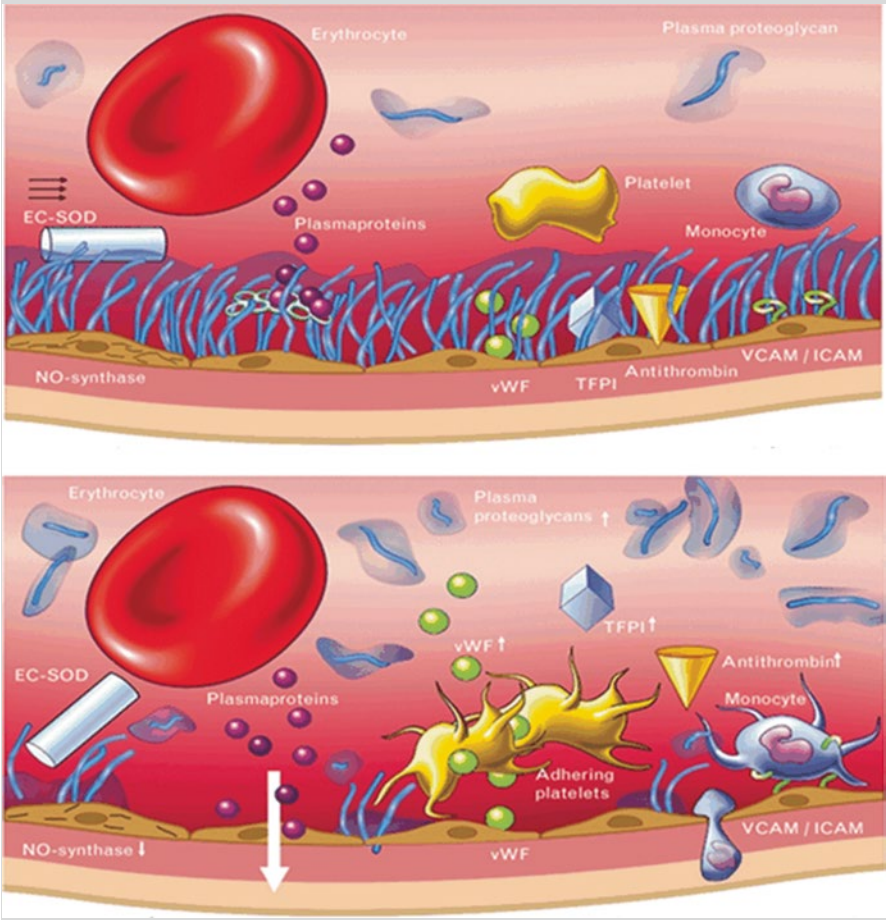

Fig. 9.3 (**a**) Normal glycocalyx [24]. (**b**) Damaged glycocalyx with loss of barrier function, Reproduced with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health, Current Opinion in Lipidology 2005;16:507-511

Only patients who are likely to show a significant increase in SV with a fluid challenge and in whom the increased SV *is considered to be beneficial* should be given a fluid challenge. Furthermore, all attempts should be made to limit the volume of fluid administered. This begets the question of how to predict fluid responsiveness? After Hughes and Magovern described the technique of central venous pressure (CVP) monitoring in 1959 this method became a standard tool for guiding fluid therapy [28]. It has now been clearly established that there is a poor relationship between the CVP and intravascular volume status and no relationship between the CVP and fluid responsiveness [29]. In 1970 the flow-directed pulmonary artery

catheter (PAC) was developed by Swan and Ganz allowing measurement of the pulmonary artery occlusion pressure (PAOP). However, the PAOP suffers from the same limitation as the CVP and multiple studies have demonstrated that, like the CVP, the PAOP is unable to predict fluid responsiveness [30, 31].

Alert
The central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) SHOULD NEVER be used to make decisions regarding fluid management.

The CVP and PAOP are a measure of right and left atrial pressure respectively. These pressure measurements have NO relationship with a patient's intravascular volume status nor are they indicators of fluid responsiveness.

The PAC may be useful when performing tribal rituals.

While there is a poor relationship between blood volume and CVP and while there is no relationship between fluid responsiveness and the CVP (or change in CVP following a fluid bolus) in any individual patient the CVP tends to increase with fluid loading. In some patients however, the CVP may fall with fluid loading due to decreased sympathetic tone and decreased venoconstriction. The change in the CVP following a fluid challenge is frequently used to guide further fluid management. This strategy was described several decades ago by Weil and Henning who proposed the 2–5 CVP Rule [32]. According to this scheme, the CVP is measured at 10 min intervals. If the change in CVP was <2 mmHg, the infusion was continued, if it was in the 2–5 mmHg the infusion was interrupted and reevaluated after a 10 min wait. If the change was >5 mmHg the infusion was stopped [32, 33]. However the 2–5 CVP rule is unable to predict fluid responsiveness in patients with both a low CVP (<12 mmHg) or a high (>12 mmHg) CVP. EGDT and the Surviving Sepsis Campaign recommend targeting a CVP >8 mmHg (8–12 mmHg on mechanical ventilation [1, 34]. This is likely a very bad idea. It is important to recall that a normal CVP is close to ZERO. Furthermore, a rapid fluid bolus is likely to distend the cardiac chambers with the release of BNP; also a very bad thing. Apart from resulting in gross fluid overload a high CVP in itself is a very bad thing.

WHY a High CVP is a Very VERY Bad Thing (see Chap. 12)

- A high CVP decreases venous return and cardiac output
  - $CO = VR = (Pms - CVP)/Rvr$ [35]
- A high CVP decreases organ perfusion pressure (PP)
  - $PP \sim MAP - (CVP + 10)$ mmHg
- Decreased microcirculatory flow [36]
- A high CVP results in high BNP levels; which increases tissue edema
  - Damages the endothelial glycocalyx [19]
  - Decreases lymphatic drainage [22, 37]

Following the "widespread" recognition that the CVP/PAOP had no utility in guiding fluid resuscitation [30], the idea that heart-lung interactions during mechanical ventilation could be used to predict fluid responsiveness gained some popularity [38, 39]. The principles underlying this technique are based on simple physiology (see Fig. 9.4) [17, 40]. Intermittent positive-pressure ventilation induces cyclic changes in the loading conditions of the left and right ventricles. Mechanical insufflation decreases preload and increases afterload of the right ventricle (RV). The reduction in RV preload and increase in RV afterload both lead to a decrease in RV stroke volume, which is at a minimum at the end of the inspiratory period. The inspiratory reduction in RV ejection leads to a decrease in left ventricular (LV) filling after a phase lag of two or three heart beats. The cyclic changes in RV and LV stroke volume are greater when the ventricles operate on the steep rather than the flat portion of the Frank-Starling curve [17, 40]. A pulse pressure variation (PPV) or stoke volume variation (SVV) of greater than 13 % were shown to be predictive of fluid responsiveness (see Fig. 9.5) [38, 39]. In a meta-analysis published in 2009 it was demonstrated that the PPV was highly predictive of fluid responsiveness (ROC

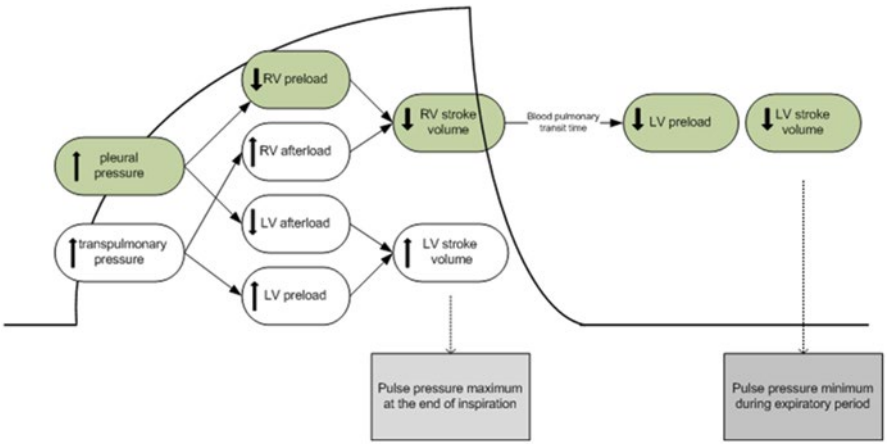

Fig. 9.4 Heart lung interaction during mechanical ventilation [41]. Reproduced with permission from Biomed Central. Crit Care 200; 4:282

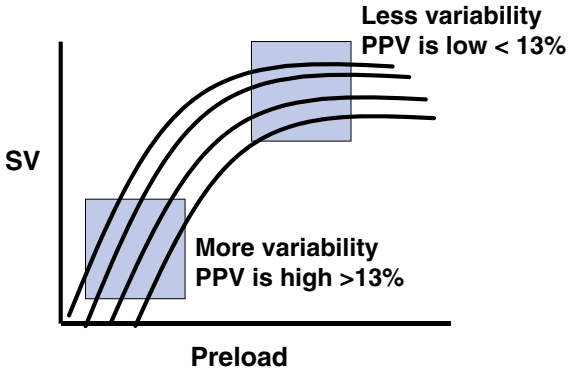

Fig. 9.5 PPV and position on Frank-Starling Curve

of 0.94) [14]. Due to its sound physiological basis, good predictive ability and apparent simplicity this technique was met with great enthusiasm and algorithms based on this principle were developed for use in the OR and ICU [42, 43]. However, what was not fully appreciated when the meta-analysis was published was that almost all the studies were performed in a highly controlled environment (usually the OR) in a highly select group of patients [14]. It soon became apparent that a large number of clinical factors interacted to limit the accuracy of the PPV/SVV in predicting fluid responsiveness [44, 45].

Conditions which need to be met (ALL) to ensure accuracy of PPV/SVV:

- Sinus Rhythm
- Volume cycled ventilation with Vt of at least 8 ml/kg IBW
- No ventilator-patient dyssynchrony
- Heart rate/respiratory rate ratio >3.6
- Normal chest wall compliance (Δ intra-pleural pressure)
- No evidence of cor pulmonale- pulmonary hypertension
- Normal intra-abdominal pressure
- Normal pulmonary compliance

In a cohort of cardiac surgical patients Lansdorp and colleagues demonstrated that PPV/SVV did not predict volume responsiveness in routine clinical practice [46]. Multiple studies have now confirmed these findings [47, 48]. In the largest study to date, Canneson and colleagues demonstrated that despite a strong predictive value, the PPV was inconclusive in predicting fluid responsiveness in 25 % of patients during general anesthesia [49]. The utility of the PPV/SVV in the ICU appears significantly worse [47, 48]. In a multicenter, point prevalence study Mahjoub and colleagues demonstrate that only 2 % of ICU patients met the validity criteria for using the PPV to assess fluid responsiveness [50]. Furthermore, only 3 % of patients with an arterial line in place satisfied all the validly criteria. These data suggest that due to the frequency of confounding factors the PPV/SVV should not be used as the primary technique for directing fluid management in the OR and ICU.

Nevertheless intravascular volume depletion should be suspected in patients who demonstrate marked PPV evident on either an arterial pressure waveform or pulse oximetric waveform. However, in these situations other tests should be performed to confirm fluid responsiveness (see below).

Echocardiographic Assessment of Fluid Responsiveness

Bed-side echocardiography allows for the rapid determination of LV and RV function, as well the detection of cardiac tamponade and major valvular disease. This evaluation plays a major role in the initial and ongoing assessment of patients with hemodynamic instability [51–54]. While echocardiography can usually support a diagnosis of severe volume depletion, it is less useful in assessing fluid responsiveness.

Static Echocardiographic Parameters

The CVP and PAOP (left atrial pressure) can be approximated by echocardiography. In spontaneously breathing patients there is a fairly good correlation between the size of the IVC and the CVP. However, as the CVP is unrelated to volume status or fluid responsiveness this becomes a meaningless exercise. Feissel et al. demonstrated that the absolute IVC size failed to predict fluid responsiveness in patients with septic shock [55]. A completely collapsed IVC is suggestive of hypovolemia, however, this assessment is usually obvious by clinical examination alone.

The RV and LV diastolic diameter or area have been used as a measure of preload. However, Tavernier et al. and Feissel et al. have demonstrated that LV size (left ventricular end diastolic area-LVEDA) is not a useful predictor of fluid, unless LV is very small and hyperkinetic [39, 56]. A meta-analysis by Marik et al demonstrated the failure of the LVEDA to predict volume responsiveness in mechanically ventilated patients [14].

Dynamic Echocardiographic Parameters

The degree of respiratory variation in venal caval cross-sectional area during both spontaneous breathing and mechanical ventilation has been proposed to be predictor of fluid responsiveness. However the respiratory variation in vena caval diameter is just an indirect measurement of the CVP, which as we well know is unable to predict fluid responsiveness. The respiratory variation of the IVC during spontaneous breathing appears to have become quite popular in the Emergency Department setting.

This technique has been poorly validated and likely to lack sufficient accuracy to be clinically useful [57, 58].

Analysis of the respiratory changes of LV stroke volume during mechanical ventilation provides a dynamic, biventricular evaluation of preload dependence. The respiratory changes of stroke volume can be estimated by Doppler analysis of velocity-time integral (VTI) during TTE or TEE.

This technique has the same limitation as those for PPV/SVV. Furthermore, this technique is very operator dependent and can only be performed by clinicians with advanced training in echocardiography.

Ultimately only two techniques are currently available which can be used to determine fluid responsiveness with a high degree of accuracy, namely the passive leg raising maneuver (PLR) and the fluid challenge [17, 40, 59, 60]. These techniques are best coupled with minimally invasive cardiac output monitors (see Chap. 10) which can track changes in SV and cardiac output dynamically and in real time [17, 40]. Changes in carotid artery flow measured by Doppler is another method to assess the response to either a fluid challenge of PLR maneuver [48, 61]. For obvious technical reasons the fluid challenge technique is preferred during anesthesia while the PLR is preferred in the ICU and post-operatively. The various methods to assess fluid responsiveness, grouped by diagnostic accuracy are listed in Table 9.1.

Passive Leg Raising (PLR)

In the initial stages of resuscitation in the emergency department, ward or ICU most patients are not intubated and are breathing spontaneously. In addition, with the reduced use of sedative agents in the ICU many critically ill patients are ventilated

Table 9.1 Techniques for assessing fluid responsiveness

Static pressure and volume parameters (*ROC ~ 0.5–0.6*)
Central venous pressure (CVP) Pulmonary artery occlusion pressure (PAOP) Inferior vena cava (IVC)/superior vena caval (SVC) diameter Flow corrected time (FTc) Right ventricular end-diastolic volume (RVEDV) Left ventricular end-diastolic volume (LVEDV) SVC/IVC variation during mechanical ventilation
Dynamic techniques based on heart-lung interactions (*ROC ~ 0.7–0.8*)
Pulse pressure variation (PPV) Stroke volume variation (SVV) Pleth variability index (PVI) Aortic blood flow (Doppler or echocardiography)
Techniques based on real or virtual fluid challenge (*ROC ~ 0.9*)
Passive leg raising (PLR) Rapid fluid challenge (200–300 cm^3)

ROC area under receiver operator characteristic curve

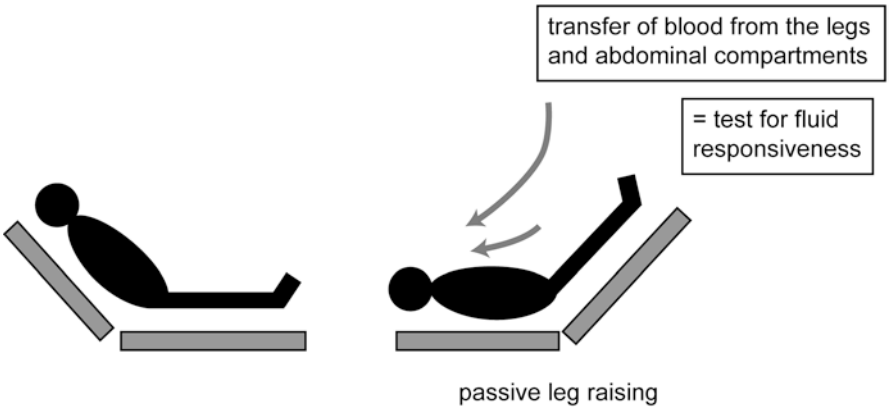

Fig. 9.6 Passive leg raising (PLR) maneuver

with modes of ventilation that allow spontaneous breathing activity. These factors limit the use of heart-lung interactions to determine fluid responsiveness.

Lifting the legs passively from the horizontal position induces a gravitational transfer of blood from the lower limbs toward the intrathoracic compartment (see Fig. 9.6) [62, 63]. Beyond its ease of use, this method has the advantage of reversing its effects once the legs are tilted down [64, 65]. Therefore, PLR may be considered a reversible "auto-transfusion". The ability of PLR to serve as a test of preload responsiveness has been confirmed in multiple studies performed in critically ill patients [59, 65–72]. The change in aortic blood flow (measured by esophageal Doppler) during a 45° leg elevation was shown to predict the changes in aortic blood flow produced by a 500 ml fluid challenge even in patients with cardiac arrhythmias and/or spontaneous ventilator triggering, situations where PPV lost its predictive ability [65]. A meta-analysis, which pooled the results of eight studies, confirmed the excellent value of PLR to predict fluid responsiveness in critically ill patients with a global area under the ROC curve of 0.95 [59]. The best way to perform a PLR maneuver to predict volume responsiveness is to elevate the lower limbs to 45° (automatic bed elevation or wedge pillow) while at the same time placing the patient in the supine from a 45° semi-recumbent position (see Fig. 9.6). Starting the PLR maneuver from a total horizontal position may induce an insufficient venous blood shift to significantly elevate cardiac preload [73]. By contrast, starting PLR from a semi-recumbent position induces a larger increase in cardiac preload as it induces the shift of venous blood not only from both the legs but also from the abdominal compartment [74]. In should be noted that intra-abdominal hypertension (an intra-abdominal pressure of >16 mmHg) impairs venous return and reduces the ability of PLR to detect fluid responsiveness [75].

Since the maximal hemodynamic effects of PLR occur within the first minute of leg elevation [65], it is important to assess these effects with a method able to track

Table 9.2 72 year old emaciated male patient with chronic lymphatic leukemia

Time	CI	SVI	Challenge/PLR	Post CI	Post SVI	ΔSVI %
9:20	2.5	20	PLR	2.6	23	9.8
10:10	2.9	24	Challenge	3.9	33	35.4

changes in cardiac output or stroke volume on a real-time basis. In this regard, the response of ascending (measured by suprasternal Doppler) [76, 77] or descending (measured by esophageal Doppler) aortic blood flow [65, 66] or velocity-time integral (measured by transthoracic echocardiography) [67, 68] following a PLR has been demonstrated to be helpful in predicting the response to volume administration. Echocardiographic/Doppler techniques require significant expertise are operator dependent and not conducive to continuous real-time monitoring. Until recently, continuous real-time cardiac output monitoring required a thermodilution pulmonary artery catheter. During the past decade, several less invasive methods have been developed. These techniques include transpulmonary thermodilution, pulse-contour analysis and bioreactance which are ideally suited to track the change in SV following a PLR maneuver (see Chap. 10). In patients in whom the SV decreases with the PLR maneuver cor-pulmonale with displacement of the interventricular septum should be suspected. An ECHO should be performed in this circumstance (see Chap. 10).

In approximately 5 % of patients the PLR will give a false negative result. This may occur due to incorrect performance of the technique. In addition, it is likely that thin/emaciated patients have a reduced venous reservoir in their legs due to loss of muscle mass, resulting in an inadequate "bolus" effect with leg raising. In patients with a borderline PLR response or in those patients who are clinically suspected to have intravascular volume depletion despite a negative PLR, a fluid challenge should be performed (see Table 9.2).

The Fluid Challenge

The gold standard to determine fluid responsiveness is the change in SV following a fluid challenge. The disadvantage of this technique is that a bolus of fluid is given to a patient who may not benefit. However, the non-responder should receive no more fluid; and the small volume given should "hopefully" do little harm. While hetastarch was previously used for fluid challenges this can no longer be recommended (5 % albumin is okay). As crystalloids redistribute very quickly the fluid bolus should be given as quickly as possible. A bolus of between 200 and 300 cm^3 is given, the volume determined in part by the rate of infusion. Muller et al reported that a "mini-fluid" challenge with 100 ml colloid over 1 min was highly predictive of fluid responsiveness [60].

Alert
A change in blood pressure following a PLR or fluid challenge is a poor guide to fluid responsiveness. SV may increase without a significant change in blood pressure [78].

The Patient is fluid responsive. So What Next!

- Nothing
  - Do not need to increase CO
  - Increased lung water
- Fluid bolus of 250–500 cm^3 LR (see below)
- Give vasoconstrictor
  - increase venous return secondary to α-agonist mediated venoconstriction (sepsis and anesthesia)

NOT all patients who are fluid responsive require a fluid bolus. Normal healthy people are fluid responsive (have preload reserve). In patients who are fluid responsive and are hypotensive or have signs of poor organ perfusion a fluid bolus (500 cm^3) should be strongly considered. However, this decision should be based on the patient's clinical status, overall fluid balance and oxygenation. Repeat fluid boluses in fluid responsive patients should be based on the same ongoing assessment. Low dose norepinephrine should be considered in hypotensive patients who are fluid-non responders (or poor responders), those with acute lung injury and those with severe sepsis (see Chap. 12). Fluid boluses should not be given to patients who are non-responders. The CXR is a poor indicator of pulmonary edema (lung water) and the measurement of extra-vascular lung water (EVLW) by transpulmonary thermodilution is recommended in those patients in whom the management of fluids and pressors is particularly troublesome (see Chap. 10)… and when all else fails consult Dr. Harry Potter.

Targets of resuscitation (see Chap. 12 Sepsis)

- MAP >65 mmHg (consider >75 mmHg in those with preexistent hypertension)
- CI >2.5 l/m^2
- Heart rate <110/min (sinus rhythm)
- Adequacy of organ perfusion
- Lactate or lactate clearance should not be used as an end-point of resuscitation (see Chap. 13)

Fluid Boluses in Volume Responsive Patients

The first description of the use of intravenous fluid in a human is attributed to Dr. Thomas Latta during the Cholera epidemic in London in 1831–1832. Dr. Latta described his experience in a letter to the editor of the Lancet [79].

Dr. Latta first attempted to replace the lost fluid and salts '*by injecting copiously into the larger intestine warm water, holding in solution the requisite salts, and also administered quantities from time to time by mouth…*' [80, 81]. He found there to be no permanent benefit and indeed he considered that the unfortunate sufferers' vomiting and purging were aggravated. Latta wrote '*finding thus, that such, in common with all the ordinary means in use, was either useless or hurtful, I at length resolved to throw the fluid immediately into the circulation*.' The injected solution was made up of '*two to three drachms of muriate of soda and two scruples of the subcarbonate of soda in six pints of water*' (equivalent to approximately ½ Ringers lactate). He described how '*having no precedent to guide me I proceeded with much caution*.' *His first patient was an elderly woman who had been given 'all the usual remedies' and who had 'apparently reached the last moments of her earthly existence, and now nothing could injure her.*' Latta inserted a tube into the basilic vein and ***injected ounce (30 ml) after ounce of fluid closely observing the patient***—at first with no visible effect—but then she began to breathe less laboriously and '*soon the sharpened features, and sunken eye, and fallen jaw, pale and cold, bearing the manifest imprint of death's signet, began to glow with returning animation; the pulse returned to the wrist…*' after six pints (2.8 l) of fluid had been injected, the woman announced in a strong voice that she was now '*free from all uneasiness*'; her extremities were warm, and Latta, thinking that his patient was now safe, left her in the charge of the hospital surgeon who described this experience (the patient ultimately died in the hands of the surgeon!!).

> ***having no precedence to guide me I injected ounce after ounce of fluid closely observing the patient—***Thomas Latta, Physician, (1798–1833)

The technique of fluid resuscitation described by Dr. Latta nearly 200 years ago has stood the test of time; and is the ONLY way to resuscitate patients…. Give a small volume of fluid (LR) and observe the patient (what a remarkable concept). This is best done by giving 250–500 ml boluses of LR and closely monitoring the response. Furthermore, unlike the fluid challenge which must be given rapidly (to

assess fluid responsiveness) fluid boluses are best given over about 30 min (to prevent excessive short lived cardiac chamber enlargement). The idea of giving large fluid boluses of 20–30 ml/kg is absurd and likely to lead to severe volume overload.

What Type of Fluid?

Now that we have some idea regarding how much fluid to give the next question is "Which fluid should we give? Previously this was a contentious issue and a difficult question to answer. In recent years this issue has been resolved and in almost all situations the fluid of choice is Lactated Ringers (LR) solution. Due to the toxicity of hetastarch solutions the age old "colloid vs crystalloid debate" is a non-issue. 0.9 % NaCl is better known as "***AbNormal Saline***" is associated with numerous complications and is only indicated in specific situations.

Lactated Ringer's (Hartmann's Solution) vs. 0.9 % NaCl (Ab-Normal Saline)

Despite differences in composition between normal saline (0.9 % NaCl) and Lactated Ringer's (LR) solution, they are frequently considered equivalent (see Table 9.3). For reasons that are unclear, NS appears to be the preferred resuscitation fluid of medical physicians while LR is the choice of surgeons. Whilst no body fluid has an electrolyte composition similar to that of normal saline, this fluid is frequently referred to as "physiologic salt solution" (PSS). 0.9 % NaCl is more correctly known as "Unphysiologic Salt Solution" (USS). Experimental and clinical data have clearly demonstrated that these fluids are NOT equivalent. Furthermore, only LR, Normosol, Isolyte and Plasmalyte solutions are balanced salt solutions. Due to the calcium content of LR (and not Plasmalyte), it has been traditionally taught that LR should not be infused in the same venous line as blood (may activate clotting). However, like much in medicine this is a MYTH [83].

Table 9.3 Electrolyte composition of normal saline and lactated ringers solution

	LR	0.9 % NaCl
Sodium (meq/l)	131	154
Chloride (meq/l)	111	154
Calcium (meq/l)	2	–
Potassium (meq/l)	5	–
Lactate (meq/l)	29	–
Measured osmolality [82] (mmol/kg H_2O)	257	285

Admission
I use the Henderson-Hesselbach approach to acid-base disorders. I have been told that this is "stupid" and old fashioned. To be honest I don't see the point of the "strong ion approach". I like to make things simple so that I can understand what's going on rather to make things so complex that no-one understands.

See Chap. 22 (Arterial blood gas analysis)

Complications Associated with 0.9 % NaCl vs. Lactate Ringers Solution

Renal Failure

The increased chloride load delivered to the macula densa results in afferent arterial constriction [84]. In health volunteers NS significantly reduces renal arterial flow and renal cortisol tissue perfusion as compared to Plasmalyte [11]. In a sequential cohort study Yunos and colleagues demonstrated that a chloride liberal fluid (NS) was associated with a much higher incidence of renal failure than critically patients resuscitated with a chloride restrictive fluid (LR and Plasmalyte) [85].

Hyperchloremic Metabolic Acidosis and DEATH

Numerous studies have demonstrated the development of a hyperchloremic metabolic acidosis in human volunteers and patients resuscitated with normal saline [86–89]. The additional loss (renal) of HCO_3 in the setting of reduced buffering capacity only adds to the acid-base burden characteristic of hypoperfused states [87]. Furthermore, resuscitation with normal saline may produce a "dilutional acidosis". In both experimental and clinical (pancreatitis) studies hyperchloremic acidosis has been demonstrated to increase the release of inflammatory mediators [90, 91]. In a prospective cohort study, Boniatti et al demonstrated that hyperchloremia was an independent predictor of death [92]. Similarly, in two large cohorts of patients undergoing non-cardiac surgery, hyperchloremia was an independently associated with increased morbidity and mortality [93, 94]. In these studies the risk of death increased with increasing chloride levels.

Lactate Generates HCO_3^-

It should be noted that the lactate (in LR) is converted to glucose (mainly in the liver); this reaction consumes hydrogen ions, thereby generating HCO_3 [95].

$$2CH_3CHOHCOO^- + 2H^+ \Rightarrow C_6H_{12}O_6$$
Lactate Glucose

Normally about 30 % of lactate is oxidized to CO_2 and water. However as discussed below in during stress lactate becomes the preferential fuel of the heart and other organs. This reaction consumes hydrogen ions, thereby generating HCO_3.

$$CH_3CHOHCOO^- + H^+ + 3O_2 \Rightarrow 3CO_2 \text{ and } 3H_2O$$

Many erroneously believe that LR may worsen or cause a "lactic acidosis"; this is impossible as lactate (the base) has already donated H^+ ions; LR generates HCO_3 in the liver and kidney. Although, the lactate concentration (base) may increase with LR this increase is associated with an increase in HCO_3 and an increase in pH (even with liver disease). This observation was elegantly demonstrated by Phillips et al, whom in a swine hemorrhagic shock model compared the acid–base status of animals resuscitated with LR and NS (see Table 9.4 below) [96].

It therefore appears to be non-sensible (stupid) to resuscitate a hypoperfused patient with a preexistent metabolic acidosis (due the hydrolysis of ATP) with a fluid that causes an acidosis rather than a fluid which reverses an acidosis. At this point it is worthy of noting that "lactic acidosis" is a misnomer (does not exist); the conversion of pyruvate to lactate consumes a hydrogen ion rather than generating a hydrogen ion (see Chap. 13).

Ringer's Lactate and Kidney Disease

"Medical tales" suggest that LR should never be given to patients' with renal disease as this may cause a severe hyperkalemia which may lead to death. As far as I can tell, such an event has never been reported. However what the perpetuators of this myth fail to recognize is that the administration of large volumes of NS is associated with a hyperchloremic metabolic acidosis, which will cause hyperkalemia through an extra cellular shift of potassium… i.e. ***NS causes hyperkalemia*** [11]. Hyperkalemia may cause vasoconstriction in the afferent arteriolar beds decreasing renal blood flow which compounds the vasoconstriction caused by hyperchloremia. Khajavi et al. compared the acid–base status in kidney transplant patients randomized to receive LR or NS [97]. In this study the mean changes of the serum

Table 9.4 Laboratory data at end of study (Phillips et al.)

	Normal saline	Ringers lactate
Lactate	1.3	6.0
HCO_3	16.7	27.8
pH	7.17	7.41

potassium was +0.5 ± 0.6 meq/l in the NS group and −0.5 ± 0.9 meq/l in the LR group ($p < 0.001$). The mean changes of pH were −0.06 ± 0.05 in the NS group and −0.005 ± 0.07 in the LR group ($p < 0.001$). Similarly, O'Malley et al. compared NS with LR in patients undergoing kidney transplant; this study had to be aborted at the first interim analysis due to the harm associated with NS [98]. In the study 19 % patients in the NS group versus zero (0 %) patients in the LR group had potassium concentrations >6 meq/l and were treated for hyperkalemia ($p = 0.05$) while 31 % of patients in the NS group versus zero (0 %) patients in the LR group were treated for metabolic acidosis ($p = 0.004$). Cho et al. compared the use of LR and NS in patients with rhabdomyolysis [99]. The urine and serum pH was found to be significantly higher in the LR group. There were no significant differences in serum potassium level and in the time taken for creatine kinase normalization. The amount of sodium bicarbonate administered and the frequency administration of diuretics was significantly higher in the NS group. Furthermore, as demonstrated above NS increases the risk of renal dysfunction and acute renal failure as compared to LR.

Ringers Lactate and Liver Disease

"Medical tales" also suggest that LR is contraindicated in patients with liver disease… as this will cause a severe lactic acidosis. This is not correct; lactate is given as the base and not the acid. Furthermore, in a murine model of acetaminophen toxicity LR has been demonstrated to improve liver recovery [100]. In a hemorrhagic shock model LR as compared to NS was associated with less hepatic, renal and pulmonary injury [101]. Furthermore, LR has been reported to be safe in patients undergoing hepatectomy [102].

Coagulopathy

Studies in surgical patients have demonstrated that as compared to LR volume replacement with NS results in greater blood loss with a greater need for blood transfusion [88]. The cause of the coagulopathy is unclear, and is only partly explained by the difference in Ca^{++} between the two solutions.

Lactate as a Metabolic Fuel

It is not an accidental quirk of nature, that the body produces lactate during stress states. The proportion of lactate uptake by the myocardium and its use a metabolic fuel increases during exercise, β-adrenergic stimulation, elevated afterload, and during shock [103–105]. During shock the heart undergoes a major shift in substrate

utilization such that it oxidizes lactate for the majority of its energy needs [105]. Revelly and coworkers demonstrated that an infusion of sodium lactate increased cardiac performance in patients with both cardiogenic and septic shock [106]. Similarly, during increased demand on brain metabolism, lactate is increasingly utilized as an energy substrate [107–109].

Albumin

Albumin is a plasma protein with an average molecular weight of 66 kDa. In healthy humans, albumin accounts for about 80 % of colloid osmotic pressure. Albumin is the major extracellular antioxidant in human plasma and also plays an important role as a transport protein. Albumin is available as 4–5 % solutions that are slightly hypotonic and iso-oncotic (see below) and as hyperoncotic 20–25 % solutions that are generally referred to as 'concentrated albumin'. Albumin for clinical use is usually suspended in sodium chloride and contains additives which stabilize albumin against heat and oxidative stress. When infused into well hydrated individuals, 4–5 % albumin will expand the plasma volume by an amount approximately equal to the volume infused; 20–25 % albumin will expand the plasma volume by approximately 4–5 times the volume infused. Since fluid does not move from the interstitium into the vascular compartment (revised Starling equation) the only way this can happen is for fluid to be withdrawn from the ESL (glycocalyx). Hyperoncotic fluid would therefore appear to dehydrate the gylcocalyx [25]. This suggests that concentrated albumin solutions should not be given as a bolus. In healthy condition, over 60 % of infused albumin is retained in the intravascular compartment in the 2 h after infusion, but in diseased states, particularly inflammatory states such as severe sepsis, retention of infused albumin may be significantly less.

Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS), randomized 6,997 ICU patients to receive 4 % albumin in 0.9 % NaCl or NaCl (SAFE study) [110]. Overall the SAFE study found no difference in outcomes, particularly mortality, in patients assigned to receive albumin or saline despite some evidence that resuscitation with albumin resulted in greater intravascular volume resuscitation; mortality rates at 28 days were 20.9 % and 21.1 %, respectively, and the relative risk of death was 0.99 (95 % CI 0.91–1.09; $p = 0.87$). Subgroup analyses suggested that albumin might be harmful in patients with traumatic brain injury (TBI) and possibly beneficial in patients with severe sepsis.

Considering the emerging evidence that albumin plays a major role in stabilizing the endothelial glycocalyx, albumin may play a role in those conditions associated with disruption of the glycocalyx (sepsis, surgery and trauma) [25, 111, 112]. In these situations albumin may be given as a 20–25 % solution to increase serum albumin concentration rather than as a volume expander. This concept is supported by the ALBIOS study. The multicenter randomized *Albumin Italian Outcome Sepsis Study* (ALBIOS) demonstrated that a 25 % albumin infusion reduced the mortality of patients with septic shock (and a serum albumin of less than 3 g/dl)

once hemodynamic stability had been achieved (ClinTrials.gov NCT00707122). In the ALBIOS study 300 ml of 20 % of albumin solution (total amount of 60 g) was infused over a 3 h period once daily in eligible patients. The use of albumin is patients with sepsis is supported by the Saline versus Albumin Fluid Evaluation (SAFE) study as well as a recent meta-analysis on this topic [110, 113, 114].

Experimental data has demonstrated a greater intra-vascular expanding effect when a 5 % albumin solution is given as an infusion over 3 h rather than as a bolus [12, 115]. This data suggests that when 4–5 % albumin is used as a volume expander or to enhance the glycocalyx it should be infused over 3 h. If 20–25 % albumin is used to stabilize the glycocalyx it may be preferable to give this as a continuous infusion at a rate of 10–15 ml/h as opposed to an infusion over 3 h. However, additional studies will be required to determine the optimal dosing strategy of albumin in this situation.

It would appear that there are limited situations where albumin maybe useful as a volume expander; the exception being in patients with cirrhosis. 4–5 % albumin should be considered the volume expander of choice in hypotensive/hypoperfused patients with cirrhosis [116, 117]. In addition, a 4–5 % albumin solution may be beneficial in patients with spontaneous bacterial peritonitis, hepato-renal syndrome and following a paracentesis. In these patients a bolus of 20–25 % albumin should be avoided. However a continuous infusion of a 20–25 % solution at a rate of 10–15 ml/h is strongly recommended following the initial bolus/short infusion of 4–5 % albumin (see Chap. 34: Liver Failure).

Hetastarches (HES)

HES solutions are produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize, or potatoes. A high degree of substitution on glucose molecules protects against hydrolysis by nonspecific amylases in the blood, thereby prolonging intravascular expansion, but this action increases the potential for HES to accumulate in reticuloendothelial tissues, such as skin, liver, and kidney [118]. Studies suggest that HES may be retained in the tissues for periods in excess of 4 years [119]. In addition to its toxicity due to tissue retention, unlike albumin, HES damages the glycocalyx.

Prior to termination for safety reasons, the VISEP study randomized 537 ICU patients to receive a 10 % pentastarch, a low-molecular-weight hydroxyethyl starch (HES 200/0.5) solution or LR for fluid resuscitation [120]. The HES solution was associated with a significantly high risk of death and renal failure at 90 days. There was a clear dose response effect, with patients receiving the highest volume of HES having the highest risk of renal failure and death. Those patients receiving the lowest volumes of HES had an increased risk of renal failure but not death.

In order to improve the "safety profile" of HES, third generation 6 % solutions were developed with a lower molecular weight (130 kD) and lower molar substitution ratios (0.38–0.45). In the Triple S study, Scandinavian investigators randomized 800 patients with severe sepsis to 6 % HES (130/0.42) or Ringer's acetate [121].

The HES solution was associated with a significant increase in the rate of death at 90 days (relative risk, 1.17; 95 % CI, 1.01–1.30; $p=0.03$) and a significant 35 % relative increase in the rate of renal-replacement therapy. The crystalloid versus Hydroxyethyl Starch Trial (CHEST) randomized 7,000 ICU patients to receive a 6 % HES (130/0.4) solution or saline [122]. Although the mortality did not differ between groups, the use of HES was associated with a significant 21 % relative increase in the rate of renal replacement therapy. The volumes of HES were much lower in the CHEST trial than either VISEP or the Triple S study, suggesting that low volumes of HES are nephrotoxic, while increased mortality is seen with the higher dosages. In light of current evidence demonstrating an increased risk of nephrotoxicity, an increased risk of death as well as increased cost, without any obvious clinical benefit, it would appear that HES solutions have NO role in the resuscitation of any critically ill patient.

So, Which Fluid?

The data presented above suggests that in almost all circumstances LR should be the fluid of choice for fluid resuscitation. There are however a few exceptions to this rule:

- Hyponatremic dehydration (0.9 % NaCl).
- Patients with acute cerebral insults at risk of cerebral edema (hypertonic solutions are preferable in these patients (0.9 % NaCl or hypertonic saline).
- 0.9 % NaCl is considered the initial fluid of choice in patients with diabetic ketoacidosis before switching to 0.45 % NaCl [123, 124]. Most patients are switched at some point to one-half isotonic saline to replace the free water loss induced by the glucose osmotic diuresis. LR does not appear to have a role in the treatment of DKA [125].
- A solution of 1 l D5W with 2–3 amps of sodium bicarbonate; severe metabolic acidosis due to ethelylene glycol or severe metabolic acidosis due to loss of HCO_3 (diarrhoea, renal tubular acidosis). This solution can also be considered in patients with renal failure and severe metabolic acidosis.

Resuscitation in Specific Disease States

Hemorrhage

In patients who have lost blood, fluid moves from the interstitial to the intravascular compartment in an attempt to restore blood volume; the hemoglobin concentration falls by hemodilution (in the absence of volume resuscitation it takes

about 72 h for Hct to stabilize). Therefore, both the intra-vascular and extra- vascular, extra-cellular compartments are decreased following blood loss. Experimental hemorrhage models have demonstrated a higher mortality when animals are resuscitated with blood alone, as compared to blood and crystalloids. Patients who have lost blood should therefore be resuscitated with crystalloid (LR), followed by blood. Trauma induced coagulopathy occurs within minutes of injury, and is associated with an increased mortality. The main strategy to treat trauma induced coagulopathy is to provide volume replacement that augments coagulation. Current consensus is that plasma should be given from the beginning of the resuscitation, alongside transfusions of packed red blood cells, in a ratio of 1 "unit" of plasma for each 1–2 units of packed red blood cells [126]. The role of platelet transfusion in this strategy is unknown [7].

In all other patients, platelets and FFP should only be transfused based on coagulation parameters and evidence of ongoing bleeding. However, transfusion of two unit of FFP should be considered after patients have received 6 units or more of blood. In both "medical" and surgical bleeding the goal should be to restore tissue perfusion and oxygenation at not to achieve a "normal" hemoglobin (a hemoglobin above 7 g/dl is the recommended goal) (See Chap. 38).

Traumatic Brain Injury

Hypotension is a powerful predictor of poor outcome following traumatic brain injury and rapid infusion of fluid to correct this hypotension is considered the standard of care [127]. Hypotonic fluids should be avoided to limit or prevent cerebral edema. This suggests that 0.9 % NaCl or hypertonic saline solutions be used in patients with TBI. In the SAFE study resuscitation with albumin was associated with a significant increase in the rate of death at 2 years among patients with TBI traumatic brain injury (relative risk, 1.63; 95 % CI, 1.17–2.26; $p = 0.003$) [128]. This outcome has been attributed to increased intracranial pressure, particularly during the first week after injury [129]. This may be explained by the fact that contrary to expectations the 4 % albumin solution used was hypo-osmolar, and may, therefore, have increased brain volume and intracranial pressure [82].

Dehydration

Patients who are dehydrated (from diarrhea, vomiting, diabetic osmotic diuresis, etc) have lost both intra-vascular and extra- vascular, extra-cellular fluid. Volume replacement with crystalloids (LR) will resuscitate both compartments. The choice of crystalloid (LR or NS) will depend on the patients' serum sodium concentration.

Sepsis (and SIRS)

As discussed in Chap. 12 LR is the resuscitation fluid of choice in patients with sepsis and SIRS.

Burns

Due to the thermal injury these patients have a massive loss of interstitial fluid as well as a generalized capillary leak. Patients should be resuscitated with crystalloid (LR) during the first 24 h.

Management of Oliguria

While primary renal diseases and urinary tract obstruction may lead to oliguria, intravascular volume depletion with renal hypoperfusion is the commonest cause of oliguria in clinical practice. The management of oliguria due to intravascular volume depletion is *fluid resuscitation*.... **Lasix is not a volume expander!** It should be noted that septic patients may remain oliguric despite adequate resuscitation and adequate renal blood flow. Additional fluids will not improve renal function in this situation.

Diuresis with loop diuretics in patients with normal or reduced effective intravascular volume is invariably associated with a fall in intravascular volume, a fall in plasma volume, a fall in GFR, and a rise in blood urea nitrogen (BUN). This will make the nurse happy because there is urine in the bag, but this will make the patients' kidney VERY UNHAPPY.

Volume depletion is associated with a greater rise in the BUN than in the plasma creatinine due to increased passive reabsorption of urea which follows the hypovolemia induced increase in sodium and water resorption in the kidney. An increasing BUN/creatinine ratio in a patient receiving a diuretic is a reliable sign of intravascular volume depletion and should prompt the immediate discontinuation of these agents.

Alert
Lasix® is the "Devils medicine"

Contrary to popular belief the GFR falls (rather than rises) with loop diuretics (an exception being the cardio-renal syndrome where high venous pressure limits GFR). In the mammalian kidney there is close coordination between the processes of glomerular filtration and tubular reabsorption. Coordination between the glomerulus and tubule is mediated by a system of tubulo-glomerular feedback which operates within the juxtaglomerular apparatus of each nephron. Microperfusion experiments have demonstrated that an increase in flow rate of tubule fluid through the loop of Henle following the use of a loop diuretic is followed by a reduction in single nephron GFR. This has been shown to be mediated via feedback control by the macula densa which is the flow dependent distal sensing site. When the tubular glomerular feedback pathway is interrupted with a loop diuretic there is an attenuation of the pressure-induced afferent arteriolar dilatation with impairment in blood flow autoregulation. in patients with extracellular volume depletion this effect is exaggerated with a dramatic fall in GFR.

Management of Volume Overload/Acute Pulmonary Edema

In patients with severe volume overload (usually iatrogenic) and/or acute pulmonary edema a loop diuretic (usually furosemide) is recommended. In patients with acute/chronic renal failure and volume overload ultrafiltration/dialysis should be performed.

i.e. Give Lasix when the kidney is working but not when it is failing or has failed. Use the Devil sparingly.

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Chapter 10
Assessment of Cardiac Function and Cardiac Output

The management of hemodynamically unstable patients requires an assessment of the patient's preload and fluid responsiveness (see Chap. 9) as well as an assessment of cardiac function. Cardiac function is best assessed by bedside echocardiography coupled with real time monitoring of cardiac output (CO). These techniques are complementary; echocardiography in the hands of the non-expert is unable to accurately measure and track CO, while CO monitors provide little information on left/right ventricular function nor the potential causes of an abnormal cardiac output. Furthermore, CO monitors are essential to determine fluid responsiveness.

Echocardiographic Assessment of Cardiac Function

All intensivists should be trained to perform "focused" echocardiography examinations which answer specific questions applicable to the management of critically ill and injured patients. These focused examinations should be viewed as an extension of the "physical examination." The American College of Cardiology/American Heart Association Clinical Competence statement on echocardiography recognizes that "*the era of the ultrasound-assisted physical examination has arrived*" [1]. The role of the focused echocardiographic examination by the non-cardiologist is in addition supported by American Society of Echocardiography, American College of Emergency Physicians, the Society of Critical Care Medicine and the American College of Chest Physicians [2–6]. It is important to emphasize that ultrasonography performed by the intensivist is an extension of the patients' evaluation rather than being a discreet imaging procedure. Furthermore, it is performed by the clinician caring for the patient rather than a consultant, and it is contemporaneous with the intensivists' evaluation rather than being temporally distinct. Unless performed by an expert echo-cardiographer, the focused exam should usually be followed by a full echocardiographic examination reported by a certified echo-cardiographer. In addition, in patients with unexplained hemodynamic instability and a grossly

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normal trans-thoracic exam, performance of a subsequent trans-esophageal, examination is important to rule out the presence of significant undetected valvular pathologies.

The goal of a focused echo examination is to determine global left ventricular (LV) systolic function, LV size, LV wall thickness, areas of gross LV dyskinesia, right ventricular (RV) size and function and as well as ventricular interdependence. It is important to note that the focused exam is performed to assess global LV function and differentiates patients into normal or minimally impaired function versus "depressed" or significantly impaired function. In addition, the LV may appear hyperdynamic/hyperkinetic with a small chamber size. Right ventricular dysfunction is common and its role underestimated in critically ill patients. The best way to quantify RV dilatation is to measure the ratio between the right and left ventricular end-diastolic areas Moderate RV dilatation usually corresponds to a diastolic ventricular ratio greater than 0.6, and severe RV dilatation to a ratio greater or equal to 1. With conditions of high strain imposed on the RV (volume and/or pressure overload) the interventricular septum flattens and the LV appears "D-shape." The focused exam in highly reliable for diagnosing pericardial effusions and pericardial tamponade. Other pathologic diagnoses (intracardiac masses, LV thrombus, valvular dysfunction, regional wall motion abnormalities, endocarditis, and aortic dissection) may be suspected on a focused exam, but additional evaluation, including referral for comprehensive echocardiography or cardiology consultation, is recommended [3].

Methods of Measuring Cardiac Output

In most instances the absolute value of the CO is less important than the response of the CO to a therapeutic intervention; i.e. fluid or an inotropic agent. In limited circumstances, most notably in the peri-operative setting, optimization of CO has been associated with improved patient outcomes (see Chap. 11).

Pulmonary Artery Catheter

Adolph Fick described the first method of CO estimation in 1870 [7]. Fick described how to compute an animal's CO from arterial and venous blood oxygen measurements. Fick's original principle was later adapted in the development of Stewart's indicator-dilution method in 1897 [8], and Fegler's thermodilution method in 1954 [9]. The introduction of the PAC in 1970 and its subsequent use in performing thermodilution measurements in humans translated the ability to measure CO from the experimental physiology laboratory to multiple clinical settings [10]. The direct Fick method was the reference standard by which all other methods of determining CO were evaluated until the introduction of the PAC. Currently the PAC is

considered the "*Gold Standard*" against which other devices are compared. Remarkably, the accuracy of the CO measurements as determined by the PAC has never been established. Electromagnetometry and ultrasound using aortic flow-probes most closely represent a true "Gold Standard" for determination of CO but can only be performed in instrumented animals [11–13]. Despite the ubiquitous use of the PAC remarkably few studies have investigated the accuracy of the CO measurements as determined by thermodilution. A number of studies have compared the thermodilution CO with that measured by the Fick technique. These studies have reported a percentage error of between 56 and 83 % (with <30 % being clinically acceptable) [14–16]. Philips at al compared thermodilution CO with surgically implanted ultrasonic flow probes in an ovine model [11]. The percentage bias and precision was −17 % and 47 % respectively; the PAC under-measured dobutamine-induced CO changes by 20 % (relative 66 %) compared with the flow probe. This study found that the PAC was an inaccurate measure of CO and was unreliable for detection of CO changes less than 30 %. Critchely et al. using a similar methodology in pigs reported a precision of 26 % [17]. These studies suggest that the true CO has to change by at least 25 % to be detected by the PAC. Furthermore, the required change may be as high as 100 % depending on the monitor being used [18]. It is likely that multiple factors interact to affect the accuracy of the thermodilution CO calculation [19].

Transpulmonary Thermodilution

Transpulmonary thermodilution (TPTD) similar to the PAC calculates the CO by the indicator dilution method using the modified Stewart-Hamilton equation. With this method a known quantity of cold injectate is delivered via a central venous catheter and mixing of the thermal indicator occurs as it passes through the right atrium and ventricle, pulmonary circulation, left atrium, ventricle and aorta. A thermistor-tipped arterial line quantifies the change in temperature over time in a large proximal artery (femoral artery). A mono-exponential transformation of the curve with extrapolation of a truncated descending limb back to baseline allows calculation of area under the curve for CO measurement. TPTD suffers from many of the errors and limitations associated with CO determined by the PAC. However, the reproducibility of the CO measurements by TPTD appears significantly better than that of the PAC with a precision of about 7 % (compared to 25 % for the PAC) [20].

The extravascular lung water (EVLW) is the amount of water that is contained in the lungs outside the pulmonary vasculature, that is, the sum of interstitial, alveolar, intracellular, and lymphatic fluids, except pleural effusion. EVLW can be calculated from the descending limb (indicator dissipation) of the TPTD curve and is an accurate method of quantifying the degree of pulmonary edema (hydrostatic and permeability) [21]. An increased value of EVLWI is thus the pathophysiological hallmark of hydrostatic as well as inflammatory lung edema. This technique has been shown to compare favorably with the double indicator dilution technique and the *ex-vivo*

gravimetric method [22–24]. Furthermore, this technique can detect small (10–20 %) increases in lung water [25]. The "normal" value for EVLWI is reported to be 5–7 mL/kg with values as high as 30 mL/kg during severe pulmonary edema. EVLW should be indexed to IBW rather than actual body weight [26]. The best EVLWI cut-off value to discriminate between normal lungs and lungs with diffuse alveolar damage is around 10 mL/kg [27]. EVLW has been demonstrated to be an accurate indicator of the severity of lung injury and a reliable prognostic indicator in patients with sepsis-induced acute lung injury [28, 29]. EVLW and the pulmonary vascular permeability index (PVPI) measured by TPTD have been demonstrated to be independent risk factors of day-28 mortality in patients with ARDS [30]. The EVLW is a very useful parameter to guide fluid removal (or not) in patients with ARDS and ARF. In addition, it is likely that using EVLW to guide fluid therapy in hemodynamically unstable ICU patients may reduce positive fluid balance, duration of mechanical ventilation and ultimately patient outcome (see Chap. 9).

Pulse Contour Analysis

The concept of pulse contour analysis is based on the relation between blood pressure, stroke volume (SV), arterial compliance, and systemic vascular resistance (SVR) [31]. If arterial compliance remains unchanged the area under the systolic portion of the arterial waveform is proportional to the stroke volume. The SV or CO can be calculated from the arterial pressure waveform if the arterial compliance and SVR is known. Although the pulse contour systems which are commercially available use different pressure-volume conversion algorithms, they are based on this basic principle. These systems can be divided into three categories:

- Pulse contour analysis requiring an indicator dilution CO measurement to calibrate the pulse contour, i.e. The LiDCO™ system (LiDCO, Cambridge, UK) and the PiCCO™ system (Pulsion, Munich, Germany), EV1000 (Edwards Lifesciences, Irvine, California, USA)
- Pulse contour analysis requiring patient demographic and physical characteristics for arterial impedance estimation, i.e. The FloTrac™ system (Edwards Lifesciences, Irvine, California, USA)
- Pulse contour analysis that does not require calibration or preloaded data, i.e. The MostCare system (Vyetech Health, Padua, Italy).

Clinical data suggests that only those pulse contour devices that are calibrated to an external method have acceptable clinical accuracy (vascular compliance is measured rather than calculated using predictive algorithms). Furthermore, these devices should be re-calibrated when vascular tone changes (e.g. use of a vasoconstrictor or vasodilator) [32]. It would appear than a number of these monitors are no better than random number generators and should be used with great caution [32].

Esophageal Doppler

The esophageal Doppler technique measures blood flow velocity in the descending aorta by means of a Doppler transducer placed at the tip of a flexible probe. The probe is introduced into the esophagus of sedated, mechanically ventilated patients and then rotated so that the transducer faces the descending aorta and a characteristic aortic velocity signal is obtained. The CO is calculated based on the diameter of the aorta (measured or estimated), the distribution of the CO to the descending aorta and the measured flow velocity of blood in the aorta. As esophageal Doppler probes are inserted blindly, the resulting waveform is highly dependent on correct positioning. The clinician must adjust the depth, rotate the probe and adjust the gain to obtain an optimal signal [33]. Poor positioning of the esophageal probe tends to under-estimate the true CO. There is a significant learning curve in obtaining adequate Doppler signals and the correlations are better in studies where the investigator is not blinded to the results of the CO obtained with a PAC [34]. The greatest utility of the esophageal Doppler appears to be in the peri-operative setting (see Chap. 11).

USCOM

A completely non-invasive Doppler technology, the USCOM (Ultrasound CO monitor, USCOM, Sydney, Australia), utilizes transaortic or transpulmonary Doppler ultrasound flow tracings to calculate cardiac output as the product of stroke volume and heart rate. Stroke volume is calculated from a proprietary algorithm applying ultrasound principles of blood velocity–time integral (VTI) measurements in the ventricular aortic/pulmonary outflow tract. Studies comparing USCOM measurements of cardiac output to those obtained with the PAC, TPTD, and aortic flow probes have shown reasonable agreement [11, 35–37]. The use of Doppler ultrasound to determine cardiac index has several inherent technological limitations. Potential sources of variation exist in the estimation of aortic/pulmonary outflow tract area, the determination of velocity-time integral as well as the variability with operator dependent measurements. With USCOM, the aortic/pulmonary outflow tract area is not directly measured, but calculated from a proprietary anthropometric algorithm based on the subject's body height. Stroke distance is simply the distance a red blood cell travels per systolic stroke. This is measured as VTI of the Doppler flow profile of each systolic stroke. Thus, the accuracy of the USCOM technology depends on obtaining accurate, reproducible VTI values. A precise VTI measurement requires a good flow signal and its correct interpretation, both of which are heavily dependent on the subject and the operator. An improper technique of poor Doppler ultrasound beam alignment with blood flow at the aortic/pulmonary outflow tract will lead to suboptimal VTI measurements. A further limitation of this technique is that it is not conducive to continuous monitoring.

Bioreactance

Due to the limitations of bioimpedance devices newer methods of processing the impendence signal have been developed. The most promising technology to reach the marketplace is the NICOM device (Cheetah Medical, Portland OR), which measures the bioreactance or the phase shift in voltage across the thorax. Phase Shifts occur only as a result of pulsatile flow, therefore the NICOM signal is correlated almost wholly with aortic flow. Furthermore, as the underlying level of thoracic fluid is relatively static, neither the underlying levels of thoracic fluid, nor their change induce any phase shift and do not contribute to the NICOM signal. NICOM is totally non-invasive; the system consists of a high-frequency (75 kHz) sine wave generator and four dual electrode "stickers" that are used to establish electrical contact with the body [38]. Within each sticker, one electrode is used by the high-frequency current generator to inject the high-frequency sine wave into the body, while the other electrode is used by the voltage input amplifier. The system's signal processing unit determines the relative phase shift ($\Delta\Phi$) between the input and output signals. Unlike bioimpedance, bioreactance-based CO measurements do not use the static impedance and do not depend on the distance between the electrodes for the calculations of SV, both factors which reduce the reliability of the result [38]. NICOM averages the signal over one minute therefore allowing "accurate" determination of CO in patients with arrhythmias. The CO as measured by bioreactance has been shown to be correlated with flow on cardiac bypass [38] as well as that measured by the Direct Fick method, thermodilution, pulse contour analysis and carotid Doppler [16, 39–43].

Utility of Cardiac Output monitoring

Determining Fluid and Inotrope Responsiveness

The measurement of SV and CO is fundamental to the hemodynamic management of critically ill patients in the ICU and unstable patients in the operating room. Changes in SV in response to a fluid challenge or inotropic agent is critical in determining fluid and inotropic responsiveness. Furthermore tracking changes in SV over time as well as the optimization of SV is emerging as an important intervention in the peri-operative period (see Chap. 11).

Driving up CI to Supranormal Values

Following the work of Shoemaker et al. in surgical patients, the concept of supranormal hemodynamic goals was extended to trauma patients as well as patients with sepsis. The premise of this strategy was that patients with both trauma and sepsis

had tissue hypoxia and had incurred an oxygen debt. The goal with this protocol was to achieve a $DO_2 > 600$ mL/min/m^2 and a CI > 4.5 L/min/m^2. Studies in trauma patients demonstrated that this strategy did not improve overall outcome [44, 45]. In these studies patients in the supranormal group who could not achieve supranormal values had a higher death rate than similar patients in the control group. These findings support the argument that achieving supranormal values is an indicator of physiologic reserve rather than being a useful endpoint of resuscitation. It is widely believed that patients with sepsis, particularly those with an increased lactate concentration, have inadequate organ and tissue blood flow with inadequate oxygen delivery. It is further assumed that the inadequate oxygen delivery leads to anaerobic metabolism, with the production of "lactic acid" and the development of an oxygen debt. It would follow from this reasoning that patients with sepsis should be managed by increasing oxygen delivery. These assumptions are however, incorrect (see Chap. 12). Patients with sepsis do not have an increased oxygen requirement neither do they have evidence of tissue hypoxia or bioenergetic failure. Attempts at increasing oxygen delivery does not improve outcome and indeed may be harmful [46, 47]. Based on these studies it would appear the most appropriate hemodynamic goals for these patients is a MAP > 65 mmHg with a normal cardiac index (>2.5 L/min/m^2). It would therefore appear that in most circumstances iatrogenically driving up the CI above normal values is not a beneficial exercise (less may be more!)

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Chapter 11
Peri-operative Fluid Optimization

More than 230 million major surgical procedures are undertaken worldwide each year [1]. Data from the USA and Europe suggests that approximately 18 % of patients undergoing surgery will develop a major postoperative complication and 3–5 % will die before hospital discharge [1–4]. If this rate is applicable worldwide approximately 40 million patients undergoing surgery each year will die or develop a major postoperative complication. Those patients who develop a postoperative complication and survive to hospital discharge have diminished functional independence and reduced long-term survival. In a landmark study Khuri and coworkers demonstrated that survival up to 8 years after major surgery was strongly related to the development within 30 days of surgery of a major postoperative complication [4]. In this study, independent of preoperative risk, the occurrence of a 30-day complication reduced median patient survival by 69 %. In both the USA and Europe there are large variations in postoperative morbidity and mortality within healthcare systems [2, 3, 5]. Interventions that reduce the risks of postoperative death and complications, particularly in high risk patients have become a priority in perioperative medicine [6]. Interventions such as the use of perioperative beta-blockers, statins and tight glycemic control have proved disappointing [7, 8]. Pre-emptive goal-directed hemodynamic therapy (GDT) appears to be a promising approach to reduce postoperative complications and deaths.

Due to the assumed intravascular deficit after fasting, the increased insensible losses with damage to the skin barrier and the large shift of fluid into the "third space" generations of anesthesiologists have infused large volumes of fluids into patients. This approach resulted in pre-operative fluid loading and the intraoperative infusion of fluid at rates of up to 20 mL/kg/h (independent of blood loss). Traditional fluid management during major surgery resulted in a positive fluid balance of several liters and a perioperative body weight gain of up to 10 kg [9]. However, the insensible perspiration and the preoperative deficits are in fact often negligible, and the "third space" appears to be myth that does not exist [9]. The excessive interstitial edema that accumulates postoperatively is likely a consequence of excessive fluid administration. Indeed, multiple studies have demonstrated that a conservative

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fluid strategy as compared to "usual fluid management" is associated with fewer postoperative complications [10]. In a multicentre study, Brandstrup and co-workers randomized patients undergoing major colorectal surgery to a restrictive fluid strategy or usual care [11]. The patients in the restrictive group received less fluid (mean 2,740 vs. 5,388 mL) and had a significantly reduced incidence of major and minor complications. However, an overly restrictive fluid strategy will decrease cardiac output and oxygen delivery and likely increase complications. Futier et al. compared a restrictive to a conservative fluid strategy in patients undergoing major abdominal surgery. In this study the complication rate was significantly higher in the restrictive group. Goal directed therapy (GDT) provides a balance between the liberal and restrictive fluid strategies. GDT is a conservative approach to fluid management that is based on optimizing each individual patient's hemodynamic profile. This approach represents a refinement of the "supranormal" hemodynamic approach pioneered by William Shoemaker in the 1980s [12].

In general GDT is based on the titration of fluids and inotropic drugs to physiological flow-related end points. Over 30 GDT studies have been performed to date and an analysis these studies suggest that peri-operative optimization of hemodynamics reduces postoperative complications in elective non-cardiac surgical patients [13–17]. In addition, GDT has been demonstrated to reduce the risk of death in high-risk patients [13–17]. On the basis of these data, the UK National Health Service's National Institute for Health and Clinical Excellence (NICE) has recommended GDT (using esophageal Doppler) for patients undergoing major or high-risk surgery [18, 19]. This guidance states that "*there is a reduction in postoperative complications… and in-hospital stay when compared with conventional clinical assessment with or without invasive cardiovascular monitoring… with an average cost saving of approximately £1,100 (about $1,800) per patient*" [18, 19]. Despite these recommendations hemodynamic optimization during major surgery has not been widely adopted [20].

A number of different technologies (pulmonary artery catheter, esophageal Doppler and pulse contour analysis, bioreactance) and treatment algorithms have been utilized to optimize peri-operative hemodynamics. Most of these studies have used both fluids and inotropic agents to optimize cardiac output. Furthermore, GDT has been initiated pre-operatively, intra-operatively or postoperatively. Most of these studies have compared GDT to standard care (liberal fluid strategy) and have demonstrated that this approach improves outcomes in elective non-cardiac surgical patients [13–17]. Few "head-to-head" studies have been performed comparing different GDT strategies, therefore the optimal approach remains unclear [21–23]. The initial preemptive hemodynamic studies used the pulmonary artery catheter and targeted the Shoemaker "supranormal" goals while more recent studies have "optimized" cardiac output using esophageal Doppler, dynamic indices of fluid responsiveness or bioreactance.

It is widely believed that an oxygen debt occurs *intraoperatively* and that this oxygen debt increases the risk of postoperative infectious complications, wound breakdown, myocardial ischemia, acute kidney injury and death [13–17]. Furthermore, it is postulated that GDT with the optimization of intraoperative

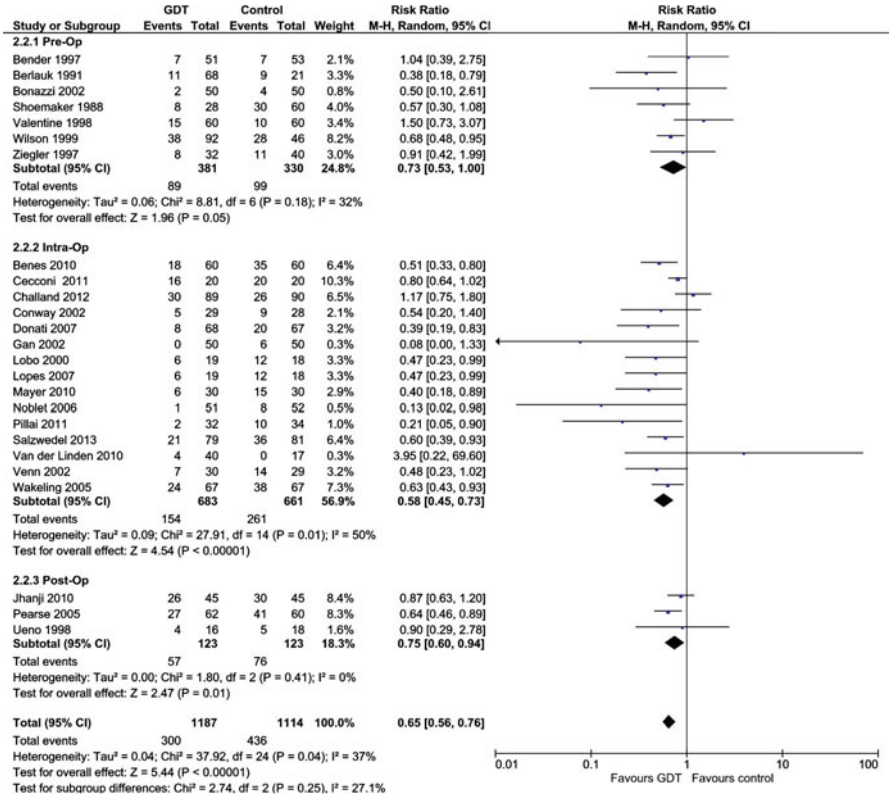

Fig. 11.1 Comparison of the risk of postoperative complications in studies that compared GDT (Protocol) versus standard therapy (control). Studies are grouped by timing of the initiation of hemodynamic optimization. Weight is the relative contribution of each study to the overall treatment effect (risk ratio and 95 % confidence interval) on a log scale assuming a random effects model. Metaanalysis performed using Review Manager 5.1

cardiac output prevents this intra-operative oxygen debt [13–17]. Figure 11.1 is a meta-analysis of GDT studies stratified by the timing of the initiation of hemodynamic optimization. This meta-analysis together with previous meta-analyses demonstrates that hemodynamic optimization improves outcome whether this intervention be initiated pre-operatively, intra-operatively or postoperatively [13–17, 24–26]. This observation casts doubt on the intraoperative oxygen debt theory. Furthermore, a critical analysis of these studies suggests that tissue dysoxia occurs postoperatively rather than intraoperatively (discussed further below). These observations have important implications for the management of surgical patients and suggest that the immediate postoperative management of high risk surgical patients may play a pivotal role in reducing postoperative complications and death. This is an important issue as the vast majority of patients who die are not admitted to an ICU after surgery. In the *European Surgical Outcomes Study* (*EuSOS*) 73 % of

patients who died were not admitted to an ICU at any stage after surgery [2]. In a study of 26,051 patients undergoing non-cardiac surgical procedures performed in a large National Health System Trust only 35.3 % of high-risk patients were admitted to a critical care unit after surgery [27].

In 1988 Shoemaker and colleagues published a now landmark study in which they measured oxygen delivery (DO_2) and oxygen consumption (VO_2) in 100 consecutive patients undergoing high-risk surgical operations [28]. They calculated the intraoperative and postoperative oxygen debt (VO_2 debt) by subtracting the measured VO_2 from the estimated VO_2 requirements corrected for temperature and anesthesia. It should be noted that the estimated VO_2 during anesthesia was calculated using a non-validated equation [28]. These authors then correlated the calculated VO_2 deficit with the subsequent development of lethal and non-lethal organ failure. In this study the cumulative VO_2 deficit averaged 33.5 ± 36.9 L/M^2 in non-survivors, 26.8 ± 32.1 L/M^2 in survivors with organ failure and 8.0 ± 10.9 L/M^2 in survivors without organ failure ($p < 0.05$). Shoemaker and colleagues noted that the oxygen debt was incurred almost exclusively during the intraoperative period. Based on these findings the authors proposed that the greater the oxygen debt incurred (during surgery) the greater the risk of organ failure and death [28]. Subsequently, these authors performed a number of pseudo-randomized studies in which patients were "randomized" to achieve supranormal hemodynamic goals (DO_2 600 mL/min/m^2 and CI > 4.5 L/min/m^2) or standard care [25, 26]. In these studies the risk of complications and death were significantly lower in the "supranormal" group. Based on the VO_2 debt incurred intraoperatively and the summation of their outcome data Shoemaker and colleagues recommended that "*in the high-risk patient*, *PA catheterization should be instituted preoperatively and that the important cardiorespiratory values be prophylactically augmented beginning in the preoperative and continued into the intraoperative and immediate postoperative periods*" [26, 28].

In their 1988 paper Shoemaker and colleagues were unable to determine "*which of these influences are operative*" to explain the intraoperative oxygen debt [28]. Furthermore, as already stated the VO_2 deficit was calculated using a formula that had not been validated [29]. At face value it would appear to be counterintuitive that anesthesia would result in an oxygen debt. General anesthesia and neuromuscular blockade reduce metabolic rate and oxygen consumption while DO_2 remains largely unchanged [30, 31]. Hypothermia occurs frequently during anesthesia which further reduces metabolic oxygen requirements [32, 33]. Indeed, in Shoemaker's pivotal paper VO_2 fell during the intraoperative period reaching a nadir and the end of surgery [28]. In this study VO_2 increased sharply after surgery reaching the pre-operative VO_2 at 1 h with the VO_2 peaking at 4 h. It is therefore difficult to understand how anesthesia induces an oxygen debt. This apparent contradiction is best resolved by an analysis of the time course of the mixed venous oxygen saturation ($SmvO_2$) or central venous oxygen saturation ($ScvO_2$) during the peri-operative period. $SmvO_2$ (or $ScvO_2$) is a reflection of the balance between DO_2 and VO_2; in patients who incur an oxygen debt the $SmvO_2$ should fall. A number of studies have monitored the $SmvO_2/ScvO_2$ in the perioperative period [23, 34–39].

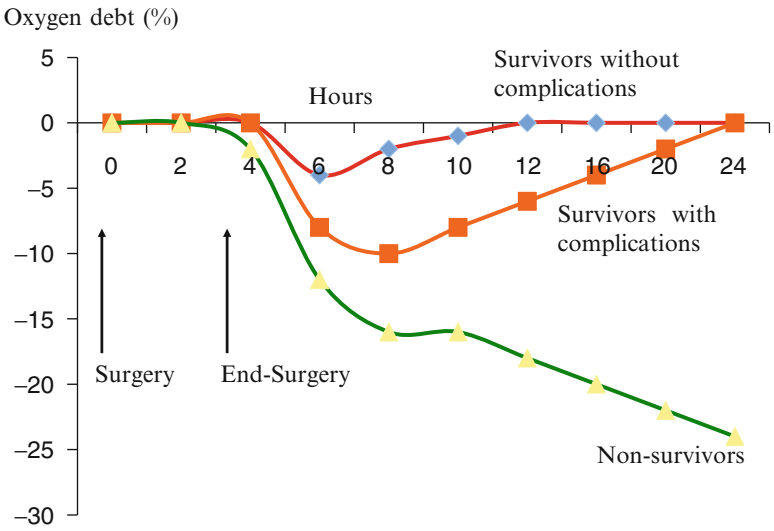

Fig. 11.2 Revised Shoemaker oxygen debt model

These studies reproducibly demonstrate that the $SmvO_2/ScvO_2$ remains stable or increases slightly during anesthesia and surgery but falls sharply in the immediate post-anesthesia period. Furthermore, the lowest postoperative $SmvO_2/ScvO_2$ was independently predictive of postoperative complications (see Fig. 11.2) [23, 34–38]. These data suggest that the oxygen debt is incurred postoperatively with the withdrawal of anesthesia (and NMB) and with the development of postoperative pain, agitation, shivering and increased sympathetic tone. Furthermore, those patients with limited cardiac reserve and those with inadequate intra-operative hemodynamic optimization are most likely to have the largest postoperative fall in $SmvO_2/ScvO_2$ and incur the largest oxygen debt. Indeed, these are the patients that have been demonstrated to be at the greatest risk of death and postoperative morbidity [23, 35].

These observations suggest that optimization of cardiac output should begin intraoperatively and continue into the postoperative period for at least 8–12 h. Both fluids and inotropic agents should be used to optimize stroke volume/cardiac output using non-invasive or minimally invasive hemodynamic monitors [39, 40]. While no GDT protocol has been demonstrated to be superior to another, we suggest the following approach which should be repeated every 15–30 min intraoperatively:

- Fluid boluses until the patient is no longer fluid responsive (esophageal Doppler, NICOM, PPV, etc.)
- Inotropic agent if CI < 2.5 L/min/m^2 after fluid optimization
- Vasopressor agent after fluid and inotropic optimization to maintain MAP >65 mmHg

All efforts should be made to prevent intraoperative hypotension, as even short episodes of hypotension (1–5 min) have been demonstrated to increase the risk of

acute kidney injury and myocardial complications [41]. The $ScvO_2$ should be monitored both intraoperatively and postoperatively in high risk patients with the goal of keeping the $ScvO_2$ above 70 % (with the use of inotropic agents, after fluid optimization) [37]. This approach would require high risk patients to be admitted to an ICU or intermediate care unit for the first postoperative day, which is in keeping current recommendations to improve surgical outcomes [2, 27].

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Chapter 12
Sepsis

Except for a few occasions patients' appear to die from the body's response to infection rather than from it

William Osler, Physician (1849–1919)

The word "sepsis" is derived from the ancient Greek word for rotten flesh and putrefaction. Since then, a wide variety of definitions have been applied to sepsis, including sepsis syndrome, severe sepsis, bacteremia, septicemia and septic shock In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) developed a new set of terms and definitions to define sepsis in a more "precise manner" [1, 2]. These definitions take into account the findings that sepsis may result from a multitude of infectious agents and microbial mediators and may not be associated with detectable bloodstream infection. The term "*systemic inflammatory response syndrome*" (SIRS) was coined to describe the common systemic response to a wide variety of insults. When SIRS was the result of a suspected or confirmed infectious process, it is termed "sepsis". Severe sepsis was defined as sepsis plus organ dysfunction. Septic shock is a subset of severe sepsis and was defined as "*sepsis-induced hypotension persisting despite adequate fluid resuscitation*" (see Fig. 12.1). While the quantity of fluid that qualifies as "adequate fluid resuscitation" is controversial, we believe septic shock is best defined as a "mean arterial pressure (MAP) less than 65 mmHg after a fluid challenge of 20 mL/Kg body weight (given 30–60 minutes) in patients with sepsis and in the absence of other causes for hypotension" (also see Chap. 14). According to the ACCP/SCCM definitions, three stages in the hierarchy of the host's response to infection were recognized, namely, sepsis, severe sepsis and septic shock, with sepsis having the best prognosis and septic shock the worst. While the use of the SIRS criteria to define sepsis is somewhat controversial [3–6], many consider sepsis to be best defined as the "*systemic response to infection with the presence of some degree of organ dysfunction*" [5].

Sepsis is amongst the most common reason for admission to ICU's throughout the world. An epidemiologic study in European ICU's demonstrated an incidence of 37 % for sepsis and 30 % for severe sepsis [7]. While the exact incidence of sepsis in the US is unclear (300–1,000 cases/100,000 population per year) the annualized incidence has been reported to have increased by between 8.7 to 13 % over the last 30 years [8–11]. The aging of the population is believed to be largely responsible for the increasing incidence of sepsis in developed counties [12]. Epidemiological data

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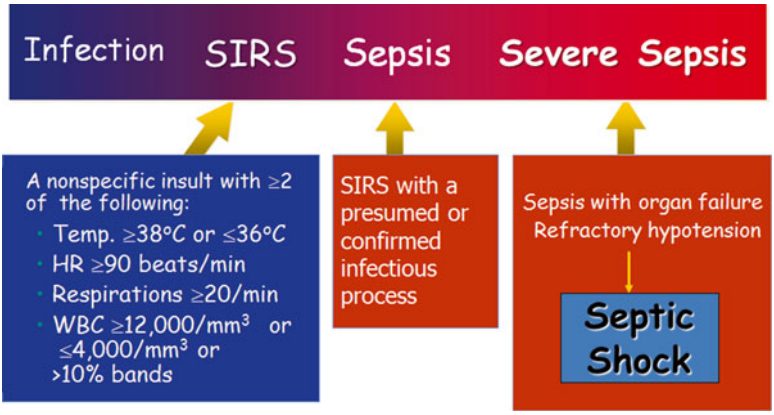

Fig. 12.1 Sepsis: defining a disease continuum

from 2004 to 2009 demonstrated a decrease in in-hospital mortality from 35 to 26 % [8]. This study estimated that there were 229,044 deaths from severe sepsis in 2009, which would place severe sepsis as the third most common cause of death in the US, after heart disease and malignant neoplasms [8]. The 1-year all-cause mortality of patients treated for severe sepsis and septic shock maybe as high as 44 % [13]. In addition, recent data suggests that patients who have had a septic episode are at an increased risk of death for up to 5 years following the acute event [14, 15]. Sepsis is reported to be more common in men and among nonwhite persons [10]. Surgical patients account for nearly one third of sepsis cases in the US; this is important as the management of "surgical" and "medical sepsis" differs somewhat [10].

Bacteriology and Sites of Infection

Bacteriologic data from sepsis trials published during the last two decades indicate the following pattern of culture results:

- Gram-positives 25 %
- Gram-negatives 25 %
- Gram-positive + Gram-negative organisms 15 %
- Fungal pathogens 3–5 %
- Anaerobes 2 %
- Culture –ve 25 %

The most common sites of infection are:

- Lung 50 %
- Abdomen/pelvis 25 %
- Primary bacteremia 15 %
- Urosepsis 10 %
- Vasculare access 5 %

Pathophysiology of Sepsis

Sepsis is an exceedingly complex condition. Exposure of human macrophages to bacterial antigens has been demonstrated to result in a significant change in the expression over 950 genes [16]. These include genes for pro and anti-inflammatory cytokines, chemokines, adhesion molecules, transcription factors, enzymes, clotting factors, stress proteins and anti-apoptotic molecules. These gene products alter the function of every cell and tissue in the body. Furthermore these mediators interact in complex positive and negative feedback loops and result in epigenetic modifications which further alter the expression of this network of mediators [17]. The early phase of sepsis is generally believed to result from the uncontrolled production of pro-inflammatory mediators the so-called "cytokine storm" [18]. However, recent data suggests that both a pro-inflammatory and an opposing anti-inflammatory response occur concurrently in patients with sepsis [19, 20]. In general, following a variable time course, patients transition from a predominantly pro-inflammatory to an anti-inflammatory immunosuppressive state [17–21].

The pathogenetic mechanism and physiological changes associated with sepsis are exceedingly complex with our understanding of this topic rapidly evolving; the reader is referred to excellent reviews on this topic [17–21]. The major pathophysiologic changes in patients with severe sepsis and septic shock include vasoplegic shock (distributive shock), myocardial dysfunction, altered microvascular flow, activation of coagulation and a diffuse endothelial injury [22, 23]. These pathophysiologic changes play a central role in the early management of patients with sepsis. The widespread endothelial injury results in a microvascular leak with tissue and organ edema, hypotension and shock. Increased endothelial permeability is caused by shedding of the endothelial glycocalyx and the development of gaps between endothelial cells (paracellular leak) [24, 25]. Vasoplegic shock, due to failure of the vascular smooth muscle to constrict, results in arterial and veno-dilatation [22]. Vasoplegic shock is believed to be due to increased expression of inducible nitric oxide synthetase with increased production of nitric oxide (NO), activation of KATP channels resulting in hyperpolarization of the muscle cell membrane, increased production of natriuretic peptides (which act synergistically with NO) and a relative vasopressin deficiency [22]. Veno-dilatation increases the size of the non-stressed blood volume decreasing venous return which compounds the intra-vascular volume deficit caused by the vascular leak.

Septic "Cardiomyopathy"

Reversible myocardial depression in patients with septic shock was first described in 1984 by Parker et al. using radionuclide cineangiography [26]. In a series of 20 patients, they reported a 50 % incidence of left ventricular (LV) systolic dysfunction, defined by an ejection fraction <40 %. Paradoxically, in this study the initial ejection fraction and ventricular volumes were normal in non-survivors and these indices did

not change during serial studies. The authors suggested that survival depends on the ability of the left ventricle to dilate and increase stroke volume. It is noteworthy that the "septic cardiomyopathy" is acute and reversible. In a series of 90 patients with severe sepsis, Jardin et al. reported that the left ventricular ejection fraction (LVEF) was depressed in all patients and normalized over a few days in the survivors [27]. In this study, LVEF was significantly lower in survivors than non-survivors, while the LVEDV was significantly smaller in non-survivors than survivors.

The initial studies evaluating cardiac function in sepsis focused on LV systolic function. However, left ventricular diastolic dysfunction has emerged as common finding in patients with severe sepsis and septic shock. Adequate filling during diastole is a crucial component of effective ventricular pump function. Diastolic dysfunction refers to the presence of an abnormal left-ventricular diastolic distensibility, filling, or relaxation, regardless of LVEF. Unlike systolic LV dysfunction, diastolic dysfunction appears to be an important prognostic marker in patients with sepsis. Impaired diastolic distensibility probably accounts for the reduced LVEDV in the studies by Parker and Jardin (referenced above). The reported incidence of systolic and diastolic function in patients with sepsis varies widely; this may be related to the population studied and the diagnostic strategies used. This data is summarized in Table 12.1. It is noteworthy that diastolic dysfunction appears to be more common than systolic dysfunction and that isolated diastolic dysfunction was present in 21 % of patients. Combined systolic and diastolic dysfunction was reported in 16 % of patients. The optimal approach to the management of septic patients with diastolic dysfunction likely differs from that of patients with systolic (or combined) left ventricular dysfunction. As diastolic dysfunction is best diagnosed by Tissue

Table 12.1 Incidence of systolic and diastolic dysfunction in patients with sepsis

Author	Year	*n*	Systolic dysfunction (%)	Diastolic dysfunction (%)	Isolated diastolic dysfunction%
Parker [26]	1984	20	50	–	–
Jardin [28]	1990	21	29	–	–
Etchecopar-Chevreuil [29]	2008	35	46	20	9
Veillard-Baron [30]	2008	67	60	–	–
Bouhemad [31]	2008	54	20	40	20
Bouhemad [32]	2009	45	18	18	–
Sturgess [33]	2010	21	67	57	–
Turner [34]	2011	153	32	–	–
Landesberg [35]	2012	262	23	54	40
Pulido [36]	2012	106	27	37	27
Mahjoub [37]	2012	83	–	57	–
Brown [38]	2012	78	26	61	23
Mourad [39]	2014	72	54	46	16
Summary		1,038	33	47	23

Summary refers to the weighted average

Doppler Imaging (TDI), patients with sepsis who are admitted to the ICU should undergo both bed-side ECHO as well as a formal echocardiographic study. Patients who have a hyperdynamic circulation on bedside ECHO, with a low stroke volume (as determined by non-minimally invasive cardiac output monitoring) and who are volume non-responders should be suspected of having predominant diastolic LV dysfunction (see case example at end of this Chapter).

Many factors may contribute to cardiac dysfunction during sepsis. Studies performed in humans have ruled out coronary hypoperfusion as a cause of LV dysfunction in sepsis. Cytokines, particularly TNF-α have been postulated to play a major role in the genesis of septic cardiomyopathy. It has been suggested that the effect of cytokines on cardiac myocytes results from an increase in intracellular nitric oxide and cGMP [40]. Tavernier et al. suggested that increased phosphorylation of troponin I was involved in the septic cardiomyopathy by reducing myofilament response to Ca^{2+} [41]. Many other additional mechanisms have been suggested including myocardial apoptosis, altered myocardial microcirculation, autonomic neuropathy, mitochondrial dysfunction, abnormal energy metabolism, abnormal adrenergic signalling, and myocardial edema, to name but a few [42–45]. It is unclear why some patients develop systolic LV dysfunction while others develop diastolic dysfunction. However, older age, diabetes, hypertension and obesity may increase the likelihood of developing diastolic LV dysfunction [35, 36]. Furthermore, aggressive fluid resuscitation may increase myocardial edema increasing the risk of diastolic dysfunction [33].

Complications Associated with Sepsis

Complications associated with severe sepsis and septic shock includes acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), disseminated intravascular coagulation (DIC), critical illness polyneuropathy and "septic encephalopathy". The risk of ARDS (and outcome) may be critically dependent on the fluid resuscitation strategy (see below). Sepsis is the leading cause of AKI in critically ill patients and is associated with a hospital mortality exceeding 50 % [46, 47]. Contrary to "classic teaching," animal models and human studies have shown that the sepsis-induced AKI occurs in the setting of preserved or increased renal blood flow [48]. A "unifying theory" has been proposed to explain the development of sepsis-induced AKI which includes the interplay between inflammation and oxidative stress, microvascular dysfunction, and the adaptive response of the tubular epithelial cell to the septic insult [48]. Activation of the coagulation cascade with the generation of fibrin is a pathologic hallmark of sepsis. Activation of coagulation during sepsis is primarily driven by the tissue factor (TF) pathway. Due to activation of the coagulation cascade almost all septic patients are thrombocytopenic (or have a falling platelet count), and indeed a normal platelet count makes the diagnosis of sepsis unlikely. An elevated D-dimer, thrombin-antithrombin complexes and a prolonged prothrombin time are found in the majority of patients with severe sepsis while anti-thrombin, protein C and protein S levels are significantly decreased.

Clinical Features and Diagnosis of Sepsis

Sepsis is a systemic disease with a variety of clinical manifestations. The initial symptoms of sepsis are non-specific and include malaise, tachycardia, tachypnea, fever and sometimes hypothermia. Although most patients with sepsis have an elevated white cell count, some patients present with a low white cell count, which in general, is a poor prognostic sign. A band count in excess of 10 % has been reported to have a high specificity (92 %) but low sensitivity for the diagnosis of sepsis (43 %) [49] Other clinical manifestations include altered mental status, hypotension, respiratory alkalosis, metabolic acidosis, hypoxemia with acute lung injury, thrombocytopenia, consumptive coagulopathy, proteinuria, acute tubular necrosis, intra-hepatic cholestasis, elevated transaminases, hyperglycemia and hypoglycemia. Patients may present with clinical features of a localized site of infection, such as cough, tachypnea and sputum production due to pneumonia; flank pain and dysuria with urinary tract infection and abdominal pain with intra-abdominal infection.

Organ Dysfunction in Severe Sepsis/Septic Shock

Cardiovascular

- Tachycardia
- Hypotension
- Decreased contractility
- Vasodilatation

Respiratory

- Tachypnea
- Decreased PaO_2/FiO_2
- ALI/ARDS

Hematological

- Thrombocytopenia
- Increased PTT/PT
- Decreased protein C
- Increased D-dimer

Neurological

- Confusion
- Agitation
- Altered consciousness
- Neuropathy
- Myopathy
- Cerebral edema

Renal

- Oliguria
- Increased s-creatinine

Hepatic

- Increase in transaminases
- Decreased albumin

Metabolic/endocrine

- AG acidosis
- Increased lactate
- CIRCI (adrenal insufficiency)
- Hyperglycemia/hypoglycemia
- Hypophosphatemia

The manifestations of sepsis can sometimes be quite subtle, particularly in the very young, the elderly and those patients with chronic debilitating or immunosuppressing conditions. These patients may present with normothermia or hypothermia. The failure to generate a temperature greater than 99.6 °F (37.5 °C) in the first 24 h of clinical illness, has been associated with an increased mortality rate. An altered mental state or an otherwise unexplained respiratory alkalosis may be the presenting feature of sepsis.

The signs and symptoms of systemic inflammation are not useful in distinguishing infectious from non-infectious causes of SIRS. Despite exhaustive microbiological tests a pathogen is not isolated in about 25 % of patients [50]. Blood cultures are considered to provide the clinical gold standard for the diagnosis of bacterial infections. However, blood cultures are only positive in between 20 and 30 % of patients with sepsis; moreover, it takes 2–3 days before the results become available. Molecular methods based on polymerase chain reaction (PCR) technology hold promise for the early diagnosis of bacterial infection and for pathogen identification. A number of bio-markers have been evaluated as more specific indicators of infection.

Procalcitonin (PCT) has to date been the most useful bio-marker to aid in the diagnosis of sepsis. PCT, a propeptide of calcitonin, is normally produced in the C-cells of the thyroid. In healthy individuals, PCT levels are very low (<0.01 ng/mL). In patients with sepsis, however, PCT levels increase dramatically, sometimes to more than several hundred nanograms per milliliter. The use of PCT for the diagnosis of sepsis and in determining the duration of antibiotics is controversial. The test is not perfect and should always be interpreted in the clinical context together with other diagnostic tests. Su et al. evaluated the diagnostic accuracy of 32 clinical signs, symptoms and laboratory tests available during a patients stay in the Emergency Department [51]. In this study, PCT was that variable that had the best diagnostic accuracy. Similarly, Tromp et al. demonstrated that PCT had the best predictive value for bacteremia with an area under the receiver operator curve (ROC) curve of 0.80, with a sensitivity of 89 % and a specificity of 58 % [52].

In this study, the predictive value of a combination of PCT plus a panel of other biomarkers, clinical signs, or analysis of serial PCT levels did not lead to a significant improvement of the predictive value of PCT alone. Wacker performed a meta-analysis to evaluate the diagnostic accuracy of PCT [53]. In this meta-analysis the sensitivity was 0.77 (95 % CI 0.72–0.81), the specificity was 0.79 (95 % CI 0.74–0.84) and the area under the ROC curve was 0.85 (95 % CI 0.81–0.88). This diagnostic accuracy is better than any other single test to diagnose sepsis. A PCT >0.5 ng/mL is highly suggestive of a bacterial infection while a level <0.1 ng/mL makes this diagnosis less likely [54]. However, the optimal diagnostic threshold is unclear and has been reported to vary from 0.25 to 1.4 ng/mL [52, 54]. This variation in diagnostic threshold may partly be explained by the case-mix of each study and the fact that patients' with gram-negative infection have significantly higher PCT levels than those with gram-positive infections [55–57]. Infection with a gram negative pathogen is highly likely in a patient with a PCT level >5 ng/mL. It should be noted that patients with fungal infections usually have much lower or "normal" PCT level [55]. In hematologic patients an elevated PCT level within 24 h after the onset of neutropenic fever is highly predictive of Gram-negative bacteremia [58]. In addition to being a very useful test to diagnose bacterial sepsis, the trend in the PCT level is useful for deciding when to discontinue antibiotics [59, 60]. Furthermore, the trend in the PCT is strongly predictive of outcome, with a persistently high level being associated with a poor outcome [61].

Don't Miss the Diagnosis of Sepsis
In many patients who present to the ED the diagnosis of sepsis is obvious, i.e. high fever, high WBC and an obvious source of infection. However, in many instances the patient may present with vague constitutional symptoms, mild hypotension and tachycardia or with a fever and myalgia that are attributed to "*a viral syndrome*". DO NOT send these patients home without further workup (unless they obviously have a viral syndrome); YOU DO NOT want to send the patient home, who then returns some time later in septic shock, and subsequently loses an arm or leg (or both) or dies. When the diagnosis is not clear you must do a WBC with differential and band count, blood lactate level and PCT.

Any one of the following features alone or in combination are suggestive of bacterial sepsis:

- Fever >38.3 °C
- Heart rate >120/min
- Systolic BP <90 mmHg
- PCT >0.5 ng/mL
- Bandemia >5 %
- Lymphocytopenia $<0.5 \times 10^3$ul
- Thrombocytopenia $<150 \times 10^3$uL
- Lactate >2.0 meq/L
- Increased neutrophil/lymphocyte ratio

Management of Sepsis

On the 8th November 2001 Emanuel Rivers and collaborators published a study entitled "*Early Goal Directed Therapy in the treatment of severe sepsis and septic shock*" in which they compared two protocols for the early resuscitation of patients with severe sepsis and septic shock (for 6 h in the Emergency Department) [62]. Both protocols used the CVP to guide fluid therapy. The "treatment arm" (EGDT) required placement of an oximetric central venous catheter with protocolized interventions to maintain the saturation of the central venous oxygen saturation ($ScvO_2$) >70 % (see Fig. 12.2). The study which enrolled 288 patients (25 were excluded after the fact) and reported a 28 day mortality of 49.2 % in the control group and 33.3 % in the EGDT group ($p = 0.01$, with an absolute reduction in the risk of death of 16 %). A number of serious concerns have been raised with regards to this study

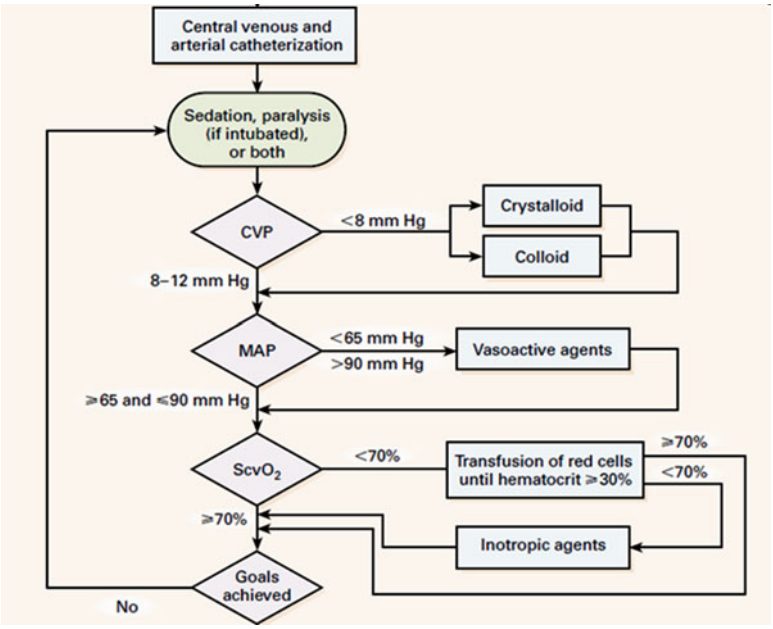

Fig. 12.2 The "infamous" River's Early Goal Directed Therapy (EGDT) protocol

including the validity of the protocol itself, the conduct of the study and the reporting of the study [63–68]. These include:

i. The results of the study appear to be biologically implausible
ii. The study was not blinded, with concerns regarding interference with the conduct of the study
iii. None of the elements of the protocol were (are) supported by any level of credible scientific evidence
iv. The mortality in the control group was significantly higher than that of any study reported at that time [69], raising the question of sub-standard care in the control arm of the study
v. The hemodynamic profile of the patients, particularly the low $ScvO_2$ (49 ± 13 %) and the high MAP (76 ± 24 mmHg), is very atypical for patients with sepsis
vi. The senior author had serious undisclosed conflicts of interest.
vii. Twenty five patients were excluded from the final analysis (for unclear reasons). When these patients are included in an intention-to-treat analysis it has been reported that "*the death gap was no longer statistically significant*." [63]

Despite the limitations of this single center study, EGDT soon became regarded as the "*standard of care*" around the world, it was endorsed by major organizations in the US (including the Institute for Health Care Improvement (IHI), Centers for Medicare and Medicaid Services (CMS), Agency for Health Care Quality and

Improvement (AHQI), Society of Critical Care Medicine) and abroad and formed the basis of the 6-h resuscitation bundle of the 2004, 2008 and 2012 recommendations of the Surviving Sepsis Campaign (SSC) [70–72]. A large number of before-and-after studies (probably >30 studies) have been published claiming that the use of the Surviving Sepsis Campaign 6-h resuscitation bundle reduced mortality (see Chap. 1 on the limitations of before-after studies) [73, 74]. However, it is noteworthy that the reported mortality has fallen when compliance with "*the bundle*" is less than 10–15 %, but has increased when compliance with the bundle is high [75–77]. Shiramizo et al. noted a fall in mortality in their patients with severe sepsis/septic shock from 41.4 to 16.2 % between 2008 and 2009 despite a decline in compliance with the 6-h resuscitation bundle from 21.1 to 13.7 % [78]. We postulate that the improved outcome with low "bundle" compliance is related to improved screening for sepsis and earlier administration of antibiotics with concomitant poor achievement of the CVP targets, while the increased mortality with high compliance of the "bundles" is related to the harm of achieving the CVP targets i.e. the benefit of early antibiotics are outweighed by the harm of achieving the CVP targets (see harms of excess fluid and high CVP) [73, 74]. This postulate is supported by the analysis of Barochia et al. who concluded that "*only antibiotics meet the stated criteria of proof for bundle inclusion*" [79].

In 2014, 13 years after the publication of the EGDT study the ProCESS study was published [80]. Process enrolled 1,341 patients, of whom 439 were randomly assigned to protocol-based EGDT (Rivers EGDT), 446 to protocol-based standard therapy, and 456 to usual care. There was no significant difference in 90-day and 1 year mortality between groups. However, in the sickest sub-group of patients (those with a baseline lactate >5.3 mmol/L) the mortality was significantly higher in the EGDT group as compared to usual care (38.2 vs. 26.4; $p = 0.05$). ProCESS has now clearly established that EGDT should be abandoned. This does not mean that patients with sepsis should not be managed by evidence based guidelines or recommendations. Unfortunately, a rational approach to the management of sepsis has been contaminated by the Rivers EGDT protocol and the Surviving Sepsis Campaign.

This section will focus on those interventions which are currently believed to improve the outcome of patients with severe sepsis and septic shock. Experimental immunomodulating interventions including the use of novel molecules and antibodies [17], extracorporeal blood purification [81] or approaches to "seal" the leaky endothelium [25] will not be discussed. The early management of patients with sepsis centers on the administration of antibiotics, limited amounts of intravenous fluids and vaso-active agents, followed by source control. Unfortunately, there is no high quality evidence (from one or more randomized controlled trials) demonstrating that any of these interventions alter outcome. It is however likely that the early detection of sepsis with the timely administration of appropriate antibiotics is the single most important factor in reducing the morbidity and mortality from sepsis [79]. It has become increasingly apparent that in many patients there is a long delay in both the recognition of sepsis and the initiation of appropriate therapy. This has been demonstrated to translate into an increased incidence of progressive organ

failure and a higher mortality [75, 82]. Clinicians therefore need to have a high index of suspicion for the presence of sepsis. The clinical features which should heighten the index of suspicion for the diagnosis of sepsis are listed above.

Antibiotic Therapy

Empiric intravenous antibiotic therapy should be started as soon as possible and within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. In a retrospective analysis of 2,600 patients, Kumar and colleagues demonstrated that the risk of dying increased progressively with an increase in the time to receipt of the first dose of antibiotic from the onset of sepsis induced hypotension [83]. Furthermore, there was a 5–15 % decrease in survival with every hour delay over the first 6 h. The choice of antibiotics is largely determined by the source or focus of infection, the patient's immunologic status and severity of infection, the risk of infection with a multi-drug resistant pathogen (see Chap. 17: The Pneumonias) as well as knowledge of the local microbiology and sensitivity patterns. Initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens and that penetrate into the presumed source of sepsis. Because the identity of the infecting pathogen(s) and its sensitivity pattern(s) are unknown at the time of initiation of antibiotics, in patients with severe sepsis and septic shock the initial regimen should include two or more antibiotics or an extended spectrum β-lactam antibiotic with the aim of treating all realistically possible microbial causes (see also Chap. 17). A number of studies have demonstrated that appropriate initial antimicrobial therapy, defined as the use of at least one antibiotic active *in vitro* against the causative bacteria reduced mortality when compared with patients receiving inappropriate therapy [84–86]. Once a pathogen is isolated, monotherapy is adequate for most infections; this strategy of initiating broad spectrum cover with two or more antibiotics and then narrowing the spectrum to a single agent when a pathogen is identified is known as "antimicrobial de-escalation."[87] Antimicrobial de-escalation has been demonstrated to be associated with a reduction in hospital mortality [88]. The indications for continuation of double-antimicrobial therapy include enterococcal infections and severe intra-abdominal infections. In addition, double antimicrobial therapy (3rd generation cephalosporin and macrolide) is recommended for patients with severe community acquired pneumonia and those with pneumococcal bacteremia (see Chap. 17) [89–91]. In order to rapidly achieve adequate blood and tissue concentrations, antibiotics should be given intravenously, at least initially. Dosing regimens should take into account whether the antibiotic "kills" by time-dependent kinetics (e.g. B-lactam antibiotics, vancomycin) or concentration-dependent kinetics (e.g. aminoglycoside) [85, 86, 92, 93]. The clinical effectiveness of β-lactam antibiotics and vancomycin is optimal when the concentration of the antimicrobial agent in the serum exceeds the minimum inhibitory concentration (MIC) of the infecting organism for at least 40 % of the dosing interval. In addition, antibiotic dosing should also take into account the patient's hepatic and renal function.

Fluid Therapy (See also Chap. 9)

Beyond the early administration of antibiotics, aggressive "supportive measures" may be harmful and the "***less is more***" paradigm appears applicable for the management of patients with severe sepsis. In these highly vulnerable patients, more intensive treatment may promote the chances of unwanted adverse effects and hence, iatrogenic injury [94]. Current teaching suggests that *aggressive fluid resuscitation* is the best initial approach for the cardiovascular instability of sepsis. Consequently large volumes of fluid (5–10 L) are often infused in the early stages of sepsis. There is however no human data that substantial (>30 mL/kg) fluid resuscitation reliably improves blood pressure or end-organ perfusion [95, 96]. This approach is likely to lead to "***iatrogenic salt water drowning***" with severe ARDS, AKI and death.

From a pathophysiological point of view, large volume fluid resuscitation in patients with sepsis is illogical and may worsen the hemodynamic derangements of sepsis. In patients with septic shock who are fluid responders (an increase in cardiac output with fluid boluses) vasodilatation with a fall in systematic vascular resistance has been observed following fluid resuscitation [97, 98]. A similar finding has been noted in an experimental sepsis model [99]. Hence, although the cardiac output increases, vasodilatation occurs and the blood pressure may remain unchanged [97]. Increased vascular shear stress consequent to the increase in cardiac output increases the expression of nitric oxide synthetase with increased release of nitric oxide [22]. In addition, increased cardiac filling pressures increase the release of natriuretic peptides which act synergistically with nitric oxide causing cGMP mediated vasodilatation [22]. Endotoxin enhances this vasodilatory response [100]. As cardiac filling pressures increase extra-vascular lung water (EVLW) increases, this is compounded by the increased vascular permeability characteristic of sepsis [101]. An increase in the central venous pressure (CVP) profoundly decreases microcirculatory flow and impairs renal function (see end-points of resuscitation below). The increased cardiac filling pressures consequent to large volume resuscitation increases the release of natriuretic peptides [102, 103]. Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx (see Chap. 9) [104–106]. This profoundly increases endothelial permeability. In addition, increased natriuretic peptides inhibit the lymphatic propulsive motor activity reducing lymphatic drainage [107–109]. Increased natriuretic peptides therefore act to sequestrate fluid into the interstitium. Humans/mammals have evolved over thousands of years to deal with hypovolemia; hypervolemia is a rather recent and largely "iatrogenic" condition.

Emerging data suggests that less than 50 % of septic patients who present to the ER (and are fluid naive) will be fluid responsive! As reviewed in Chap. 9 only patients who are fluid responsive should be given fluids; fluids are likely to be harmful in non-responders. This suggests that patients' fluid responsiveness status should be evaluated prior to fluid therapy. In addition, it is important to emphasize that the Frank-Starling curve is shifted downwards and to the right in sepsis, with septic patients showing a diminished response to fluid loading. Depressed left ventricular performance with a reduced response to fluid infusion in patients with sepsis and

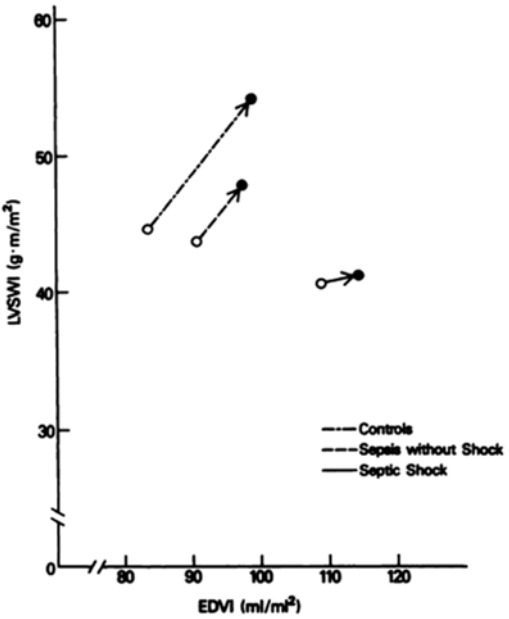

Fig. 12.3 Frank Starling relationship for control patient's and those with sepsis and septic shock. Data points plotted represent the mean pre-volume and post-volume infusion values of EDVI and LVSWI for each group. Reproduced with permission from the American College of Chest Physicians [110]

septic shock was demonstrated by Ognibene et al. in a study published in 1988 [110]. Using data obtained from a pulmonary artery catheter and radionuclide cineangiography they compared the change in left ventricular stroke work index ((LVSWI) in critically ill control subjects, patients with sepsis but without shock and patients with septic shock. The septic patients had both a reduced LVEF and increased end-diastolic volume index (EDVI) suggesting systolic LV dysfunction. However, the change in EDVI was less in the patients with sepsis and septic shock than the controls, suggesting an element of diastolic dysfunction. The LVSWI response after volume infusion (about 1,000 mL NS) was significantly less in patients with septic shock when compared with critically ill control subjects ($p<0.05$). Patients in septic shock had a minimal increase in LVSWI in response to volume infusion (see Fig. 12.3).

Due to the endothelial injury, capillary leak and increased hydrostatic pressures less than 5 % of infused crystalloid remains intravascular within 3 h after infusion resulting in an further increase in EVLW and tissue edema [111]. Tissue edema impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage and disturbs cell-cell interactions; these effects contribute to progressive organ dysfunction. These effects are pronounced in encapsulated organs, such as the liver and kidneys, which lack the capacity to accommodate additional volume without an increase in interstitial pressure, resulting in compromised organ blood flow [112]. This leads to AKI and hepatic congestion with cholestasis and impaired hepatic function. Increased EVLW (pulmonary edema) impairs gas exchange, reduces lung compliance and increases the work of breathing. Increased EVLW is a strong independent predictor of death [113–115]. Myocardial edema due to excess fluid administration compounds the myocardial

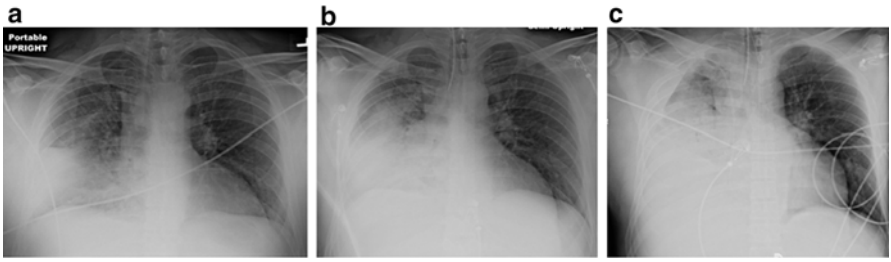

Fig. 12.4 (**a**–**c**) 44 year old male with Pneumococcal pneumonia. (**a**) Initial Chest radiograph (CXR) in emergency room; (**b**) CXR 4 h later after 4 L crystalloid (pt now intubated); (**c**) CXR 12 h after admission, after 9 L of crystalloid, central venous pressure (CVP) = 10 mmHg. Patient died 6 h later of refractory hypoxemia

dysfunction of sepsis [99]. Bowel edema results in malabsorption, ileus and bacterial translocation.

In patients with pneumonia, large volume fluid resuscitation results in severe pulmonary edema/ARDS (see Fig. 12.4). The chest radiographs presented in Fig. 12.4 represents a typical case of "*fatal iatrogenic salt water drowning*." This patient was resuscitated according to the EGDT and the Surviving Sepsis Campaign bundles, in which fluids are administered until the CVP >12 mmHg [62, 72]. We know that patients' with sepsis have damaged endothelium (especially at the site of infection, i.e. the lung) with increased permeability and that almost all the of administered crystalloid will leak into the tissues (i.e. the lung). This course of events is clearly evident from the CXR progression outlined in Fig. 12.3. Furthermore, patients with sepsis are primarily not dehydrated but suffering from vasoplegic shock with an increase in the non-stressed blood volume (veno-dilatation); it is therefore totally illogical (and stupid) to give large volumes of fluid to patients with sepsis.

The harmful effects of aggressive fluid resuscitation on the outcome of sepsis are supported by experimental studies as well as data accumulated from clinical trials [99, 116]. Multiple clinical studies have demonstrated an independent association between an increasingly positive fluid balance and increased mortality in patient with sepsis [7, 47, 114, 117–120]. In a secondary analysis of the *Vasopressin in Septic Shock Trial* (VASST), Boyd and colleagues demonstrated that a greater positive fluid balance at both 12 h and 4 days were independent predictors of death [121]. In a recent study Micek and colleagues demonstrated that a positive fluid balance at 8 days was the strongest independent predictor of hospital mortality [122]. In this study the 24 h fluid balance was 37.5 mL/kg (about 2.5 L) in the survivors compared to 55.3 mL/kg (3.9 L) in those who died. In patients with sepsis, Zang et al. demonstrated a strong correlation between the net fluid balance, the increase in BNP and death [103]. A number of studies have "paradoxically" demonstrated that a positive fluid balance was associated with an increased risk for AKI (see below; the danger of right atrial hypertension) [47]. Bouchard et al. demonstrated that in patients with AKI fluid overload was independently associated with mortality [120]. In the Fluid and Catheter Treatment Trial (FACTT) trial the conservative fluid strategy was associated with a trend towards a reduced require-

ment for renal replacement therapy [123]. There are no reported studies that have demonstrated that a liberal fluid strategy leads to improved patient outcomes [124]. The most compelling data that fluid loading in sepsis is harmful comes from "*The Fluid Expansion as Supportive Therapy* (FEAST)" study performed in 3,141 sub-Saharan children with severe sepsis [125]. In this randomized study aggressive fluid loading was associated with a significantly increased risk of death. Furthermore, there was no subgroup of patients that benefited from aggressive fluid resuscitation [126]. This study is frequently dismissed (by proponents of the Surviving Sepsis Campaign) using the argument that a study conducted in children cannot be extrapolated to adult patients [96]. This argument is absurd as studies performed in rats (who generally differ quite considerably from humans) are frequently extrapolated to humans yet the FEAST study was done in humans, albeit little ones.

In patients with sepsis almost 100 % of infused crystalloids will filter into the interstitium. This combined with decreased lymphatic drainage results in severe tissue edema and increased extravascular lung water.

THIS DOES NOT SEEM TO BE A GOOD THING or to MAKE ANY SENSE!

In contemporary sepsis studies between 1.5 and 4.0 L of fluid were given in the first 24 h [103, 122, 127]. This compares to 4.9 ± 2.9 and 13.4 ± 6.3 L at 6 and 72 h respectively in the intervention arm of the Early Goal Directed Therapy (EGDT) study [62]. In the Australasian Resuscitation of Sepsis Evaluation (ARISE) study which used the same entry criteria as the EGDT study, 2.2 ± 1.9 L of fluid were given in the first 6 h [127]. The hospital mortality was 23 % in the ARISE study compared to 30 % in the intervention arm of the EGDT study. In the VASST study optimal survival occurred with a positive fluid balance of approximately 3 L at 12 h [121]. In some patients, hypotension and tachycardia do resolve with limited fluid resuscitation. However, fluids alone will not reverse the hemodynamic instability of patients with more severe sepsis; in these patients' fluids alone are likely to exacerbate the vasodilatory shock and increase the capillary leak, tissue edema and organ dysfunction. Based on these data we suggest limiting the initial fluid resuscitation to approximately 20 mL/kg. Furthermore, we recommend this fluid be given as 250–500 mL fluid challenges. Ideally, all patients should undergo assessment of

fluid responsiveness prior to receiving any fluid. These recommendations differ fundamentally from those of the most recent Surviving Sepsis Campaign Guidelines which suggest "*a minimum fluid challenge of 30 mL/kg*" and that "*greater amounts of fluid may be needed in some patients* (Grade 1C)." [72] The EGDT protocol has no limit on the amount of fluid given; the target is a CVP >8 mmHg (12–15 mmHg if on a ventilator) regardless of the amount of fluid given [62]. This is likely to be a highly lethal approach as discussed below (see end-points of resuscitation). The fluid of choice in almost all septic patients is Ringers Lactate (this is reviewed in detail in Chap. 9). An infusion of 20 % albumin, to help restore the endothelial glycocalyx, may have a role in resuscitated patients with septic shock who have a low serum albumin (< 3 g/dL) (see Chap. 9) [128].

It is noteworthy that the amount of fluid given in the first 6 h and from 7 to 72 h was significantly less in the ProCESS EGDT patients than in the Rivers' EGDT patients (See Table 12.2). As patients were resuscitated according to the same protocol this would appear to be odd. However, it should be noted that the mean CVP at 6 h was 13.8 ± 4.4 in the Rivers' EGDT group. Assuming a normal distribution, 50 % of patients in the Rivers' EGDT would have achieved CVPs greater than the mean value of 13.8 mmHg. Thus most patients in the Rivers' EGDT study had CVPs outside the stated goal (>8–12 mmHg). It is possible that the enormous amount of fluid administered in the Rivers study partly accounted for the mortality difference between the EGDT arms of the Rivers' and ProCESS studies. Furthermore, the use of vasopressors in the first 6 h of EGDT was significantly greater in ProCESS than in the Rivers' study; this suggests the earlier use of pressors for blood pressure support in ProCESS (as we currently suggest; see below and Fig. 12.5)

The optimal time to start a vasopressor agent in patients with sepsis has not been well studied. However, after receiving 20 mL/kg of crystalloid it seems unlikely that additional fluid boluses will increase the mean arterial pressure (MAP) in patients who remain hypotensive [95, 96]. We would therefore recommend the initiation of a vasopressor agent (norepinephrine) in patients who remain hypotensive (MAP <65 mmHg) after receiving 20 mL/kg of crystalloid solution. Additional fluid boluses (250 cm^3) may be given once the "target" norepinephrine dose is achieved (about 0.1–0.2 μg/kg/min) and this is should be based on a dynamic assessment of volume responsiveness and ventricular function (see Fig. 12.5). We suggest using the passive leg raising manoeuvre (PLR) coupled with minimally invasive cardiac output monitoring to assess volume responsiveness (see Chap. 9).[129, 130] In cases of life-threatening hypotension (diastolic blood pressure <40 mmHg), treatment with vasopressors should be started concurrently with fluid administration [131]. As discussed in Chap. 9, Ringers Lactate is the fluid of choice. An albumin infusion should be considered in patients with a albumin concentration <3 g/dL.

Table 12.2 Contrasting use of fluids and vasopressors (and mortality) in the EGDT arms of the Rivers' and ProCESS studies

Study	Fluid 0–6 h (mL)	Fluid 7–72 h (mL)	Fluid 0–72 h (mL)	Vasopressors (%) 0–6 h	60 day mortality (%)
Rivers EGDT	4,981	8,625	13,443	27.4	44.3
ProCESS EGDT	2,805	4,428	7,220	54.9	21

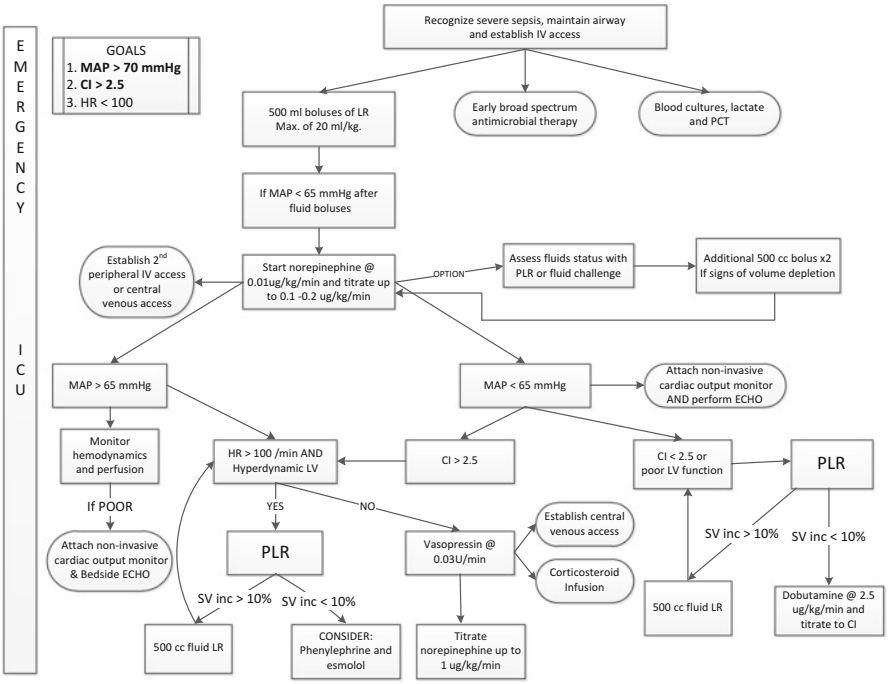

Fig. 12.5 Suggested initial approach to the management of patients with severe sepsis and septic shock. *MAP* mean arterial pressure, *LR* Lactated Ringers solution, *CI* cardiac index, *LV* left ventricle, *PLR* passive leg raising, *PCT* procalcitonin

Vasopressors and Inotropic Agents

A low MAP is a reliable predictor for the development of organ dysfunction. When the MAP falls below an organs autoregulatory threshold, organ blood flow decreases in an almost linear fashion [132]. Since the autoregulatory ranges of the heart, brain and kidney are above 60 mmHg [132], a MAP below this level will likely result in organ ischemia. An analysis of a large ICU database demonstrated that the risk of kidney injury and death increased sharply as the MAP fell below 60 mmHg [133]. Varpula and colleagues studied the hemodynamic variables associated with mortality in patients with septic shock [134]. These authors calculated the area under the curve (AUC) of various MAP thresholds over a 48 h time period. The highest AUC values were found for a MAP <65 mmHg (AUC 0.83, 95 % CI, 0.772–0.934). Due to the shift of the autoregulatory range (to the right) in patients with chronic hypertension a higher MAP may be required in these patients. The *Assessment of Two Levels of Arterial Pressure on Survival in Patients With Septic Shock* (SEPSISPAM) is a multicenter randomized controlled trial recently completed in France [135]. In this study patients with septic shock were randomized to achieve a target MAP of 65–70 or 80–85 mmHg. The primary outcome was 28 day mortality. Secondary outcomes

included 90 day mortality and organ failures. *A priori* a secondary analysis was planned in patients with and without a history of hypertension. Overall there was no difference in either primary or secondary end-point between the two treatment groups. However the incidence of organ failures (particularly renal dysfunction) was higher in the sub-group of patients with chronic hypertension in the lower MAP group. Furthermore, much like the Varpula study, the time below the 65 mmHg (but not 80 mmHg) threshold was an independent predictor of death. It is important to recognize that the MAP in the 65–70 mmHg group exceeded the target threshold, with the average MAP being about 75 mmHg. Panwar et al. investigated the relationship between the mean perfusion pressure (MPP) deficit and the risk of AKI in 51 shocked patients [136]. The MPP deficit was calculated as the difference between the patients estimated basal MPP and the MPP achieved in the ICU. These authors demonstrated that the risk of AKI was related to the degree of the MPP deficit and the time spent with a >20 % MPP deficit. Based on these data we suggest targeting an initial MAP of 70 mmHg in patients with septic shock. In those patients with a history of chronic hypertension we would suggest targeting a slightly higher MAP (75–80 mmHg) [136].

In patients with sepsis, norepinephrine increases blood pressure, as well as cardiac output, renal, splanchnic, cerebral and microvascular blood flow while minimally increasing heart rate [137–139]. Furthermore, while not widely appreciated, norepinephrine causes α-1 adrenergic receptor mediated veno-constriction; this effect increases the stressed blood volume and increases the mean systemic pressure (Pms) with a significant increase in venous return and cardiac output [140, 141]. It should be noted that approximately 60 % of the blood volume is in the veins; the unstressed blood volume increases with venodilation (see Fig. 12.6) Cardiac output (CO) equals venous return (VR). VR is related to the difference between Pms and CVP. Therefore, one can increase CO by increasing Pms and/or *reducing the CVP*, according to the following equation [142]:

$$\mathrm{CO} = \mathrm{VR} = \left(\mathrm{Pms} - \mathrm{CVP}\right) / \mathrm{Rvr}$$

The early use of norepinephrine restores blood pressure and organ blood flow with a significant fluid sparing effect. Hamzaoui et al. have demonstrated that the early administration of norepinephrine largely reverses the hemodynamic abnormalities of severe vasodilatory shock [143]. Abid and colleagues demonstrated that the early use of norepinephrine in patients with septic shock was a strong predictor of survival [144]. In situations in which norepinephrine is not available epinephrine is a suitable alternative agent [145, 146]. In patients with septic shock dopamine is associated with an increased mortality when compared to norepinephrine and is best avoided [147, 148]. Similarly phenylephrine is not recommended, as in experimental models it decreases cardiac output as well as renal and splanchnic blood flow [149]. Furthermore, phenylephrine has not been well studied in patients with sepsis.

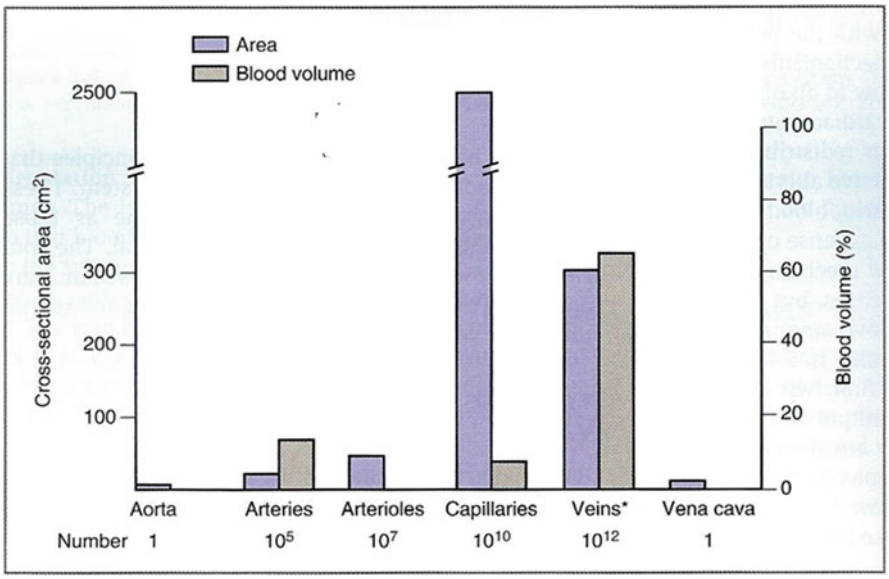

Fig. 12.6 Distribution of blood volume throughout the circulatory system

In patients who remain hypotensive or have evidence of inadequate organ perfusion despite fluid optimization and an adequate dose of norepinephrine (approximately 0.1–0.2 μg/kg/min) we recommend further hemodynamic assessment to exclude ventricular dysfunction. Global biventricular dysfunction has been reported in up to 60 % of patients with septic shock [26, 30]. Ventricular function is best assessed by bed-side echocardiography and confirmed by minimally invasive cardiac output monitoring. Dobutamine at a starting dose of 2.5 μg/kg min is recommended in patients with significant ventricular dysfunction (milrinone is an alternative agent) [30]. The dose of dobutamine should be titrated to hemodynamic response as determined by minimally invasive cardiac output monitoring [30, 150]. This approach differs from the EGDT protocol which suggests the use of an inotropic agent based on the CVP (> 8–12 mmHg) and a central venous oxygen saturation ($ScvO_2$) of <70 % (without an evaluation of ventricular function or cardiac output) [62]. Bouferrache et al. demonstrated a poor agreement in the use of inotropic agents when treatment was guided by transesophageal echocardiography as compared to the EGDT protocol in patients presenting with septic shock [151].

Contrary to well established dogma, it appears to be reasonably safe to initiate norepinephrine via a peripheral venous catheter with few complications [152]. This is a remarkable observation as the greatest "resistance" to the early initiation of norepinephrine is the requirement for a central line. Placement of a second 18 or 20 gauge peripheral catheter will allow for the early initiation of norepinephrine. Once the dose reaches the threshold of about 0.2 μg/kg/min it is recommend to insert a central venous catheter at this time. Furthermore, central venous catheterization is recommend with the use of multiple vasopressor agents and in patients who require

Extravasation Injuries from Vasopressors
Prevention

- Avoid the hand/wrist and ante-cubital fossa
- Avoid using "Crappy" IV's
- A protocolized extremity check
- Antidotes and a worksheet in the room with the patient.
- 10 mg of Phentolamine Mesylate can be added to each liter of solution containing norepinephrine. The pressor effect of norepinephrine is not affected.

Step I

If the patient is relying on the agent for their hemodynamics, switch the pressor to another IV or place an immediate central line.

Step II

Do not pull the cannula yet

Step III

Suck out as much fluid as you can

Step IV

Administer subcutaneous phentolamine mesylate (Regitine) using a 25 G or smaller needle. Phentolamine is available as 5 mg per 1 mL vials. Place in 9 mL of NS. A dose of 0.1–0.2 mg/kg (up to a maximum of 10 mg) should then be injected through the catheter and subcutaneously around the site. Administer as soon as the extravasation is detected, even if the area initially looks just a little white or OK. You should see near immediate effects; otherwise consider additional dose. Now pull the catheter.

Step V

Consult Plastics

vaso-pressors for >48 h. Extravasation is a rare complication of well managed peripheral venous catheters; if this should occur the the steps outlined above are recommended.

Vasopressin reverses the "relative vasopressin deficiency" seen in patients with septic shock and increases adrenergic sensitivity [22, 153]. Terlipressin is an alternative (Terlipressin is not FDA approved in the US) [154, 155]. Vasopressin may be effective in raising blood pressure in patients with refractory hypotension however the optimal time to initiate this drug is not clear. The VASST trial randomized patients with septic shock to norepinephrine alone or norepinephrine plus vasopressin at 0.03 units/min [156]. By intention to treat analysis there was no difference in outcome between groups. However, an *a priori* defined subgroup analysis demonstrated that survival among patients receiving <0.2 μg/kg/min norepinephrine at the time of randomization was better with the addition of vasopressin than those receiving norepinephrine at a dose >0.2 μg/kg/min. We therefore suggest the addition of vasopressin at a dose of norepinephrine between 0.1 and 0.2 μg/kg/min. Thereafter

the dose of norepinephrine should be titrated to achieve a MAP of at least 65 mmHg. It is important to emphasize that vasopressin is administered as a fixed dose of 0.03 units/min and should not be up-titrated. Our suggested treatment algorithm for the hemodynamic stabilization of patients with septic shock is provided in Fig. 12.5. It is however important to emphasize that "*patients are not airplanes and doctors are not pilots"*;[157] each patient is unique, with a unique response to invading pathogens and a unique response to treatment, therefore this algorithm must be dynamically adapted to each patient as his/her clinical course evolves.

B-Blockers and Phenylephrine in Septic Shock

As part of the stress response in patients with sepsis and septic shock there is massive sympathetic activation with very high levels of circulating catecholamines (see Chap. 13) [158]. Septic patients often have an elevated heart rate, even after excluding common causes of tachycardia such as hypovolemia, fever, pain, and agitation. In volume depleted patients tachycardia constitutes the main mechanism that compensates for the decrease in stroke volume. However, tachycardia persisting after fluid resuscitation may indicate an inappropriate degree of sympathetic activation. Persistent tachycardia has been demonstrated to be a poor prognostic sign in patients with sepsis [27]. In 1987 Parker and colleagues reported that an initial heart rate of <106 beats/min and a heart rate at 24 h of <95 beats/min were strong predictors of survival [159]. In a retrospective analysis of critically ill patients with a high risk of cardiac complications, a heart rate >95 beats/min was associated with a greater occurrence of major cardiac events and cardiac death (48.7 % vs 13.3) [160]. These factors have led investigators to consider the use of β-blockers in the management of "fully resuscitated" septic patients with persistent tachycardia [161, 162]. However, reducing heart rate with β-blockers in the early phase of septic shock may potentially lead to an inappropriately low cardiac output with a consequent decrease in organ blood flow increasing the risk of organ failure.

Morelli et al. have investigated the role of esmolol infusion (short acting β1-selective β blocker) in "resuscitated" patients with septic shock patients requiring norepinephrine to maintain a MAP of at least 65 mmHg despite "appropriate" fluid resuscitation, and who had a persistent heart rate >95 beats/min [163]. The esmolol was titrated to achieve a heart rate between 80 and 94 bpm. In their pilot study of 25 patients, they demonstrated that although there was a significant decrease in cardiac index, microvascular flow index (MFI) increased [163]. In a followup study, using the same inclusion criteria, these authors randomized 77 patients to receive a continuous infusion of esmolol and 77 patients to standard treatment [164]. Twenty-eight day mortality was 49.4 % in the esmolol group vs 80.5 % in the control group (HR 0.39; CI 0.26–0.59; $p<0.001$). In the patients receiving esmolol there was a significant increase in the LVSWI and SVI. It is important to emphasize that a highly select group of patients were enrolled into this study; these patients may represent only a small fraction of patients presenting with sepsis. The mortality in the control

group was higher than that of any study published in the last two decades (even higher than the Rivers' EGDT control arm). Inexplicably, the patients in the control group received on average 21.2 L of fluid during the first 96 h. Patients in the esmolol group received on average 17.9 L of fluid in the first 96 h, which was significantly less than the control group ($p<0.001$) and may partly explain the outcome difference. Furthermore, echocardiography was not performed and it is therefore unclear how many patients had severe isolated diastolic dysfunction. In addition to attenuating the stress response, β-blockers modulate cytokine production, decrease energy expenditure and modulate protein, fat and carbohydrate metabolism.

This data suggests that β-blockers should be avoided in the initial resuscitation of patients with severe sepsis/septic shock, in patients who are fluid responsive and in patients with predominant systolic LV dysfunction. β-blockers would appear to have a role in tachycardic septic patients with predominant LV diastolic dysfunction. Furthermore, it appears to be counter intuitive to simultaneously use an infusion of norepinephrine (β1, β2, α1 agonist) and esmolol. In this situation it would appear more rational to use phenylephrine (α1 agonist) to achieve arterial and venoconstriction together with esmolol (for improvement of diastolic dysfunction) (see Fig. 12.5). Only a short acting β-blocker should be used (esmolol), its dose closely titrated and the effects of this combination on cardiac output, blood pressure and SVI be closely monitored (see case at end of chapter).

Resuscitation End-Points

A large number of hemodynamic, perfusion, oxygenation and echocardiographic targets have been proposed as resuscitation goals in patients with severe sepsis and septic shock [72, 151, 165]. Most of these targets, however, are controversial and not supported by outcome data. The Surviving Sepsis Campaign guidelines recommends a CVP of 8–12 mmHg (12–15 mmHg if mechanically ventilated), a central venous oxygen saturation ($ScvO_2$) >70 % and a urine output >0.5 mL/kg/h as targets for resuscitation [72]. As discussed in Chap. 9 (and below) the CVP should not be used to guide fluid therapy. The use of $ScvO_2$ to guide the resuscitation of septic patients is equally problematic. Septic patients usually have a normal or increased $ScvO_2$ due to reduced oxygen extraction [166, 167]. Indeed, a $ScvO_2$ >70 % is considered a diagnostic criterion for severe sepsis [6]. In a large, multicenter, goal directed study conducted by Pope et al., a high (>90 %) but not a low (<70 %) initial $ScvO_2$ was an independent predictor of death [168]. In a paper by Nee and Rivers which reviewed the outcome of patients enrolled into the Surviving Sepsis Campaign database, they conclude that the "*attainment of a CVP of >8 mmHg and* $ScvO_2$ *of >70 % did not influence survival in patients with septic shock*" [169]. The ProCESS study demonstrated that titrating therapy to achieve a target $ScvO_2$ did not improve outcome, and indeed appeared to be harmful in the sickest group of patients [80]. While urine output may be a valuable marker of renal perfusion in hypovolemic states, this clinical sign becomes problematic in sepsis associated AKI where experimental

models show that oliguria occurs in the presence of marked global renal hyperemia [170–172]. Titration of fluids to urine output may therefore result in fluid overload.

The Surviving Sepsis Campaign guideline recommends "*targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion*" [72]. This recommendation is based on the notion that an elevated lactate is a consequence of tissue hypoxia and inadequate oxygen delivery [6] and is "supported" by two studies which used "lactate clearance" as the target of resuscitation [173, 174]. However, the concept that sepsis is associated with tissue hypoxia is unproven and likely incorrect (see below and Chap. 13) Increasing oxygen delivery in patients with sepsis does not increase oxygen consumption [175–177]. Previous studies have demonstrated that targeting supramaximal oxygen delivery does not improve outcome and may be harmful [178, 179].

These data would suggest that achieving a MAP of at least 65 mmHg should be the primary target in the resuscitation of patients with septic shock. Furthermore, while attempts to achieve a supranormal cardiac index may be potentially harmful, we would suggest targeting a normal cardiac index (> 2.5 L/min/m^2) [178]. While a falling arterial lactate concentration is a sign that the patient is responding to therapy (attenuation of the stress response), titrating therapy to a lactate concentration is devoid of scientific evidence [176, 177]. Additional end-points of resuscitation remain unproven at this time.

The Dangers of a HIGH CVP

Not only has the CVP failed as a useful measure for the assessment of preload and fluid responsiveness [180], but a CVP >8 mmHg is independently associated with a higher mortality and increased risk of AKI in patients with sepsis [121, 181]. This suggests that the CVP component of the 6-h resuscitation bundle as widely promoted by the Surviving Sepsis Campaign may lead to harm [72].

It is important to note that a **normal CVP is ZERO** and not 8–12 mmHg as the Surviving Sepsis Campaign might lead some to believe (see Fig. 12.7) [72].

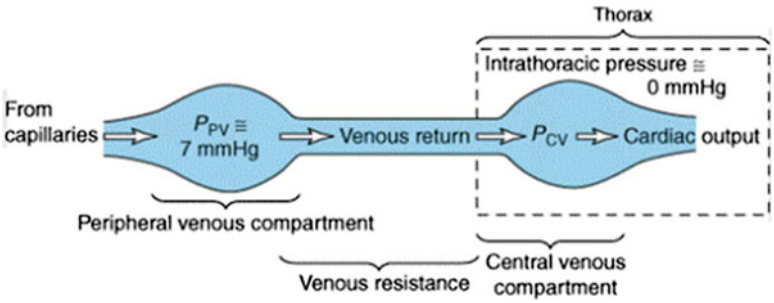

Fig. 12.7 Normal venous pressures

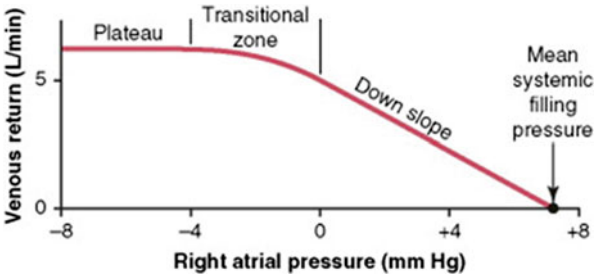

Fig. 12.8 Relationship between the central venous pressure, the mean systemic filling pressure and venous return [182]. Reproduced from Guyton and Hall Textbook of Medical Physiology, with permission from Saunders Elsevier

Furthermore, the mean systemic filling pressure (MSFP) is 7 mmHg with a normal venous pressure slightly less than 7 mmHg. The gradient between MSFP and CVP is the pressure that drives venous return. As the CVP increases the pressure gradient for venous return falls and cardiac output falls (see Fig. 12.8). When the ability of the circulation to increase the MSFP is overcome and the CVP equals the MSFP, the cardiac output falls to zero [182].

In addition to influencing venous return, a high CVP is transmitted backwards increasing venous pressure. The increase in venous pressure has a profound effect on microcirculatory flow and organ function. The kidney is particularly affected by congestion and increased venous pressure, which leads to increased renal subcapsular pressure and lowered RBF and glomerular filtration rate (GFR) [124]. Furthermore, increased renal interstitial pressure may collapse intrarenal collecting lymphatics which compromise lymph flow [183]. The detrimental effect of high venous pressure on renal function was established by F.R Winton in an elegant set of experiments performed in 1930s [184]. This investigator attached the kidneys of a dog to a heart-lung circulation by means of cannulae inserted into the artery and veins of kidneys and then independently altered venous and arterial pressure. Dr Winton demonstrated that increasing venous pressure dramatically decreased urine production related to an increase in intratubular pressure and a decrease in GFR. More recently, Legrand and colleagues investigated the association between hemodynamic variables and AKI in patients with sepsis [181]. In this study the CVP was the only hemodynamic variable associated with the development of AKI; cardiac output, ScvO2 and MAP were unable to predict the development of AKI. These authors noted a linear relationship between increasing CVP and AKI; there was a trend for higher CVP to be associated with worse renal outcome for all levels of CVP above 4 mmHg, with a CVP of 15 mmHg being associated with an 80 % risk of new or persistent AKI, compared to approximately 30 % at a CVP of 6 mmHg. Similarly, in patients with acute decompensated heart failure, Mullens et al. demonstrated a near linear relationship between increasing CVP and worsening renal function [185]. In this study worsening renal function occurred significantly less frequently in patients with a CVP <8 mmHg. Furthermore, similar to the findings of Legrand and colleagues, the CVP was the only hemodynamic parameter that predicted worsening renal failure, with the CI, systolic blood pressure and PCWP being similar between those patients who maintained renal function as compared to those

with worsening renal function. In a subanalysis of the ESCAPE trial, Nohria et al. demonstrated a significant correlation between baseline renal function and the CVP, there was, however no correlation between baseline renal function and CI, PCWP or SVRI [186]. In patients with pulmonary hypertension, Damman and colleagues demonstrated that increased CVP was independently associated with a reduction of GFR [187]. These data suggest that a high CVP independent of cardiac output increases the risk for "congestive kidney failure." Most clinicians fluid load patients with oliguria; this intervention sets into motion a vicious cycle, with fluid loading further increasing in renal venous pressure with a further decline in urine output. This observation may partly explain the findings from the SOAP study in which septic patients without AKI had a significantly lower cumulative fluid balance than those with AKI [47]. Furthermore, in this study the mean daily fluid balance was significantly more positive among non-survivors versus survivors with AKI. Similarly, in those patients receiving renal replacement therapy (RRT) mean daily fluid balance was significantly more positive in those patients who died. In an analysis of the VASST study, Boyd et al. demonstrated that at 12 h after enrollment, patients with a CVP <8 mmHg had the lowest mortality rate followed by those with central venous pressure 8–12 mmHg [121]. The highest mortality rate was observed in those with central venous pressure >12 mmHg. Furthermore, contrary to the overall effect, patients whose CVP was <8 mmHg had improved survival with a more positive fluid balance.

In addition to increasing renal venous and interstitial pressure, a high CVP will result in an increase in hepatic and intestinal venous pressure causing hepatic and intestinal congestion and impaired microcirculatory flow. Indeed, in a study of 70 patients with sepsis, Vellinga and colleagues demonstrated that the sublingual microvascular flow index (MFI) and percentage of perfused vessels (PPV) was significantly lower with a patients with a high CVP (>12 mmHg) than a low CVP: 1.44 ± 0.94 vs. 1.89 ± 0.91, $p = 0.006$; and 88 ± 21 vs. 95 ± 8 %, $p = 0.006$) [188]. The CI, MAP and perfusion pressure (MAP-CVP) did not differ significantly between the high and low CVP groups. In a multivariate logistic regression analysis, the only significant predictor for an abnormal MFI was a CVP >12 mmHg. Because microcirculatory driving pressure is the difference between post-arteriolar minus venular pressure, a relatively mild increase in CVP may considerably influence the capillary perfusion pressure and microcirculatory flow [188]. As the pressure drop in the vascular system occurs upstream at the level of small arterioles (resistance vessels), the microcirculation is considered a low pressure compartment (see Fig. 12.9). Therefore, mean capillary pressure is much closer to venous than to arterial pressure. Therefore, as long as the MAP is within an organs autoregulatory range, the CVP becomes the major determinant of capillary blood flow. This suggests that venous pressure has a much greater effect on microcirculatory flow than the MAP.

Increased cardiac filling pressures (CVP) increase the release of natriuretic peptides [102, 103]. Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx [104–106]. This profoundly increases endothelial permeability. In addition, increased natriuretic peptides inhibit the lymphatic propulsive motor activity reducing lymphatic drainage [107–109]. A high CVP may therefore

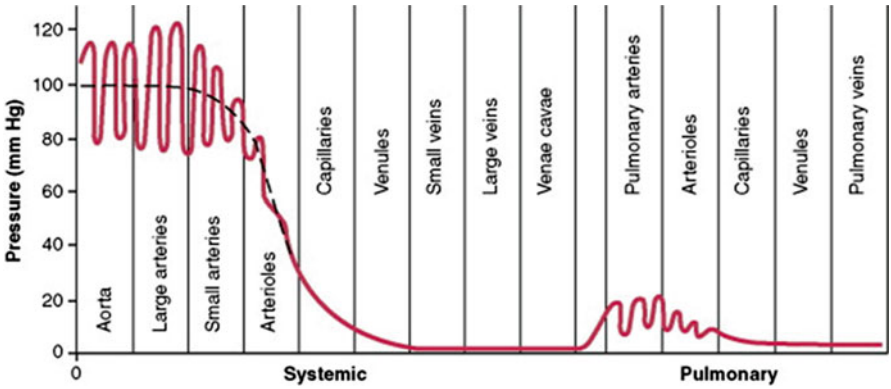

Fig. 12.9 Pressures through the circulatory system [189]. Reproduced from Guyton and Hall Textbook of Medical Physiology, with permission from Saunders Elsevier

increase (compound) tissue edema independent of the effect on venous pressure. All these studies provide highly suggestive data that a CVP >8 mmHg might contribute to increasing the risk of organ dysfunction, AKI and death in patients with sepsis.

The CVP depends on the patient's volemic status, right heart function and surrounding venous pressure increased by mechanical ventilation. While the CVP cannot predict fluid responsiveness and is a poor indicator of intravascular volume status, in general the CVP increases with zealous fluid administration [62, 121]. In addition, "iatrogenic" right ventricular dysfunction is common in ICU patients and may result in further increases in CVP. Acute cor pulmonale (with increased CVP) is common in patients receiving mechanical ventilation with high mean airway pressures. Indeed, in patients with ARDS Vieillard-Baron and colleagues reported an incidence of cor pulmonale of 56 % when plateau pressures were >35 cm H_2O, 32 % when plateau pressures were between 27 and 35 cm H_2O and 13 % when plateau pressures were <27 cm H_2O [190]. Consequently, these authors have postulated that the so-called "lung protective strategy" may better be referred to as the heart (and kidney) protective strategy [190]. These data suggest that in patients with a central venous catheter in place (not femoral) [191] and hemodynamic instability, that the CVP should be monitored with all attempts made to keep the CVP <8 mmHg (what a remarkable turn of events!!)

Does Tissue Hypoxia and Mitochondrial Dysfunction Exist in Sepsis?

It is widely believed that tissue hypoxia is an important factor leading to organ dysfunction and death in patients with severe sepsis. There is however scant data that tissue hypoxia actually occurs or that cellular energy crises develops. While

sepsis is considered to be hypermetabolic condition oxygen consumption and energy expenditure are broadly comparable to that of normal people, with energy expenditure decreasing with increasing sepsis severity [192–194]. Therefore there is no requirement that oxygen delivery increase with sepsis. Ronco and colleagues determined the critical oxygen delivery threshold for anaerobic metabolism in septic and nonseptic critically ill humans while life support was being discontinued [195]. In this study there was no difference in the critical oxygen delivery threshold between septic and non-septic patients. The critical oxygen delivery threshold was 3.8 ± 1.5 mL/min/kg (266 mL/min in a 70 kg patient); assuming a hemoglobin concentration of 10 g/L this translates into a cardiac output of approximately 2 L/min. It is likely that only pre-terminal moribund patients with septic shock would have such a low cardiac output.

Hotchkiss and Karl in a seminal review published by over 20 years ago demonstrated that cellular hypoxia and bioenergetic failure does not occur in sepsis [196]. Using phosphorus 31 NMR spectroscopy to monitor concentrations of high energy phosphates these authors demonstrated normal concentrations of ATP in the leg muscle of septic rats [197]. Jepson et al. confirmed these findings [198]. Similarly, Solomon et al. demonstrated that sepsis-induced myocardial depression was not due to bioenergetic failure [199]. Using the hypoxic marker [^{18}F]Fluoromisonidazole, Hotchkiss et al. were unable to demonstrate evidence of cellular hypoxia in the muscle, heart, lung and diaphragm of septic rates [200]. Additional studies support these findings. In a porcine peritonitis model Regueira et al. demonstrated a significant increase in arterial lactate concentration yet there was no significant change in hepatic and muscle mitochondrial oxidative function [201]. Furthermore hypoxia-inducible factor 1 alpha (HIF-1α) expression was not detected in any of the organs studied. Using polarographic needle electrodes Boekstegers and coworkers were unable to demonstrate skeletal muscle hypoxia in the bicep muscle of patients with sepsis [202]. More recently, tissue oxygen saturation (StO_2) has been measured non-invasively in patients with septic shock using near-infrared spectroscopy. While the StO_2 in these studies had prognostic value, the StO_2 levels were not in the hypoxic range [203–205]. In the study by Pareznik et al. thenar StO_2 was comparable between volunteers, and patients' with infection, severe sepsis and septic shock [206]. Some investigators, however, have demonstrated an increased tissue oxygen tension in the organs of animals and patients with sepsis [207, 208]. Despite "microcirculatory failure", Boekstegers et al. demonstrated abnormally high skeletal muscle oxygen tension in septic patients with organ failure [209]. The high muscle oxygen tension was associated with high whole body oxygen delivery and low whole body oxygen extraction.

In addition to hypoxic hypoxia it has been suggested that mitochondrial dysfunction is an important factor leading to organ dysfunction and failure in sepsis [210]. Fink coined the term "cytopathic hypoxia" to describe this condition [211]. Multiple defects in mitochondrial function have been described in animal models and patients with sepsis. These include abnormal autophagy, decreased biogenesis (mitochondrial numbers), decreased activity of the components of the electron transport chain (particularly complex I) and uncoupling of oxidation

phosphorylation [210–218]. Increased nitric oxide and deceased glutathione have been postulated to play a pathogenetic role in these abnormalities [212, 216, 217]. However, despite over two decades of research, this topic remains controversial [215, 219]. An extensive review by Jeger et al. concluded that "*the data does not support the view that mitochondrial dysfunction is the general denominator for multiple organ failure in severe sepsis and septic shock*" [220]. However, mitochondrial dysfunction is common in patients with established multi-system organ failure and those dying from sepsis [210, 212, 220]. It is likely that as sepsis evolves the release of inflammatory mediators induce mitochondrial inhibition [215]. This may explain the progressive reduction in tissue oxygen consumption associated the rise in tissue oxygen tension as sepsis progresses. In these patients it is unclear if the mitochondrial dysfunction plays a role in the development of organ failure or is merely part of the hibernation process [215, 219].

Blood Transfusion

The 2012 Surviving Sepsis Campaign Guidelines state that "*during the first 6 h of resuscitation, if $ScvO_2$ is less than 70 % …then dobutamine infusion… or transfusion of packed red blood cells to achieve a hematocrit of greater than or equal to 30 % in attempts to achieve the $ScvO_2$ goal are options"* [72]. In septic patients, RBC transfusions do not acutely increase tissue oxygen uptake; paradoxically, they have been demonstrated to impair microcapillary flow and tissue oxygenation (see Chap. 38) [175]. In addition, the release of cell-free hemoglobin from banked blood may be particularly deleterious in septic patients [221, 222]. A recent study by Dr. Dellinger's Group demonstrated that "*transfusion of PRBCs was associated with worsened clinical outcomes in patients with septic shock treated with EGDT*" [223]. Blood transfusions are associated with an increased risk of secondary infections, MODS and death and should only be considered in patients with a hemoglobin <7 g/dL [224, 225].

Corticosteroids

The use of low-dose corticosteroids in patients with severe sepsis remains controversial [226]. It has been proposed that inadequate cellular glucocorticoid activity (Critical Illness Related Corticosteroid Insufficiency) due to either adrenal suppression or glucocorticoid tissue resistance results in an exaggerated and protracted proinflammatory response [227]. In addition to down regulating the proinflammatory response, corticosteroids may have additional beneficial effects including increasing adrenergic responsiveness [228] and preserving the endothelial glycocalyx [229]. Since corticosteroids enhance local immune defences but reduce global NF-kappa B expression and cause a predominant TH2 immunosuppressive state, steroids are likely to be beneficial early in the course of the disease but likely to compound the immunosuppression when given later in the course of sepsis. The time dependent initiation of the use of corticosteroids has not been taken into

consideration in those studies (and meta-analyses) which have analyzed the benefits/risk of steroids in sepsis. Park et al. who in a retrospective analysis of 178 patients with septic shock found that corticosteroids were only of benefit if given within 6 h after the onset of septic shock-related hypotension [230]. In the *Corticosteroid Therapy of Septic Shock Study* (CORTICUS), the initial time frame for the initiation of corticosteroids was 24 h, which was then increased to 72 h [231]. It is further important to recognize that in the CORTICUS study over 60 % of the patients were surgical patients. It has now been well established that surgery induces an immunosuppressive TH2 state and that this occurs within hours of surgery [232]. Post-surgical patients who develop sepsis remain in a predominant TH2 state [232]. It would therefore appear counterproductive to give septic post-surgical patient corticosteroids as this is only likely to compound the immunosuppressive state and increase the risk of secondary infections (as was demonstrated in the CORTICUS study). While the mortality benefit of corticosteroids in septic shock is controversial, low-dose hydrocortisone has been demonstrated to significantly reduce vasopressor dependency with a favorable side effect profile [226, 233]. Furthermore, the combination of low dose corticosteroids and vasopressin has been associated with decreased mortality and organ dysfunction in patients with septic shock [234–236]. Based on these data we would suggest treatment with hydrocortisone concomitant with the initiation of vasopressin for the management of severe vasodilatory septic shock.

Source Control

It has been known for centuries that, unless the source of the infection is controlled, the patient cannot be cured of his/her infective process and that death will eventually ensue. It is important that specific diagnoses of infection that require emergent source control be made in a timely manner (e.g., necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction) and surgical consultation be immediately obtained [72, 237]. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess) [72, 238]. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established [239].

Case Example

38 year old obese female with Guillain-Barré Syndrome requiring mechanical ventilation who developed ventilator associated pneumonia (see Tables 12.3 and 12.4).

Table 12.3 Evolution of hemodynamic profile over time

	Time 1	Time 2	Time 3
Heart rate beat/min	142	138	96
Blood pressure mmHg	110/55	108/58	115/65
CI L/m2	3.1	3.0	3.3
SVI mL/m2	22	21	34
PPV (%)	15	14	8
PLR Δ SVI	+2 %	–	–
Fluid Challenge Δ SVI	−7 %	–	–
Norepinephrine μg/min	12	–	–
Phenylephrine μg/min	–	150	150
Esmolol μg/kg/min			50

Table 12.4 Echocardiographic variables at Time 1 and Time 3

	Time 1	Time 3
LV diastolic diameter (N: 3.6–5.4 cm)	3.7	4.6
LV systolic diameter (N: 2.3–4.0 cm)	2.1	2.7
Mitral E to A (10–1.5)	0.71	1.1
E' velocity (>8 cm/s)	7.1	13.6

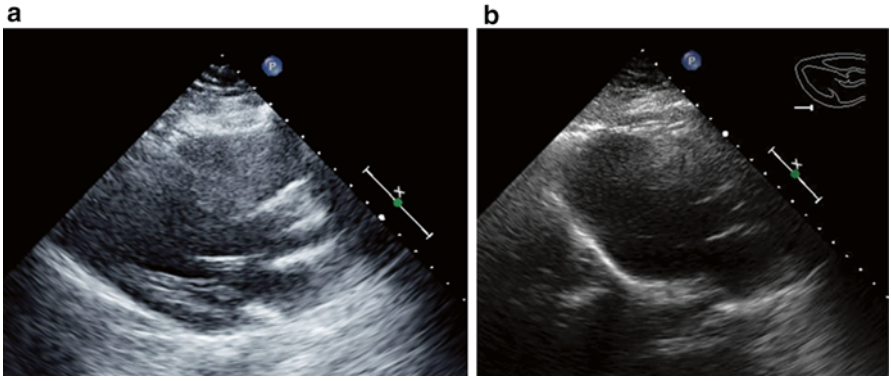

Fig. 12.10 Bedside ECHO's. (**a**) On norepinephrine (time 1); (**b**) on phenylephrine and esmolol (time 3)

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Chapter 13
The Stress Response, Stress Hyperglycemia and Stress Hyperlactemia

Any intelligent fool can make things bigger, more complex, and more violent. It takes a touch of genius—and a lot of courage—to move in the opposite direction

—Albert Einstein, Theoretical Physicist (1879–1955)

The Stress Response

Exposure of the host to diverse noxious stimuli results in a stereotypic and coordinated response, referred to by Hans Selye as the "*general adaption syndrome*" (or stress response) which serves to restore homeostasis and enhance survival [1]. The stress response is mediated primarily by the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathoadrenal system (SAS). Activation of the HPA axis results in increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) (see Fig. 13.1) [2]. CRH stimulates the production of ACTH by the anterior pituitary, causing the zona fasciculata of the adrenal cortex to produce more glucocorticoids (cortisol in humans) [3]. Activation of the SAS results in the secretion of epinephrine and norepinephrine from the adrenal medulla and sympathetic nerves and to an increased production of inflammatory cytokines such as interleukin-6 (IL-6) [2].

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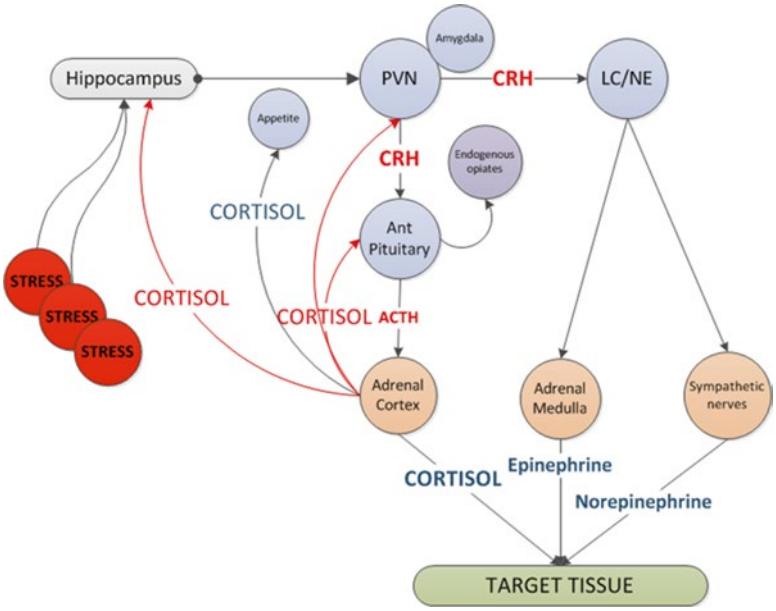

Fig. 13.1 Activation of the stress response. *CRH* corticotrophin releasing hormone, *PVN* paraventricular nucleus, *LC/NE* locus ceruleus norepinephrine system, *ACTH* adrenocorticotrophic hormone, *CRH* corticotrophin

In general, there is a graded response to the degree of stress. Cortisol and catecholamine levels correlate with illness severity, the type of surgery, the severity of injury, the Glasgow Coma Scale and the APACHE score [3]. Adrenal cortisol output increases up to tenfold with severe stress (~300 mg hydrocortisone/day) [3]. In patients with shock, plasma concentrations of epinephrine increase 50-fold and norepinephrine levels increase tenfold [4]. The adrenal medulla is the major source of these released catecholamines [4]. Adrenalectomy eliminates the epinephrine response and blunts the norepinephrine response to hemorrhagic shock [4].

The stress response acts via multiple genomic and nongenomic mechanisms to enhance cardiovascular reserve and provide a ready source of fuel (glucose and lactate) for the brain, and heart, allowing the organism to take appropriate action (flight or fight) while preventing excessive activation of the immune system [2].

The increase in serum cortisol during stress protects the organism against developing post-traumatic stress disorder (PTSD) [5]. The fight and flight response is essential for survival and is present in the most primitive of species. Furthermore, within species the degree of activation of the HPA axis has evolved to match the degree of stress to which the organism is exposed [6] (see Fig. 13.2). Dysfunction of the stress response is illustrated in Fig. 13.3.

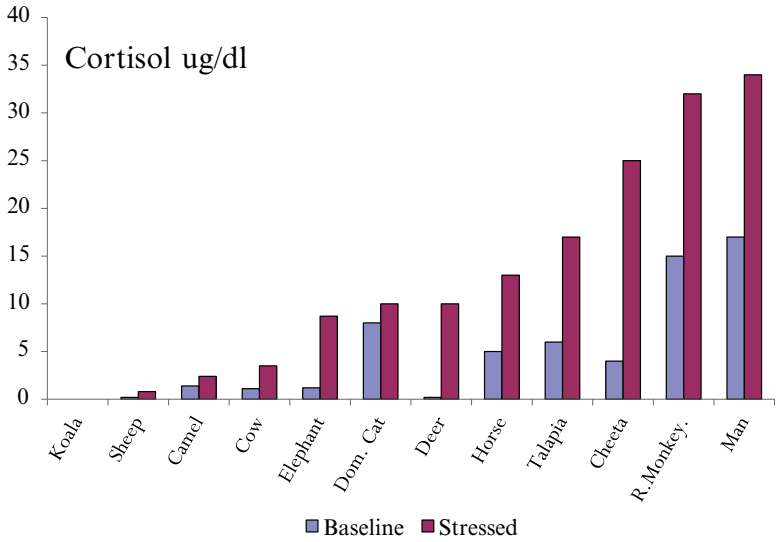

Fig. 13.2 Baseline and stress cortisol level amongst various species

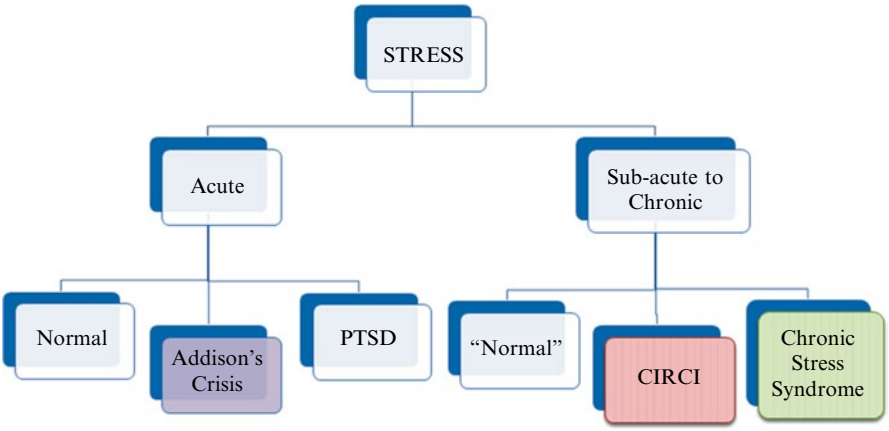

Fig. 13.3 Dysfunction of the stress response. *CIRCI* Critical illness related steroid insufficiency (see Chap. 39)

Modulators of the stress response

- Nicotine, alcohol, medications
- Genetic factors
  - Glucocorticoid receptor and CRH receptor polymorphisms
- Sex hormone levels
  - Male/female
  - Phase of menstrual cycle
  - Oral contraceptives

- Previous exposure to stress/physical abuse
- Maternal stress and fetal programming
- Obesity
- Position in social hierarchy
- Educational level

Chronic stress syndrome is characterized by: (see also Chap. 8)

- Stress hyperglycemia
  - Oxidative injury
- Immune suppression
  - Decreased cell mediated immunity
  - Infections
- Neuropsychiatric
  - Cognitive dysfunction
  - Memory
- Muscle wasting

Cardiovascular Effects of the Stress Response

Increased sympathetic tone and the increased release of epinephrine and norepinephrine from the adrenal medulla, act on the cardiovascular system to increase heart rate, myocardial contractility and venous return, thereby increasing cardiac output. The increased blood flow is preferentially redistributed to the adrenal glands, myocardium, brain and skeletal muscles. It is noteworthy that norepinephrine increases venous return by α-1 mediated venoconstriction. In addition, norepinephrine increases lymphatic return to the venous system by increasing lymphatic duct contraction [7]. Cortisol increases blood pressure through several mechanisms involving the kidney and vasculature. In vascular smooth muscle, cortisol increases sensitivity to vasopressor agents such as catecholamines and angiotensin II [8, 9]. These effects are mediated partly by the increased transcription and expression of the receptors for these hormones [8, 9].

Immune Effects of the Stress Response

Native CD4+ Th0 cells are bipotential and serve as precursors of Th1 and Th2 cells. Th1 cells play an important role in killing intracellular pathogens whereas Th2 cells are important for antibody production. Th1 cells primarily secrete interferon-γ (IFN-γ), interleukin-2 (IL-2) and tumor necrosis factor-β (TNF-β) which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines (anti-inflammatory cytokines), primarily interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13

(IL-13) which promote humoral immunity and depress cell mediated immunity [10]. Importantly, Th2 cytokines inhibit macrophage activation, T cell proliferation, and the production of pro-inflammatory cytokines. Epinephrine and norepinephrine act synergistically with glucocorticoids to induce a Th2 shift [25]. Glucocorticoids shift the Th1/Th2 balance by decreasing the synthesis of type 1 cytokines and increasing the synthesis of type 2 cytokines, by acting directly on CD4+ T cells and indirectly by inhibiting IL-12 production by monocytes [11]. The Th1/Th2 switch during acute stress serves to prevent over-activation of the immune system. This immune switch explains the immuno-paresis and increased risk of infection associated with trauma and surgery, as well as following prolonged stress [12].

Metabolic Effects of the Stress Response

The stress response results in a multiple endocrine and metabolic effects including stress hyperglycemia, stress hyperlactemia, lipolysis with the release of free fatty acids, proteolysis with the release of amino acids, as well as inhibition of the thyroidal, growth hormone and gonadal axes.

Stress Hyperglycemia

The neuroendocrine response to stress is characterized by excessive gluconeogenesis, glycogenolysis and insulin resistance. Stress hyperglycemia, however, appears predominantly by increased hepatic output of glucose (gluconeogenesis) rather than impaired tissue glucose extraction. Cortisol increases blood glucose concentration through the activation of key enzymes involved in hepatic gluconeogenesis and inhibition of glucose uptake in peripheral tissues such as the skeletal muscles [13]. Both epinephrine and norepinephrine stimulate hepatic gluconeogenesis and glycogenolysis; norepinephrine has the added effect of increasing the supply of glycerol to the liver via lipolysis. Stress hyperglycemia and insulin resistance are evolutionarily preserved responses which allows the host to survive during periods of severe stress [14]. Insects, worms and all verterbrates including fish develop stress hyperglycemia when exposed to stress [14, 15].

Glucose is largely utilized by tissues that are non-insulin dependent, and these include the central and peripheral nervous system, bone marrow, white and red blood cells and the reticuloendothelial system [16]. Cellular glucose uptake is mediated by plasma membrane glucose transporters (GLUT) which facilitate the movement of glucose down a concentration gradient across the non-polar lipid cell membrane [16]. Insulin increases GLUT4 mediated glucose transport in adipose tissue and skeletal muscle by increasing translocation of GLUT4 from intracellular stores to the cell membrane [16]. Thermal injury and sepsis have been demonstrated to increase expression of GLUT-1 mRNA and protein levels in the brain and macro-

phages [17, 18]. Concomitantly, stress and the inflammatory response result in decreased translocation of GLUT-4 to the cell membrane. It is likely that pro-inflammatory mediators particularly TNF-α and IL-1 are responsible for the reciprocal effects on the surface expression of these glucose transporters. During infection, the upregulation of GLUT1 and downregulation of GLUT-4 may play a role in redistributing glucose away from peripheral tissues towards immune cells and the nervous system.

For glucose to reach a cell with reduced blood flow (ischemia, sepsis), it must diffuse down a concentration gradient from the blood stream, across the interstitial space and into the cell. Glucose movement is dependent entirely on this concentration gradient, and for adequate delivery to occur across an increased distance, the concentration at the origin (blood) must be greater. Stress hyperglycemia results in a new glucose balance, allowing a higher blood 'glucose diffusion gradient' which maximizes cellular glucose uptake in the face of maldistributed microvascular flow [19]. In patients with infection and tissue injury the increased energy requirements of activated macrophages and neutrophils are regulated by enhanced cellular glucose uptake related to the increased glucose diffusion gradient and increased expression of glucose transporters [20, 21]. In addition, acute hyperglycemia may protect against cell death following ischemia by promoting anti-apoptotic pathways and favoring angiogenesis. These mechanisms ensure adequate glucose uptake by immune cells and neuronal tissue in the face of decreased microvascular flow. Indeed, two independent groups of investigators using microdialysis and brain pyruvate/lactate ratios demonstrated that attempts at blood glucose normalization in critically ill patients with brain injury were associated with a greater risk of critical reductions in brain glucose levels and brain energy crisis [22, 23]. Similarly, Duning and colleagues demonstrated that hypoglycemia worsened critical illness induced neurocognitive dysfunction [24]. Multiple studies have demonstrated that even moderate hypoglycemia is harmful and increases the mortality of critically ill patients [20, 21]. Iatrogenic normalization of blood glucose may impair immune and cerebral function at a time of crises. In summary, these data suggest that stress hyperglycemia provides a source of fuel for the immune system and brain at a time of stress and that attempts to interfere with this evolutionary conserved adaptive response is likely to be harmful [25].

The association between hyperglycemia and adverse clinical outcomes is complicated by the pre-existing diabetes. Observational data has demonstrated that the association between increasing blood glucose and mortality was much stronger among non-diabetic than among diabetic patients [26, 27]. Egi and colleagues demonstrated that in patients with a high HbA1c (>7 %) there was an inverse relationship between ICU glycemic control and mortality—higher blood glucose levels during ICU stay were associated with lower mortality [28]. Biological adjustment to preexisting hyperglycemia might explain this phenomenon. These observations generate the hypothesis that glucose levels that are considered safe and desirable in other patients might be undesirable in diabetic patients with chronic hyperglycemia. In diabetic patients whose glucose has been poorly controlled prior to ICU admission, rapid and substantial lowering of their blood glucose levels during their acute illness/surgery may worsen outcomes.

Chronic hyperglycemia in patients with diabetes is associated with a myriad of harmful complications. The adverse outcomes associated with chronic hyperglycemia are attributed to the pro-inflammatory, pro-thrombotic and pro-oxidant effects observed with increased glucose levels [29]. The duration and degree of hyperglycemia appears to be critical in determining whether hyperglycemia is protective or harmful. Acute hyperglycemia limits myocardial injury following hypoxia and ischemia [30, 31]. However, in experimental models chronic hyperglycemia is associated with an increased the rate of myocyte death and increased infarct size [31, 32]. These data suggest that acute hyperglycemia may be protective and may result in greater plasticity and cellular resistance to ischemic and hypoxic insults. It is possible that severe stress hyperglycemia (BG >220 mg/dL) may be harmful; this postulate however remains unproven. Furthermore, it is unclear at what threshold stress hyperglycemia may become disadvantageous.

Treatment of "Stress Hyperglycemia"

Numerous studies in both ICU and hospitalized non-ICU patients have demonstrated a strong association between hyperglycemia and poor clinical outcomes, including mortality, morbidity, length of stay, infections and overall complications. These studies have included patients following trauma, burns and surgery as well as in patients with cerebrovascular accidents and acute coronary syndromes. Furthermore, this association is well documented for both the admission as well as the mean glucose level during the hospital stay [25]. In addition to hyperglycemia, glucose variability has been demonstrated to be an independent predictor of poor outcome [33]. Badawi and colleagues demonstrated a progressive increase in the adjusted relative risk of mortality for ICU patients for the maximum average daily glucose from 110 mg/dL to greater than 300 mg/dL, when compared to patients whose highest average daily glucose was 80–110 mg/dL [34].

Based on these data clinicians, researchers and policy makers have assumed the association between stress hyperglycemia and poor clinical outcomes to be causal with the widespread adoption of protocols and programs for in-hospital glycemic control. These individuals who believe that strict glycemic control will "cure all the ills of the world" cite the 2001 study by Van den Berghe to support their argument [35]. There are however a number of serious factors which limit the generalizability of this study, including:

i) this was a single center, unblinded study with highly "invested" investigators,
ii) patients received intravenous glucose on arrival to the ICU at a dosage of 200–300 g/day, equivalent of 2–3 L of 10 % glucose per day (quite bizarre),
iii) parenteral nutrition was provided to almost all patients within 24 h of ICU admission, even those who could tolerate enteral or oral nutrition (a very unusual practice),

iv) the mortality of patients who had undergone cardiac surgery (the majority of patients) in the control group was twice the national average for the US (very scary!) and
v) the unadjusted relative reduction in mortality was 42 %, an effect exceeding that of any other interventional trial in critically ill patients (similar to the Rivers EGDT study) stretching the biological plausibility of the findings [36].

NO other study has been able to reproduce the "Leuven Glycemic Control Study" [35]. Indeed, NICE-SUGAR, a large randomized, multi-center, multinational trial performed in 6,104 ICU patients, demonstrated that intensive glucose control increased mortality [37]. More recently the CGAO-REA study group performed a RCT testing tight computerized versus conventional glucose control in 34 French ICU's [38]. In this study tight computerized glucose control using a clinical computerized decision support system did not significantly change 90-day mortality but was associated with more frequent severe hypoglycemia episodes in comparison with conventional glucose control. A metaanalysis which evaluated "tight glycemic control" in the ICU concluded that "*tight glycemic control is associated with a high incidence of hypoglycemia and an increased risk of death in patients not receiving parenteral nutrition. Furthermore, there is no evidence to support the use of intensive insulin therapy in general medical-surgical ICU patients who are fed according to current guidelines"* [39]. Hyperglycemia has been assumed to increase infarct size and worsen outcome in patients who have suffered an ischemic stroke [40]. Consequently, tight glycemic control has been recommended in patients who have suffered an ischemic stroke [40]. However, the INSULINFARCT Trial demonstrated that intensive versus subcutaneous insulin in patients with hyperacute stroke significantly increases infarct size [41]. Recently de Mulder et al randomized 294 patients with Acute Coronary Syndrome with an admission BG level between 140 and 288 mg/dL to tight glycemic control (85–100 mg/dL) or conventional glucose management [42]. In this study intensive glucose control did not reduce infarct size, but was associated with an increased risk of death and second myocardial infarction. The current American College of Physicians Guidelines recommends a target BG level of 140–200 mg/dL in medical/surgical ICU patients with hyperglycemia [43]. It does not recommend intensive insulin therapy because of the high likelyhood of hypoglycemia and the absence of benefit. It should be noted that "tight glycemic control" is very labor intensive; nurses spend hours a day on this mindless task (which together with other mindless tasks) limits the amount of time they actually spend looking after their patient!

Tight glycemic control is currently considered the standard of care in patients undergoing cardiac surgery. This practice is based on retrospective data and before-after studies [44–46]; which as discussed in Chap. 1, are no better than "*The 10 Tales of Witchcraft*." Agus et al. performed a RCT comparing tight glycemic control to standard of care in 980 pediatric patients undergoing cardiac surgery [47]. Continuous glucose monitoring was used to avoid hypoglycemia. In this study none of the outcome measures differed between groups. More recently Macrae and colleagues performed a multicenter randomized trial of glucose control comparing 72–126 mg/dL with a target of <216 mg/dL in 1,369 pediatric ICU patients [48].

Sixty percent of patients had undergone cardiac surgery and patients were followed for up to 1 year. In this study there was no difference in clinical outcomes overall or in any predefined subgroup of patients. Gandhi et al compared intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery [49]. In this study there was an increased risk of death and stroke in the intensive insulin group. More recent cohort studies in patients undergoing cardiac surgery have demonstrated a lower risk of complication in patients treated with moderate rather than tight glycemic control [50]. This is likely due to the fact that hypoglycemia with intensive insulin therapy is independently associated with an increased risk of postoperative complications [51]. More recent publications on this topic recommend a "more liberal" blood glucose target (140–180 mg/dL) in patients undergoing cardiac surgery [52].

It would appear that van Den Berghe and colleagues hoodwinked the entire world into this thing called "tight glycemic control"; an approach which appears to increase the risks of complications and death amongst diverse populations of critically ill patients. It should also serve as a lesson regarding the widespread change of clinical practice based on a single center, unblinded study [53]. Common sense would suggest that a few days of moderate hyperglycemia in the ICU should be of no adverse consequence and indeed is probably a protective response. It is possible, however unproven, that prolonged moderate hyperglycemia may be deleterious in Chronically Critically Ill patients (see Chap. 8). "Conservative" glycemic control (BG 140–180 mg/dL) should be considered in these patients.

So What to Do!

- Don't obsess about glycemic control
- Check HbA1C on admission in all diabetic patients
- Non-diabetics and diabetics with HbA1C <7 %
  - Target BG between 140 and 200 mg/dL
- Diabetics with HbA1C >7 %
  - Target BG between 160 and 220 mg/dL

How to Achieve These Goals?

- Avoid IV glucose and never use TPN
- Use an enteral formula with a higher fat (omega-3) to CHO ratio and don't overfeed
- Limit the dose of corticosteroids. ? administer as a continuous infusion
  - Consider adding insulin (see below)
- Stop oral hypoglycemic agents in diabetic patients

- 24 h trial of 6-hourly insulin sliding scale (continuous tube feed patients)
  - Consider basal long acting insulin in diabetics
- Consider basal long acting insulin (low dose)+bolus insulin in patients receiving bolus tube feeds (See Chap. 32)
- Insulin infusion if above measures fail or in patients with severe hyperglycemia (BG >300 mg/dL).
- In ICU's that have 1:1 nursing (not the case in the US), it may be preferable to initiate an insulin infusion in patients' with a blood glucose >200 mg on two or more occasions rather than attempting glycemic control with subcutaneous insulin.

Glucose Control and Steroids

There is little data that treatment of glucocorticoid induced hyperglycemic in the acute care setting improves outcome. However, efforts to minimize the fluctuations in blood glucose levels may be beneficial and contribute to overall glycemic control. In patients receiving stress doses of corticosteroids (see Chap. 39), hydrocortisone may be given as an infusion at a rate of 8–10 mg/h; a continuous infusion results in a smoother glucose profile than intermittent boluses [54, 55]. The addition (or increased dose) of basal long acting insulin should be considered in patients receiving a glucocorticoid infusion. Similarly, as the biological effect of dexamethasone is about 20 h [56], the addition of a long acting insulin should be considered in these patients (neurosurgical patients). Patients with a COPD exacerbation (see Chap. 24) and those receiving steroids for immunosuppression usually receive methylprednisolone once daily. Prednisone and prednisolone demonstrate a peak biological effect at 4–8 h and a duration of approximately 12–16 h [57]. This pattern mirrors that of NPH insulin [56]. Consequently, concomitant NPH insulin should be considered in these patients. In patients receiving >40 mg/day a dose of 0.4 U/kg NPH is recommended, 0.3 U/kg in those receiving 30 mg/day and 0.2 U/kg in those receiving 20 mg/day [56].

Stress Hyperlactemia

It is widely believed that in critically ill patients when oxygen delivery fails to meet oxygen demand an oxygen debt with global tissue hypoxia ensues [58, 59]. This results in anaerobic metabolism and increased lactate production [58, 59]. An increased blood lactate concentration is therefore regarded as evidence of anaerobic metabolism and tissue hypoxia [58]. It follows from this reasoning that patients with an elevated blood lactate should be treated by increasing oxygen delivery. In 2004 Nguyen and colleagues reported that "lactate clearance", defined as the percentage decrease in lactate from emergency department presentation to 6 h, was an independent predictor of mortality [58]. They concluded that "*lactate clearance in*

the early hospital course may indicate a resolution of global tissue hypoxia and that this is associated with decreased mortality rates." This study popularized the concept of "lactate clearance" and has led to a number of studies which have used "lactate clearance" as the major end-point of hemodynamic resuscitation in critically in patients with sepsis (see also Chap. 12) [60–62].

We believe that these arguments are flawed and that in most situations lactate is produced aerobically as part of the stress response—hence the term stress hyperlactemia. Based on this argument it would be illogical to attempt to increase oxygen delivery in patients with an increased lactate concentration in order to treat a non-existent oxygen debt. Indeed, such an approach may be harmful [63]. Furthermore, as indicated below, the condition known as "lactic acidosis" may be a myth that does not exist.

Lactate Metabolism

Lactate is produced by glycolysis and metabolized by the liver and to a lesser degree by the kidney. Lactate is produced in the cytoplasm according to the following reaction:

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \leftrightarrow \text{lactate} + \text{NAD}^+$$

This reaction favors lactate formation, yielding a tenfold lactate/pyruvate ratio. In physiological conditions, lactate is produced by muscles (25 %), skin (25 %), brain (20 %), intestine (10 %) and red blood cells (20 %) [64]. Cytosolic lactate increases under most if not all circumstances where cytosolic pyruvate also increases. Logically, therefore, lactate accumulation may not imply a state of anaerobic glycolysis but simply a state of accelerated glycolysis (glycolytic flux >citric acid cycle flux) or a state of decreased pyruvate dehydrogenase activity both of which would logically lead to cytosolic pyruvate accumulation. Arterial lactate concentration is dependent on the balance between its production and consumption. In general, this concentration is less than 1 mmol/L, although daily production of lactate is actually 1,500 mmol/L [64, 65]. Generated lactate can be transformed into oxaloacetate or alanine via the pyruvate pathway or can be utilized directly by periportal hepatocytes (60 %) to produce glycogen and glucose (glycogenesis and glucogenesis; Cori cycle). The kidney also participates in the metabolism of lactate (30 %), with the cortex classically acting as the metabolizer by glucogenesis and the medulla as a producer of lactate. Pyruvate is metabolized by the mitochondrial aerobic oxidation pathway via the Krebs cycle. This reaction leads to the production of large quantities of ATP (36 molecules of ATP for one molecule of pyruvate) (see Fig. 13.4).

Hypoxia blocks mitochondrial oxidative phosphorylation, thereby inhibiting ATP synthesis and re-oxidation of NADH. This leads to a decrease in the ATP/ADP ratio and an increase of the NADH/NAD ratio. A decrease in the ATP/ADP ratio induces both an accumulation of pyruvate, which cannot be utilized by way of phosphofructokinase stimulation, and a decrease in pyruvate utilization by inhibiting pyruvate carboxylase, which converts pyruvate into oxaloacetate [64]. Consequently,

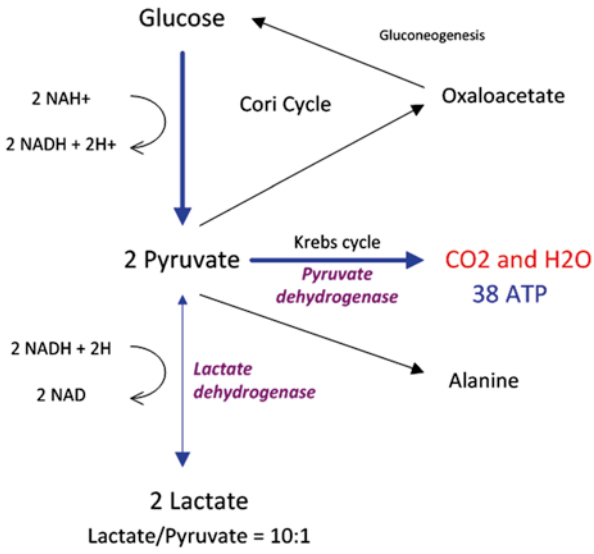

Fig. 13.4 Glycolytic pathway

the increase in lactate production in an anaerobic setting is the result of an accumulation of pyruvate which is converted into lactate stemming from alterations in the redox potential. Classic teaching suggests that increased production of lactate results in an acidosis, known widely as a lactic acidosis [66]. Close examination of glycolysis reveals that complete metabolism of glucose to lactate results in no net release of protons and, thus, does not contribute to acidosis. In fact, during the production of lactate from pyruvate, protons are consumed and acidosis is inhibited [67]. Furthermore, lactate oxidation and lactate consumption via gluconeogenesis consume hydrogen ions and are alkalinizing processes (see also Chap. 12). This implies that "lactic acidosis" is a condition that does not exist [67].

Lactate as a Marker of Illness Severity

An elevated blood lactate concentration (hyperlactatemia) is a typical finding during exercise and in critical illness, most notably sepsis, cardiogenic shock, cardiac surgery and liver failure. In essentially all situations of severe disease-related physiological stress, an elevated blood lactate concentration has reproducibly and consistently been demonstrated to be an independent predictor of mortality [68–72]. Over 50 years ago Weil and colleagues demonstrated an exponential increase in the mortality of critically ill patients with increasing blood lactate concentrations [73, 74]. More recent studies suggest that the mortality increases linearly above a lactate concentration of 1.4 mmol/L and that this association is independent of organ dysfunction or the presence of shock [65, 68, 75].

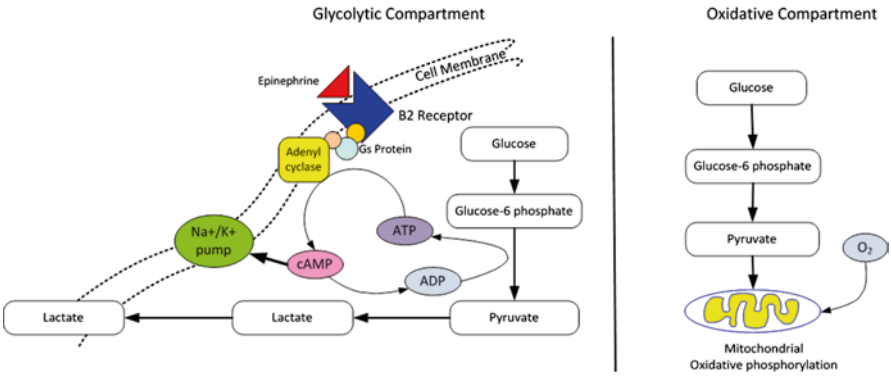

Fig. 13.5 Epinephrine-increased glycolysis is coupled to Na+/K+-ATPase activity. From James et al [78]. Adapted with permission

Lactate as a Marker of Metabolic Stress

Cytosolic glycolytic flux is functionally divided into two distinct compartments that utilize separate glycolytic enzyme pools. The first pathway participates in oxidative metabolism via the Krebs cycle. The second pathway is linked to activity of the Na+/K+-ATPase pump (see Fig. 13.5) [64]. ATP produced by this pathway is used to fuel this membrane pump. Numerous studies have demonstrated that epinephrine, via β2-adrenoceptor stimulation, increases cAMP production, inducing the stimulation of glycogenolysis and glycolysis as well as activation of the Na+/K+-ATPase pump, which in turn will consume ATP, thereby producing ADP [76, 77]. The generated ADP via phosphofructokinase stimulation will reactivate glycolysis and hence generate more pyruvate and thereafter lactate.

Several studies performed over four decades ago provide strong evidence that hyperlactacidemia noted during shock states was unlikely to be caused by tissue hypoxia [79, 80]. These studies showed that hyperlactacidemia accompanying hemorrhage could be largely prevented by pretreatment with combined alpha and beta adrenergic-receptor blockade [81]. Subsequent experimental studies confirmed that elevated arterial lactate in shock was due not to lack of oxygen but to increased lactate production that could be mimicked by epinephrine infusion and blocked by adrenergic receptor blockade [82–86]. It has now been well established that epinephrine released as part of the stress response in patients with shock stimulates Na+/K+-ATPase activity. Increased activity of Na+/K+-ATPase leads to increased lactate production under well-oxygenated conditions in various cells, including erythrocytes, vascular smooth muscle, neurons, glia, and skeletal muscle [77, 78]. This concept was confirmed by Levy and colleagues who in patients with septic shock demonstrated that skeletal muscle was the leading source of lactate formation as a result of exaggerated *aerobic* glycolysis through Na+/K+-ATPase stimulation [87]. Selective inhibition of Na+/K+-ATPase with ouabain infusion stopped over-production of mus-

cle lactate and pyruvate. The lungs also seem to play an important role in lactate release in patients with septic shock probably associated with the presence of infiltrating inflammatory cells suggesting that lactate release by the lung may be a stereotyped response to organ stress. The hypermetabolic state with increased Na+/K+-ATPase activity results in accelerated glycolysis and generates pyruvate and lactate at an increased rate. If glycolysis occurs at a rate that exceeds that of oxidative metabolism, some pyruvate may not be oxidatively metabolized in the Krebs cycle and will be converted to lactate.

Lactate as a Metabolic Fuel

The primary metabolic fate of radiolabelled lactate is oxidation (via pyruvate and the citric acid cycle). Approximately half of available lactate is disposed of via oxidation at rest, and 75–80 % during exercise [88]. Isotope studies demonstrate simultaneous lactate uptake and release in exercising human skeletal muscle [89]. Myocyte compartmentalization (glycolytic and an oxidative compartments) has been proposed as the most logical explanation for such simultaneous lactate production and utilization in muscle [89]. The glycolytic compartment is close to the myofibrils and their glycogen stores and is associated with glycogenolysis/glycolysis and lactate release into the circulation. The oxidative compartment is in close proximity of the mitochondria is considered responsible for lactate oxidation. This "intracellular lactate shuttle" (ILS) hypothesis holds that, in a way that mirrors the whole body lactate shuttle, lactate produced as the result of glycogenolysis and glycolysis in the cytosol is balanced by oxidation in the mitochondria of the same cell [90]. Not all lactate produced in muscle is disposed by oxidation within the same cell. Some is exported to adjacent cells, tissues and organs for use, following the theory of the cell-to-cell lactate shuttle (CCLS). The CCLS hypothesis holds that lactate supplied from the interstitium and vasculature can be taken up and used in highly oxidative cells (red skeletal muscle cells and cardiac myocytes, hepatocytes and neurons) to serve as oxidative or gluconeogenic substrate. The first recognized CCLS is the Cori Cycle.

Lactate produced in the cytosol is transported across lipid bilayer membranes by a family of monocarboxylate transport proteins (MCT) [91, 92]. Lactate can then be converted to pyruvate within mitochondria rather than the cytosol by mitochondrial LDH and then oxidized. Pyruvate leaves the intermembrane space where it is formed and is transported through MCT1 to the mitochondrial matrix for subsequent oxidative catabolism via the TCA (tricarboxylic acid cycle). Hashimoto et al found that MCT1 and related genes are differentially upregulated by lactate [93]. Thus, lactate has a signalling role as a pseudo-hormone or "lact-hormone". Elevated lactate concentrations act as a key factor in the coordination of lactate oxidation by up-regulating total mitochondria mass and the abundance of the mitochondrial lactate oxidation complex (MCT1, CD147, COX and LDH). Increasing expression of lactate transporters on cellular membranes allowing a more effective ILS.

Heart Metabolism and Lactate

The main energy supply for the heart is the oxidation of fatty acids, however this organ is able to metabolize glucose, lactate and amino acids in varying proportions. In a normal heart at rest, approximately 60–90 % of ATP generated comes from β-oxidation of fatty acids and 10–40 % comes from pyruvate formed by glycolysis and the conversion of lactate [94]. Although fatty acids have a higher yield of ATP per fatty acid molecule, it costs more oxygen in the process. Fatty acid metabolism not only results in lower ATP production efficiency, but cardiac mechanical performance is also lower at a given rate of oxygen consumption [95]. Increased intracellular free fatty acids have been shown to activate uncoupling proteins allowing protons to leak into the mitochondria without generating ATP [96]. An increase in mechanical efficiency of the left ventricle was observed when β-oxidation process was inhibited [97].

The proportion of lactate uptake by the myocardium and its use a metabolic fuel increases during exercise, β-adrenergic stimulation, elevated afterload, fast pacing and during shock [98–101]. Lactate may account for up to 60 % of cardiac oxidative substrate and could exceed glucose as a source of pyruvate in the presence of elevated lactate levels [98, 99, 102]. During shock the heart undergoes a major shift in substrate utilization such that it oxidizes lactate for the majority of its energy needs [101, 103]. Accelerated lactate clearance could therefore compromise cardiac performance during shock [104]. In a rat endotoxin model, Levy et al inhibited lactate production with a selective β2 adrenergic blocker, enhanced it metabolism with dichloroacetate or studied a combination of both interventions [86]. In this study lactate deprivation was associated with cardiovascular collapse and early death of the animals. Lactate infusion has been reported to increase cardiac output in anesthetized pigs [105]. Similarly, Revelly and coworkers demonstrated that an infusion of sodium lactate increased cardiac performance in patients with both cardiogenic and septic shock [106]. These studies suggest that lactate serves as an important energy source during acute hemodynamic stress and maybe an important survival response.

Brain Metabolism and Lactate

Blood lactate is also taken up and subsequently oxidized by neurons in the conscious healthy human brain or converted to glycogen in astrocytes. With progressive increases in blood lactate, net brain lactate uptake and the contribution of lactate to cerebral oxidative utilization displays a linear increase [102, 107, 108] Lactate account for about 7 % of cerebral energy requirement under basal conditions and up to 25 % during exercise. During hypoglycemia and ischemia astrocyte production of lactate has been demonstrated to support neuronal ATP requirements, via the so called “astrocyte-neuron lactate shuttle” [109–112]. In animal experiments, administration of exogenous lactate has been shown to reduce structural brain damage in

cerebral ischemia and brain trauma [113, 114]. The maximal protective effective in animal has been observed when the interstitial lactate concentration was between 4 and 7 mmol/L [113]. These data suggest that hyperlactemia in the setting of acute stress may have a protective effect on the brain and minimize cerebral dysfunction.

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Chapter 14
Understanding the Vital Signs: BP, HR, RR, TEMP, SaO_2 … and SV

It is by no accident that the five (now six) vital signs are called ***VITAL SIGNS.*** Yet, many clinicians do not appreciate the importance of these VITAL signs nor how to interpret them. The initial assessment of every ICU and ER patient requires a thoughtful review of the five vital signs; this has an essential role in triage decisions and the initial treatment strategy. Any patient with an abnormal vital sign is at an increased risk of death. The risk of death is compounded by derangements of multiple vital signs [1]. In addition, the trends in the vital signs are VITALLY important in tracking a patient's progress. This chapter reviews the Five Vital Signs… and introduces the 6th vital sign.

Blood Pressure

Blood pressure is the most important of the six vital sign. Organ blood flow is driven by the difference in the pressure between the arterial and venous sides of the circulation. The mean arterial pressure (MAP)[1] minus the central venous pressure (CVP) is the driving force for organ blood flow while the difference between post-arteriolar and venular pressure determines microcirculatory flow. As discussed in Chap. 12, venous pressure has a much greater effect on microcirculatory flow than the MAP. As long as the MAP is within an organs autoregulatory range (see below), the CVP becomes the major determinant of capillary blood flow. Microcirculatory flow and organ function "is best" with a higher MAP and a lower CVP (not higher CVP).

It should however be realized that CO and TPR and interdependent with changes in CO effecting TPR and changes in TPR effecting CO.

[1] MAP = cardiac output (CO) × total peripheral resistance (TPR).

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The Brain-Heart Distance and the Giraffe Theory of Blood Pressure Determination in Humans

As first suggested by Harvey Cushing in 1901 [2], any reduction in cerebral blood flow to the cardiovascular control centers (in the brainstem) will result in activation of these centers which will proportionally increase systemic blood pressure (BP) and return cerebral blood flow to a new homeostatic level. According to this theory the MAP at all times in all individuals is determined by the pressure needed to perfuse the brainstem. It should also be recalled that the hydrostatic pressure changes by 0.77 mmHg for every 1 cm change in vertical distance. This theory explains the increase in blood pressure in humans from birth to adulthood, the higher high blood pressure in taller than shorter individuals and the progressive increase in blood pressure as the length of the Giraffe's neck grows with aging (see Fig. 14.1) [3]. This theory suggests that the cardio-cranial distance is a major factor determining BP. Furthermore, an increase in brainstem blood flow will result in homeostatic changes that lower BP; i.e. the brainstem is continually adjusting BP to ensure just the right perfusion pressure and blood flow. This may explain the lower blood pressure in humans at night (lying down during sleep) than during the day and the observation (that is not widely appreciated) that chronically bed ridden patients have a lower than normal BP as they require a lower BP to perfuse their brainstem. This observation also accounts for the cephalad location of the heart in terrestrial snakes as compared with aquatic snakes…. else terrestrial snakes would faint when they tried to climb a tree [4].

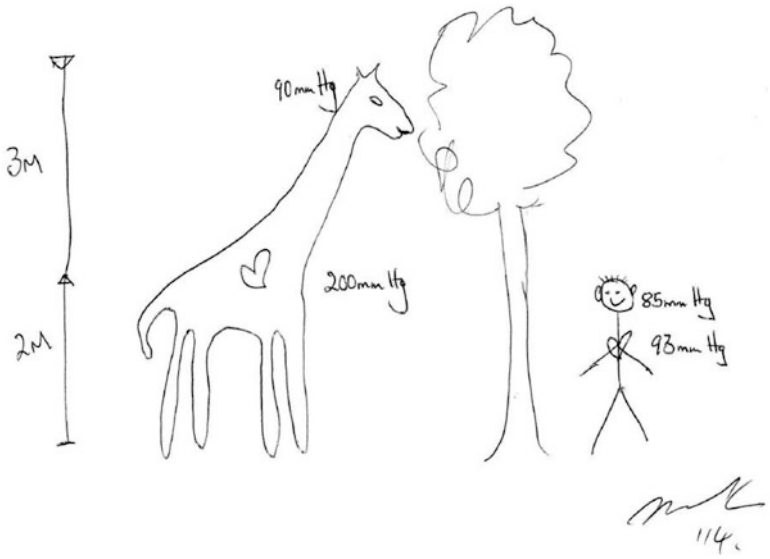

Fig. 14.1 Mean arterial pressures in a Giraffe and man at the level of the heart and brain

FYI: Birds have a higher BP than humans. Birds have larger hearts and a much higher cardiac output (CO) than that of mammals corrected for body mass. The high CO accounts for the high BP. The high CO is necessary to meet the high metabolic demands of flight. For example, during flight a pigeons heart rate increases to about 670/min, with a cardiac output of 1 L/min and an oxygen consumption of 200 mL/min.

What's a Normal Blood Pressure?

The definition of a "normal" blood pressure (BP) is somewhat problematic for the following reasons:

- The BP varies widely between groups of people, influenced by ethnic, genetic, lifestyle and cultural factors as well as the degree of industrialization.
- The BP measured in a physician's office/clinic differs from the mean ambulatory BP. The PAMELA study investigated clinic and ambulatory blood pressure in 1,438 non-hypertensive Italian patients [5]. This study demonstrated that a clinic BP measurement of 140/90 mmHg was equivalent to a 24 h ambulatory blood pressure value of 125/80 mmHg and a daytime value of 130/85 mmHg.
- The Framingham Heart study demonstrated a progressive increase in BP with aging, beginning in childhood and continuing into adulthood (see Fig. 14.2) [6]. This trend is associated with a greater increase in systolic blood pressure (SBP) than diastolic blood pressure (DBP). Furthermore, while SBP continues to rise until the eighth or ninth decade, DBP tends to remain constant or decline after the fifth or sixth decade; as a consequence, pulse pressure increases progressively with age and the rate of rise accelerates after age 50 years. The pulse pressure has been demonstrated to be a strong predictor of cardiovascular disease [7]. Due to the diverging patterns of change in SBP and DBP with aging, the change in MAP is less than that of either the SBP or DBP.

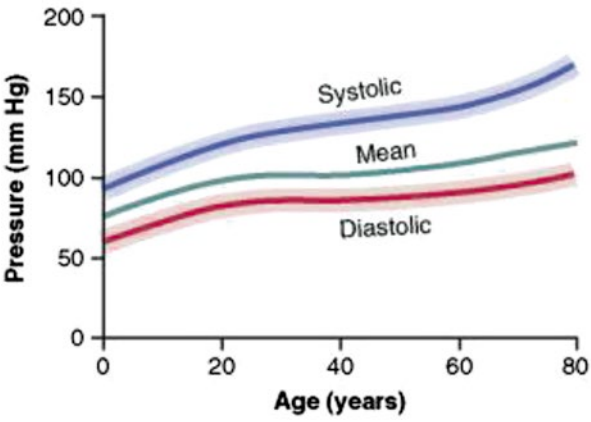

Fig. 14.2 Changes in blood pressure with aging [9]. Reproduced from Guyton and Hall Textbook of Medical Physiology, with permission from Saunders Elsevier

- There is a sex difference in blood pressure trends; women's blood pressure start lower than men's, catches up by the sixth decade, and frequently become slightly higher thereafter.
- Night time blood pressure is about 15 % lower than ambulatory daytime pressure. In the PAMELA study the average daytime BP was 120/80 mmHg (MAP 93) while that at nighttime was 108/64 mmHg (MAP 78). In the IDACO study, which evaluated the relationship between BP and outcomes, an ambulatory 24 h BP of 125/75 mmHg (MAP 92) was considered "normal"; the daytime and nighttime thresholds were 130/85 (MAP 100), and 110/70 (MAP 83) mmHg respectively [8].
- It should be noted that none of the publications referencing normative values have corrected for the height of the subject (as discussed above).
- As a consequence of these and other factors the BP values used to define and classify hypertension are continuously evolving (and changing). The current JNC 8 treatment thresholds are as follows [7]:
  - Patients >60 years SBP >150 and DPB >90 mmHg
  - Patients <60 years DBP >90 mmHg

BP Thresholds for the Intensivist/Anesthesiologist

From the perspective of the intensivist a MAP between 75 and 100 mmHg can be considered "normal." As the intensivist/anesthesiologist has a limited role in patients' long-term BP management the threshold values for long term treatment is of "lesser importance". However, the BP thresholds that require immediate intervention are critically important. The blood pressure thresholds that are relevant are those associated with:

- Hypertensive crisis and acute end-organ damage: Diastolic >110 mmHg (see Chap. 28)
- Hypotension with organ ischemia: MAP <65 mmHg (see below)

Non-Invasive Blood Pressure (NIBP) vs Arterial Line Blood Pressure (IAP) and Systolic Blood Pressure (SBP) vs Mean Arterial Pressure (MAP)

Lehman et al. compared 27,022 simultaneously measured invasive arterial blood pressure (IAP) recordings with NIBP using a large ICU database [10]. Their analysis demonstrated that systolic NIBP was higher than systolic IAP at pressures less than 95 mmHg and lower than systolic IAP at pressures >95 mmHg. In hypotensive patients with a SBP <60 mmHg the average difference between the two techniques

was 10 mmHg. However, the agreement between the NIBP and IAP was much better when comparing the MAP's rather than the SBP's. Furthermore, the risk of acute kidney injury (AKI) and death were significantly different between NIBP and IAP, when using the SBP but not the MAP. The risk of AKI and death increased sharply as the MAP fell below 60 mmHg.

The MAP is a better indicator of organ perfusion than the SBP. Furthermore, agreement between NIBP and IAP is much better between the MAP than the SBP. The MAP is the true driving pressure for organ blood flow and should be recorded in all ICU patients. However, the pulse pressure may be important in patients with vascular aneurysms, the DBP in patients with hypertensive emergencies and the SBP in patients with an intracerebral bleed. This suggests the MAP, SBP and DBP should be recorded in ALL ICU patients.

Central vs Peripheral Blood Pressure Measurement

Many clinicians assume that the peripherally measured systolic, diastolic, mean and pulse pressures represent these pressures throughout the arterial tree. However, the arterial pressure waveform undergoes characteristic morphological changes as it travels from central to peripheral vessels. These complex, dynamic changes involve reflection and summation of pressure waves, modulated by factors such as stroke volume, heart rate and arterial elastance [11]. Compared with arterial pressure waveforms measured in the central arteries (e.g. aorta or femoral artery), those at the periphery (e.g. radial artery) characteristically have steeper upstrokes, higher systolic peaks, a later appearing diastolic notch, more prominent diastolic waves and lower end-diastolic pressure. In health, distal pulse amplification results in higher systolic arterial pressures at the periphery, while DPB and MAP are relatively preserved. The differences between the central and peripheral pressures are increased with some vasodilating agents, in shock and with tachycardia. A large difference between central and peripheral systolic blood pressures may occur in the elderly who have poorly complaint blood vessels. When using a radial arterial line for BP monitoring, the alteration in the distal arterial waveform provides a compelling reason to use the MAP rather than the SBP (once again).

After CABG and in shocked ICU patients on vasopressor agents there may be a reversed radial artery to aortic pressure gradient (systolic aortic pressure higher than radial SBP by up to 60 mmHg) [11–14]. In these patients the difference between the MAP is less than that of the SBP, however this difference may still be as large as 20 mmHg. Baka et al. have suggested that radial artery constriction could be responsible for this pressure gradient [15]. In these patients the femoral artery is the preferred site for arterial pressure monitoring [11–13].

Blood Pressure Autoregulation

In all regional circulations including renal, splanchnic, cerebral and coronory beds, blood flow is autoregulated [16, 17]. When blood pressure falls below a given value (autoregulatory threshold), such autoregulation is lost. Below the autoregulatory threshold organ blood flow decreases in an almost linear fashion. The fall in blood flow is likely to occur at a higher blood pressure in patients with long-standing hypertension (see Fig. 14.3). Furthermore, different vascular beds will lose autoregulation at different blood pressure values. For example, the mammalian kidney does so at a MAP of about 70 mmHg, the brain at between 60 and 70 mmHg while the coronary circulation require a MAP of about 50–55 mmHg [16, 18, 19]. The EEG demonstrates features of ischemia when the MAP falls below 50 mmHg [20]. However, there is a wide a range of individual lower and upper limits of the autoregulation ranges in health and disease. The pressure-flow relationship of the kidney has a steeper slope than that of other regional beds. Thus, for a given fall in blood pressure, the proportional fall in blood flow would be expected to be particularly sharp for the kidney. These observations explain why renal function is particularly vulnerable to hemodynamic instability.

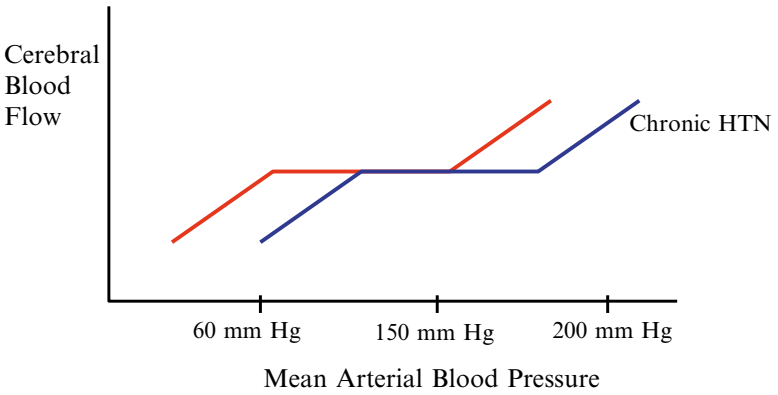

Fig. 14.3 Normal range of cerebral autoregulation and the right shitted curve with chronic hypertension

MAP, Organ Failure and Death

Walsh and colleagues evaluated the association between intraoperative hypotension and postoperative acute kidney injury (AKI) and cardiac injury in 33,330 non-cardiac surgeries [21]. In this study the risk of AKI was greatest for the time spent with a MAP of <60 mmHg and myocardial injury for a MAP less than 55 mmHg. In patients with a MAP <55 the risk of AKI and cardiac injury increased linearly with time spent below this threshold with periods of hypotension as short as 1–5 min being associated with a significantly increased risk of AKI and cardiac injury. Aronson et al. evaluated the association of SBP and mortality in 7,504 patients undergoing CABG surgery [22]. These authors calculated the "area under the curve" (AUC) of all SBP excursions greater than 135 mmHg and less than 95 mmHg. They reported that the AUC <95 mmHg, AUC for 20 % below the patients baseline SBP, minutes <95 mmHg and mean incursion nadir <95 mmHg were all highly predictive of 30 day mortality.

In the study by Lehman et al. cited above a MAP <60 mmHg was a strong predictor of AKI and death in ICU patients [10]. Varpula and colleagues studied the hemodynamic variables associated with mortality in patients with septic shock [23]. These authors calculated AUC of various MAP thresholds over a 48 h time period. The highest AUC values were found for a MAP <65 mmHg (AUC 0.83, 95 % CI, 0.772–0.934). Due to the shift of the autoregulatory range (to the right) in patients with chronic hypertension a higher MAP may be required in these patients. The *Assessment of Two Levels of Arterial Pressure on Survival in Patients With Septic Shock* (SEPSISPAM) is a multicenter randomized controlled trial recently completed in France (ClinicalTrials.gov NCT01149278). In this study patients with septic shock were randomized to achieve a target MAP of 65–70 or 80–85 mmHg. The primary outcome was 28 day mortality. Secondary outcomes included 90 day mortality and organ failures. *A priori* a secondary analysis was planned in patients with and without a history of hypertension. Overall there was no difference in either primary or secondary end-point between the two treatment groups. However the incidence of organ failures (particularly renal dysfunction) was higher in the subgroup of patients with chronic hypertension in the lower MAP group. Furthermore, similar to the Varpula study, the time below the 65 mmHg (but not 80 mmHg) threshold was an independent predictor of death. It is important to recognize that the MAP in the 65–70 mmHg group exceeded the target threshold, with the average MAP being about 75 mmHg. Panwar et al. investigated the relationship between the mean perfusion pressure (MPP) deficit and the risk of AKI in 51 shocked patients [24]. The MPP deficit was calculated as the difference between the patients estimated basal MPP and the MPP achieved in the ICU. These authors demonstrated that the risk of AKI was related to the degree of the MPP deficit and the time spent with a >20 % MPP deficit.

These data suggest that in most ICU patients and those undergoing surgery the MAP should be maintained above 65–70 mmHg. In those patients with a history of hypertension the MAP should be kept above 80 % of their baseline value. In hypertensive patients in whom the baseline BP is not known, a target MAP of 75–80 mmHg may be desirable.

Patients with ESRD receiving hemodialysis, patients with systolic heart failure, chronically critically ill patients and bedridden patients frequently have a low blood pressure and tolerate MAP's as low as 55 mmHg. As long as the patient is mentating adequately and is not symptomatic these patients do not need pressor therapy. Why should the heart waste energy generating a higher pressure that is required? Adrenal insufficiency should however be excluded (see Chap. 39). Do not treat these patients with Midodrine, Florinef or snake oil; you are treating yourself and not the patient.

Circulatory Shock

Shock is traditionally defined as "*circulatory failure that results in inadequate cellular oxygen utilization*" [25]. This definition is problematic as oxygen delivery has to fall to very low levels before oxygen consumption falls and most patients with "shock" have normal levels of oxygen consumption. Ronco and colleagues determined the critical oxygen delivery threshold for anaerobic metabolism in critically ill humans while life support was being discontinued [26]. The critical oxygen delivery threshold was 3.8 ± 1.5 mL/min/kg (266 mL/min in a 70 kg patient); assuming a hemoglobin concentration of 10 g/L this translates into a cardiac output of approximately 2 L/min; it is likely that only pre-terminal moribund patients with "shock" would have such a low cardiac output. Furthermore, while an elevated lactate concentration is widely believed to be a marker of anaerobic metabolism, an overwhelming body of evidence suggests that in most clinical situations, that lactate is produced aerobically as part of the stress response (see Chap. 13). While it is unclear how best to define shock, we believe "circulatory shock" is best defined as

"*a potentially life threatening reduction in systemic organ blood flow.*" The clinical diagnosis of shock is then based on a constellation of clinical and hemodynamic features which include hypotension, tachycardia, increased respiratory rate and decreased urine output. Typically, the SBP is less than 90 mmHg or the MAP is less than 65 mmHg. While altered mentation, notably obtundation, disorientation and confusion is common, patients may be remarkably lucid despite profound hemodynamic compromise (due to blood flow redistribution to the brain).

Shock results from four potential, and not necessarily exclusive, pathophysiological mechanisms: (i) hypovolemia, (ii) decreased systolic cardiac function, (iii) circulatory obstruction (e.g., pulmonary embolism, cardiac tamponade, or tension pneumothorax) or distributive factors (sepsis or anaphylaxis) [25]. The first three mechanisms are characterized by low cardiac output while distributive shock is characterized by decreased systemic vascular resistance. Characterization of the type(s) and cause of shock is essential in order to provide appropriate therapy.

Pulse Rate

$$\text{Cardiac output}\left(\text{CO}\right) = \text{Heart rate}\left(\text{HR}\right) \times \text{stroke volume}\left(\text{SV}\right)$$

Sinus tachycardia is always an ominous sign. The HR is increased usually due to a fall in SV and/or a hypermetabolic state with an increased oxygen demand. In most critically ill patients, tachycardia is a compensatory response following a fall in SV. Assuming a normal heart rate of 70/min; a heart rate of 140/min would indicate that the SV has halved… a very bad situation. Always determine the cause of a sinus tachycardia (ECHO, SV determination) … and NEVER EVER treat an unexplained sinus tachycardia with a beta-blocker … this will predictably result in DEATH (a few exceptions do exist, e.g. Thyrotoxicosis). The higher the heart rate the more life threatening the situation… AND a tachycardia >110/min in an elderly patient is a VERY ominous sign. Tachycardia in combination with hypotension (SBP <110 or MAP <75 mmHg) and a high respiratory rate (>20/min) is a deadly TRIO [1]. ICU patients with cardiac risk factors and a persistent tachycardia (HR >95/min) are at an increased risk of having an acute cardiac event [27].

More common causes of sinus tachycardia

- Hypovolemia/dehydration
- Blood loss
- Myocardial dysfunction
- Sepsis
- Fever
- Hypoxemia
- Anxiety/delirium/agitation
- Substance withdrawal; alcohol, opiates, etc.
- Thyrotoxicosis

- Pulmonary embolism
- Severe anemia
- Drug induced; dopamine, epinephrine, etc.
- Drug toxicity with sympathomimetic agent; cocaine, etc.

Respiratory Rate (& Pattern)

A 'breath' is an inspiration followed by expiration and can be seen by observing the movement of the chest wall. The normal respiratory rate in adults is between 12 and 20/min. and should be counted for one full minute. Depth of breathing should also be recorded, as either 'shallow', 'normal' or 'deep', along with whether accessory muscles are used. The depth of breathing can easily be followed on the bedside monitor which uses trans-thoracic impedance to determine the respiratory rate and produce a respiratory waveform (see Fig. 14.4). The respiratory rate, depth of breathing, patient position (supine vs upright) and work of breathing should be evaluated. A patient lying flat (on one or two pillows) breathing comfortably with good chest excursions at a rate 16–18 breaths/min is "A" okay. However an increase in the depth and rate of breathing (hyperventilation) indicates impending respiratory failure (type 1), while a low respiratory rate (bradypnea) is a sign of type II respiratory failure. A respiratory rate above 20/min is an early warning sign of patient decompensation; while a rate above 26/min indicates impending "doom". Kussmaul breathing is usually associated with a metabolic acidosis (e.g. ketoacidosis) while Cheyne-Stokes breathing is seen in moribund patients most notably with severe systolic heart failure. Biot's respiration is an abnormal pattern of breathing characterized by groups of quick, shallow inspirations followed by regular or irregular

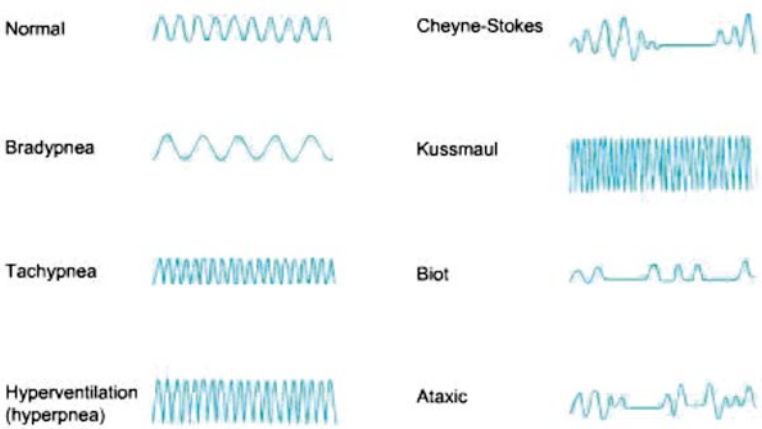

Fig. 14.4 Patterns of spontaneous breathing

periods of apnea. It generally indicates a poor prognosis. Biot's respiration is caused by damage to the medulla oblongata due to strokes or trauma or by pressure on the medulla due to uncal or tentorial herniation. Ataxic respiration is an abnormal pattern of breathing characterized by complete irregularity of breathing, with irregular pauses and increasing periods of apnea. As the breathing pattern deteriorates, it merges with agonal respirations. Ataxic respiration is related to Biot's breathing, having similar causes.

Temperature

The patient's temperature is the "least vital" of all the vital signs. However, patients' temperature should be measured on presentation and at least 6 hourly once in the ICU. Core rather than peripheral temperatures should be recorded. Alterations in temperature are important in the diagnosis of infection. (See Chap. 18, Fever in the ICU).

Pulse Oximetry

Pulse oximetry is invaluable in the assessment and management of patients with hypoxemia; cyanosis only becomes obvious clinically at saturation below 80 %… much too late. The value of pulse oximetry in patient care has been so great that pulse oximetry has been referred to as the "fifth vital sign" and arguably the greatest advance in patient monitoring since electrocardiography [28, 29]. Continuous monitoring of arterial saturation (SaO_2) by pulse oximetry is now considered the standard of care in the ICU, OR and PACU. In addition, continuous pulse oximetry is required in all patients undergoing conscious sedation as well as ER patients with respiratory failure, those patients receiving supplemental oxygen and during endotracheal intubation [30]. While pulse oximetry is the standard of care in these settings there is no data that proves that this technology improves outcome [31]. Moller et al. performed a remarkable study (published in 1993) in which 20,802 surgical patients in Denmark were randomly assigned to be monitored or not with pulse oximetry in the OR and PACU [32]. In this study there was a 19-fold increase in the incidence of diagnosed hypoxemia in the oximetry group as compared to the control group, however, the two groups did not differ in cardiovascular, respiratory, neurologic, or infectious complications. Despite the findings of this study "common sense" should dictate that pulse oximetry improves the safety of patients managed in the ICU, OR, PACU and ER, and that the failure to prove a benefit does not mean that the technology is not beneficial. By alerting the clinician to the presence of hypoxemia, pulse oximeters can lead to a more rapid treatment of serious hypoxemia and possibly avoid serious complications. Moreover, pulse oximetry can reduce the requirement/frequency of arterial blood gas analysis. Pulse oximetry is invaluable in the titration of fractional inspired oxygen concentration (FiO_2) and

flow rate (nasal canula) in patients' receiving supplemental oxygen/assisted ventilation. In these settings pulse oximetry should prevent hypoxemia (PaO_2 < 60 mmHg) as well as hyperoxia (PaO_2 >200 mmHg) conditions associated with an increased risk of death (see below).

Pulse oximetry provides an estimation of the arterial oxygen saturation of hemoglobin (SaO_2), which is related to the partial pressure of oxygen in arterial blood (PaO_2). Compared with the measurement standard (multiwavelength CO oximeter), pulse oximeters have a mean difference (bias) of between 0.2 and 1 % and a standard deviation (precision) of less than 2 % when SaO_2 is above 80 % [33]. With modern pulse oximeters the bias is about 1.5 % and the precision less than 2 % with oxygen saturations between 60 and 80 % (data from Nellcor). Patients with hemoglobinopathies (e.g. Sickle hemoglobin) are at risk of having inaccurate pulse oximetry readings. A falsely elevated SaO_2 will be obtained in patients with elevated levels of carbon monoxide and methemoglobin. In addition, patient movement, arrhythmias, nail polish (black, green, blue), hypotension and skin pigmentation can affect pulse oximetry readings [33–37]. Pulse oximetry has been found to be reliable with SBP readings greater than 80 mmHg [37]. Low perfusion states such as hypotension, low cardiac output, vasoconstriction, vasoactive drugs and hypothermia produce a low signal-to-noise ratio resulting in inaccurate readings. Several studies comparing black and white patients reported no significant pigment-related errors in pulse oximeters at normal saturations [38, 39]. "Older" generation pulse oximeters overestimated SaO_2 in dark-skinned individuals at saturations below 80 % (bias of 2–4 %), however this discrepancy appears less with newer generation pulse oximeters (data from Nellcor) [40, 41]. High-intensity lighting, typically fluorescent lights, may also lead to false readings. The SaO_2 level displayed should only be assumed to be accurate when there is a high-quality plethysmographic tracing displayed on the monitor (see Fig. 14.5). Ideally, the display will show a pulse wave with a demonstrable dicrotic notch. Ultimately, the clinician must look at the patient, and if the pulse oximeter (or any other monitor) does not seem to be behaving in a way that is consistent with the clinical picture that is presented, the clinician must determine the cause of the discrepancy.

As the oxygen–hemoglobin dissociation curve is sigmoidal in shape, at high PaO_2, or when the patient is on the "flat part of the curve," large changes in PaO_2 level will lead to only minor changes in SaO_2 level (see Fig. 14.6). At lower levels of PaO_2, relatively small decreases in oxygen tension can lead to rapid decreases in oxygen saturation. A PaO_2 of 60 mmHg usually is associated with a SpO_2 level of about 90 %. The "knee" of the oxygen–hemoglobin dissociation curve is at about 90 %. Below this value oxyhemoglobin saturation decreases more rapidly as oxygen tension declines (see Fig. 14.6 and Table 14.1). On most pulse oximeters the default setting for the low oxyhemoglobin saturation alarm is therefore 90 %, and this should be regarded as the target for oxygenation in most patients.

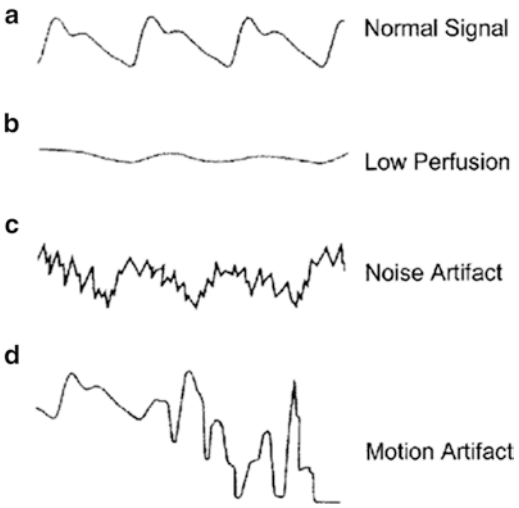

Fig. 14.5 Pulse oximetric waveforms

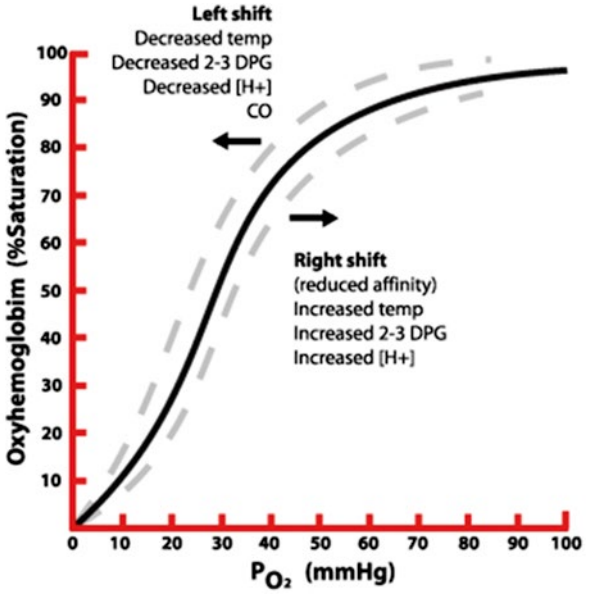

Fig. 14.6 Oxygen-hemoglobin dissociation curve

Equation for calculation of arterial oxygen content:

$$\mathrm{CaO_2} = \left(\mathrm{Hb} \times 1.34\,\mathrm{ml} \times \mathrm{SaO_2}\right) + \left(\mathrm{PaO_2} \times 0.03\right)$$
$$\text{and}\,\mathrm{DO_2} = \mathrm{CaO_2} \times \text{cardiac output}$$

As is evident from the arterial oxygen content equation oxygen delivery is dependent almost entirely on the saturation of arterial blood and cardiac output and not on the PaO_2 (which contributes to the small amount of oxygen dissolved in serum).

Table 14.1 Relationship between arterial oxygen saturation and partial pressure of oxygen

SaO_2	PaO_2 (mmHg)
10	10.3
20	14.5
30	19.2
40	22.8
50	26.6
60	31.2
70	36.9
80	44.5
90	57.8
95	74.2
97.5	99.4
100	700

While respiratory failure is usually defined as a PaO_2 <60 mmHg it is in reality the SaO_2 which should be used to make clinical decisions and the titration of oxygen therapy. However, determining the "*safe degree of hypoxemia*" for an individual subject is exceedingly difficult. The brain is the most sensitive organ to hypoxemia, and visual, cognitive, and electro-encephalographic changes develop when the oxyhemoglobin saturation is less than 80–85 % in normal subjects [42]. Therefore, in most patients, a SaO_2 of 90–92 % results in an adequate level of oxygenation. It is important to note that *non-hypoxemic patients do not benefit from oxygen therapy* [29]. The recommended target saturation range for critically ill patients not at risk of hypercapnic respiratory failure is 92–96 %; however emerging data suggests that targeting a saturation of 90–92 % may be preferable [43]. In patients with severe acute respiratory distress syndrome (ARDS), a SaO_2 target of 86–90 % is acceptable in order to minimize pulmonary oxygen toxicity. Patients chronically exposed to lower oxygen saturation levels adapt to these conditions; this is clearly evident in patients with cyanotic heart disease and mountain climbers. Patients with Fallot's tetralogy are able to mentate with arterial saturations in the 60's [44]. Hillary and Tenzing used supplemental oxygen to achieve the first ascent of Mt. Everest in 1953. Twenty-five years later Messner and Habeler ascended Mt.Everest without supplemental oxygen [45]. The *Caudwell Xtreme Everest Research Group* performed blood gas analysis (from femoral arterial blood) at the balcony of Mt Everest (27,559 ft) in climbers not receiving supplemental oxygen (see Fig. 14.7) [45]. These data clearly indicate that the "acclimatized" human brain can function at quite low levels of SaO_2. In patients with COPD or other known risk factors for hypercapnic respiratory failure (e.g. morbid obesity, chest wall deformities or neuromuscular disorders), a target saturation range of 86–90 % is generally recommended (see Chap. 24) [29]. However, these patients may tolerate a SaO_2 as low as 80–88 % without cognitive dysfunction. The decision to accept lower values should be based on each individual patient's circumstances [42].

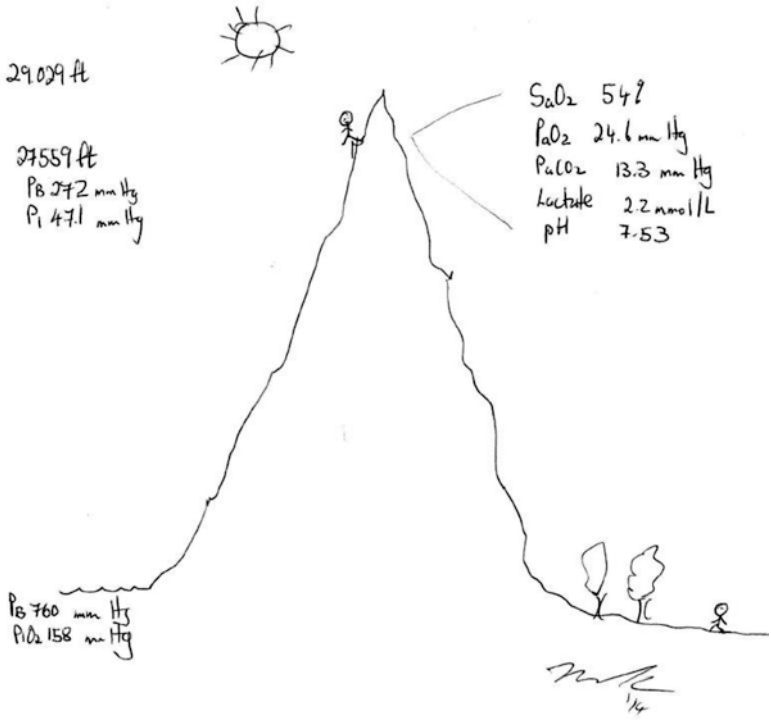

Fig. 14.7 Arterial blood gas analysis at the Balcony of Mt Everest

The SUPPORT study group randomized 1,316 premature infants to a target oxygen saturation of 85–89 % or 91–95 % [46]. Death before discharge occurred more frequently in the lower-oxygen-saturation group (in 19.9 % of infants vs. 16.2 %; relative risk, 1.27; 95 % CI, 1.01–1.60; $p=0.04$), whereas severe retinopathy among survivors occurred less often in this group (8.6 % vs. 17.9 %; relative risk, 0.52; 95 % CI, 0.37–0.73; $p<0.001$). This study highlights the risks of both hypoxemia and hyperoxia, particularly in the developing brain.

It is important to remember that pulse oximetry only reflects the state of oxygenation of the patient. It does not provide any information regarding the patient's ventilation.

Alveolar hypoventilation is the main form of respiratory failure postoperatively and results from combinations of central respiratory depression, muscular weakness, and upper airways obstruction. Alveolar hypoventilation is also common in patients receiving opiates. As arterial carbon dioxide ($PaCO_2$) tension rises so does alveolar carbon dioxide tension (PCO_2); alveolar PO_2 falls, leading to arterial hypoxemia. If the patient is breathing room air then the saturation will fall early and is a reasonably sensitive indicator of hypoventilation. The situation is different if the patient is receiving supplemental oxygen. The alveolar PO_2 will now be much higher and alveolar PCO_2 will have to rise much further before hypoxemia sufficient to produce measurable desaturation occurs [37, 47]. It is therefore critical to realize that when patients are receiving supplemental oxygen, they may have normal SpO_2 levels but be in respiratory failure with hypercapnia and respiratory acidosis. These patients may suffer a cardiac arrest despite normal oximetry. End-tidal CO_2 ($ETCO_2$) monitoring is "mandatory" in these patients.

Too Much Oxygen Kills

Oxygen is a treatment for hypoxemia, not breathlessness, nor pain, nor anxiety, nor hemorrhage, nor wound infection, nor cardiac ischemia, nor..... Although supplemental oxygen is often given "automatically" to patients admitted to hospital, oxygen therapy has no proven benefit in non-hypoxemic patients and is likely to be harmful. In addition, a high oxygen fraction has been suggested to prevent adverse outcomes after surgery and anesthesia, including wound infections and postoperative nausea and vomiting (kinda stupid, see below). The deleterious effects of hypoxia are well known and physicians may be overly concerned about avoiding hypoxia and give additional oxygen 'to be on the safe side'. HOWEVER, hyperoxia is also to be avoided as too much oxygen is toxic.

It is essentially impossible to get a PaO_2 of much about 100 mmHg if you only have 21 % oxygen to breathe, which is all we had for millennia. There's no evolutionarily response to deal with hyperoxia.

There are two main clinical concerns with the administration of supplemental oxygen: the potential development of hypercapnia; and the harmful effects of hyperoxemia itself. The danger of excess oxygen and its association with hypercapnia is well recognized in patients with COPD [48].

- Oxygen can cause carbon dioxide retention in patients with COPD.
- The degree of carbon dioxide retention that develops in response to oxygen is varied.
- There is evidence to suggest that high concentration oxygen causes more carbon dioxide retention and more acidosis than low concentration oxygen

- There is a suggestion that incremental and gradual increases in inspired oxygen may be possible in some patients without major increases in $PaCO_2$.
- There is definite evidence that even patients treated with low concentration oxygen may develop progressive carbon dioxide retention and acidosis

Cameron et al. studied the outcome of patients suffering a COPD exacerbation who had a blood gas analysis within 4 h of presentation to the ER [49]. Hyperoxemia occurred in 61/254 (24 %) presentations and was strongly associated with serious adverse outcome compared with normoxia (OR 9.17, 95 % CI 4.08–20.6). In this study hypoxemia was also associated with an increased risk of serious adverse outcome compared with normoxia (OR 2.16, 95 % CI 1.11–4.20).

High FiO_2 is toxic to the lung [50]. In healthy humans, exposure to 100 % oxygen may lead to atelectasis, impaired mucociliary clearance and tracheobronchitis, alveolar protein leakage and enhanced expression of leukotrienes by alveolar macrophages and increases in alveolar neutrophils [50]. High FiO_2 may cause alveolar injury indistinguishable from ARDS. Barber et al. investigated the pulmonary effects of mechanical ventilation with 100 % oxygen compared to air in ten brain dead patients [51]. The most sensitive indicator of impaired lung function was a decrease in the PaO_2 during breathing of pure oxygen. Within a few hours the PaO_2 declined in the 100 % oxygen group and fell sharply after 30 h, while the PaO_2 (on 100 % O_2) remained stable in the air group. After 50 h the PaO_2 (on 100 % O_2) averaged above 400 mmHg in the air group but only 120 mmHg in the oxygen group. Radiographic changes and total lung weight (at autopsy) supported these physiologic findings. It is assumed that the lung damage caused by hyperoxia is mediated by excess production of reactive oxygen species (ROS). Generation of ROS such as superoxide anion ($\bullet O_2^-$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($\bullet OH$) occur in cells exposed to high concentrations of oxygen and are believed to play a central role in the pathogenesis of hyperoxia-induced lung injury. Cell death is a prominent feature of hyperoxia-induced lung injury. Both apoptotic and necrotic features are present in lungs following prolonged exposure to hyperoxia [52, 53]. Mitochondrial mediated cell injury by ROS has been identified as a critical event in both apoptotic and necrotic forms of cell death in hyperoxia [54]. In animals, prolonged hyperoxia causes histopathological changes similar to those seen in ARDS. Baboons exposed to 100 % oxygen demonstrated a progressive reduction in forced vital capacity and functional residual capacity and proliferative epithelial changes and interstitial fibrosis [55–57]. Apart from its effects on the lungs, oxygen may also lead to systemic toxicity. Normobaric hyperoxia has been associated with an increase in vascular resistance and a decrease in cardiac output [58–60]. Similarly, studies in healthy subjects have shown that hyperoxia is associated with a decrease in cerebral blood flow by 11–33 % [61, 62]. The damaging effects of hyperoxia-generated ROS, although prominent in the respiratory epithelium and endothelium can cause systemic cellular and organ injury. Animal data from stroke models demonstrate that hyperoxia is associated with increased oxidative stress, worst ischemia-induced brain damage, and overall mortality [63–65]. In addition, exposure to sub-lethal hyperoxia has been demonstrated to impair innate immune responses resulting in an increased susceptibility to infection [56].

Hyperoxia may be particularly bad in the setting of ischemia-reperfusion injuries. The normal response of most tissues to ischemia involves a fairly rapid and fundamental change in how oxygen is trafficked. Hypoxia-inducible factor is rapidly upregulated which then drives the transcription of genes and activation of enzymes that work to shut off oxidative phosphorylation and switch the ischemic cells to an increased reliance on anaerobic glycolysis for ATP production. Simultaneously there are changes in the subunit composition of complexes in the electron transport chain (most notably Complex IV, or cytochrome c oxidase). These are adaptive molecular changes to deal with ischemia. These changes become deleterious when oxygen supply is abruptly restored with the increased production of ROS production. Hyperoxia compounds this problem. Finally, there's the issue of free heme. In most critically ill patients the concentration free heme is increased, either from red cell lysis and breakdown of hemoglobin or from myocyte injury with the release and breakdown of myoglobin [66]. The heme groups will redox cycle and generate large quantities of ROS. All that is required is oxygen, and driving up the available oxygen supply will exacerbate this problem. This may be particularly dangerous in patients with sepsis where the presence of proinflammatory cytokines further increases ROS production [67].

De jong and colleagues evaluated the FiO_2 and PaO_2 of 3,322 patients during their first 5 days of mechanical ventilation [50]. In this study a high PaO_2 during the first 24 h after admission was independently associated with increased hospital mortality. As one would expect, these authors demonstrated a "U Shaped" relationship between PaO_2/FiO_2 and mortality; hypoxia kills, but so does hyperoxia. Rincon and colleagues performed a retrospective multicentre cohort study which evaluated 1,212 ventilated traumatic brain injured (TBI) patients [68]. In this study arterial hyperoxia was independently associated with a higher in-hospital case fatality. Similarly, Davis et al. investigate the association between hypoxemia and hyperoxia in 3,420 TBI patients in the San Diego County trauma registry. These authors demonstrated that both hypoxemia and hyperoxemia were associated with increased mortality and a decrease in good neurological outcomes [69]. Kilgannon et al. investigated the relationship between hyperoxia and outcome in 4,459 patients following cardiac arrest [70]. Over ascending ranges of oxygen tension, they demonstrated a linear trend of increasing in-hospital mortality and decreasing survival as functionally independent. On multivariable analysis, every 100 mmHg increase in PaO_2 was associated with a 24 % increase in mortality risk (odds ratio 1.24; 95 % CI 1.18–1.31). Similarly, in patients treated with mild therapeutic hypothermia after sudden cardiac arrest Janz et al. demonstrated that higher levels of the maximum measured PaO_2 were associated with increased in-hospital mortality and poor neurological status on hospital discharge [71]. Rincon et al. studied 2,894 ventilated stroke patients with acute ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage who had arterial blood gases within 24 h of admission to the ICU at 84 ICU's in the US [72]. Mortality was higher in the hyperoxia group as compared with normoxia (odds ratio 1.7; (95 % CI 1.3–2.1) and hypoxia groups (odds ratio 1.3; 95 % CI, 1.1–1.7).

Current American Heart Association (AMA) and Advanced Cardiac Life Support (ACLS) guidelines recommend oxygen prior to acute reperfusion therapy [73, 74]. In a study of 50 patients with STEMI (reported in 1968) oxygen administration before and during reperfusion was associated with a rise in blood pressure, an increase systemic vascular resistance and a fall in cardiac output; undesirable effects in the setting of myocardial ischemia [58]. In a double-blind, randomized in-hospital study (reported in 1976), 200 patients with myocardial infarction were allocated to receive supplemental oxygen or air administered by face mask for the initial 24 h in hospital [75]. There was no significant difference in mortality, incidence of arrhythmias or use of analgesics between the groups. A Cochrane meta-analysis which included this study and two additional small studies demonstrated an increased risk of death with supplemental oxygen therapy; RR 3.03 (95 % CI 0.93–9.83) [76]. An ongoing RCT should will help resolve this issue; however, there is currently NO DATA to support the AHA guidelines recommending supplemental oxygen therapy [77].

Both experimental and clinical data clearly demonstrate the toxicity of hyperoxia which appears to be more harmful to the host than hypoxemia. The human has developed elaborate mechanism to compensate for hypoxemia and may tolerate "permissive hypoxemia" with minimal adverse effects. However, the human has not evolved to deal with hyperoxia which appears to be associated with significant adverse effects. Furthermore, there appears to be a dose-dependent association between supranormal oxygen tension and risk of adverse outcomes. There is no data to support the use of "therapeutic hyperoxia" in any clinical disorder (except for short term treatment of carbon monoxide poisoning) and this iatrogenic misadventure should be vigorously prevented. These data provide further support for the principle of titrating supplemental oxygen therapy to target oxygen saturations as indicated below:

- Critically ill patients not at risk of hypercapnic respiratory failure: 90–92 % (to 94 %)
- Severe ARDS: 86–90 %
- COPD/Asthma/Chronic restrictive/chronic interstitial disease: 86–90 %

Perioperative supplemental oxygen has been proposed to decrease the incidence of surgical site infection (SSI). Bactericidal activity of neutrophils is mediated by oxidative killing, a critical defense against bacterial pathogens [78]. Oxidative killing is dependent on the production of bactericidal superoxide radicals from molecular oxygen. The rate of this reaction, which is catalyzed by the NADPH-linked oxygenase, is dependent on the partial pressure of oxygen in the tissue [78]. Due to disruption of local vascular supply wounds have a lower partial pressure of oxygen than normal tissue. Furthermore, it has been demonstrated that hyperoxia increases angiogenesis-stimulating vascular endothelial growth factor (VEGF) release promoting wound healing [79]. It has therefore been proposed that "*an easy method of improving tissue oxygen tension is to increase the concentration of inspired oxygen*" and that "*this intervention will reduce the risk of SSI* (surgical site infection)" [80]. These assumptions appear to be illogical for a number of reasons. Most importantly, as already discussed increasing the PaO_2 in non-hypoxic patients has a minimal

effect on oxygen delivery and tissue oxygen tension but is likely to increase systemic organ damage mediated by ROS. Furthermore, a higher arterial PaO_2 may not improve tissue oxygenation in devitalized and poorly perfused tissue. In addition, as alluded to above, a high PaO_2 will cause systemic vasoconstriction and decrease cardiac output, two effects likely to decrease tissue oxygen delivery. Nevertheless, the concept of supplemental postoperative oxygen was popularized following the study of Greif et al. published in 2000 [80]. These investigators randomized 500 patients undergoing colorectal resection to receive 30 % or 80 % FiO_2 during the operation and for 2 h afterwards. SSI occurred in 5.2 % of patients who received the high concentration of oxygen as compared with 28 % in the normoxia group ($p=0.01$). There was no difference in any other reported outcome variable including length of hospital stay. This trial must be interpreted with caution, as it was terminated when a one-sided p-value of 0.01 was observed with a 54 % relative risk (RR) reduction in SSI (seems biologically implausible). Generally, trials stopped early for benefit should always be interpreted with great caution, especially when the intervention effect is larger than expected, potentially at a 'random high', and the number of events is small. Following this study a number of RCT's have been reported which have been unable to replicate the findings of Grief et al. The PROXI trial randomized 1,400 patients undergoing major abdominal surgery to receive either 80 % or 30 % oxygen during and for 2 h after surgery [81]. There was no difference in the rate of SSI or any other outcome variable. Pryor et al. randomized 165 patients undergoing major abdominal surgery to a FiO_2 of 80 % or 35 % intraoperatively and postoperatively for 2 h [82]. In an intention to treat analysis, the incidence of infection was significantly higher in the group receiving FiO_2 of 80 % than in the 35 % group (25 % vs. 11.3 %, $p=0.02$). The apparent beneficial effect in another trial is actually not statistically significant when analyzed by true intention-to-treat, as SSI occurred in 22/150 patients assigned to 80 % oxygen compared with 35/150 patients assigned to 30 % oxygen ($p=0.077$ with the two-sided Fisher's exact test) [83]. A meta-analysis which included seven RCT's failed to demonstrate a reduction of SSI with the use of supplemental oxygen therapy [84]. Considering the systemic toxicity of hyperoxia this strategy should not be used to reduce SSI. However, evidence-based interventions which have been demonstrated to significantly reduce the risk of SSI should be considered in these patients (see Chap. 16) [85].

Analysis of the Oximetric Waveform

Analysis of the pulse oximeter waveform can provide very useful information. The pulse oximeter plethysmographic waveform differs from the arterial pressure waveform by measuring volume rather than pressure changes in both arterial and venous vessels. As such the size of the waveform provides an indirect assessment of stroke volume. Furthermore, as an extension of pulse pressure analysis during mechanical ventilation, dynamic changes in both the peak and amplitude of the pulse oximeter

plethysmographic waveform have been used to predict fluid responsiveness [86]. The dynamic change of the plethysmographic waveform with positive pressure ventilation has shown a good agreement with the pulse pressure variation and is useful in assessing fluid responsiveness (see Chap. 9) [87–89]. The "Pleth Variability Index" (PVI) is an automated measure of the dynamic change in the Perfusion Index (PI) that occurs during a respiratory cycle (Masimo Corporation, Irvine, CA). The PI is the infrared pulsatile signal indexed against the non-pulsatile signal and reflects the amplitude of the pulse oximeter waveform. The PVI can predict fluid responsiveness non-invasively in mechanically ventilated patients [90, 91]. While the *"eye-ball oximetric waveform test*" has not been studied, this is a very useful indicator of intravascular volume depletion in patient's receiving mechanical ventilation. This test is performed as follows:

Look at the oximetric and respiratory waveforms simultaneously; if the size/amplitude of the oximetric waveform diminishes during positive pressure ventilation the patient is likely to be volume depleted; this then requires further hemodynamic evaluation (see Chap. 9).

In addition to measuring the arterial saturation, modern pulse oximeters can also measure:

- The pleth variability index (PVI)
- The respiratory rate
- Hemoglobin concentration [92]

Stroke Volume: The 6th Vital Sign

As discussed in Chap. 10, stroke volume (SV) can now be readily measured non-invasively in the ICU, ER, and operating room. Both the trend of the SV (particularly in the OR) as well as the change of the SV following a therapeutic intervention is VITALLY important in the management of critically ill and injured patients. Furthermore, it is vital to realize that changes in blood pressure, pulse rate, respiratory rate and arterial oxygen saturation are late signs of circulatory collapse.

With circulatory compromise the SV falls much earlier than any change in the other vital signs. This implies that a patient with an abnormality of one or more of the traditional vital signs is "in trouble"; however, normal vital signs do not indicate that "all is well." This is best illustrated by the study of Guly et al. using data from the UK Trauma Audit and Research Network database [93]. The estimated blood loss of 164,785 patients was recorded and classified using the ATLS classes of shock [94] The ATLS class was then correlated with the presenting SBP, HR, and RR. A can be seen from Fig. 14.8 patients in Class 4 shock (who had lost more than 40 % of their blood volume) had vital signs within the normal range….. REMARKABLE.

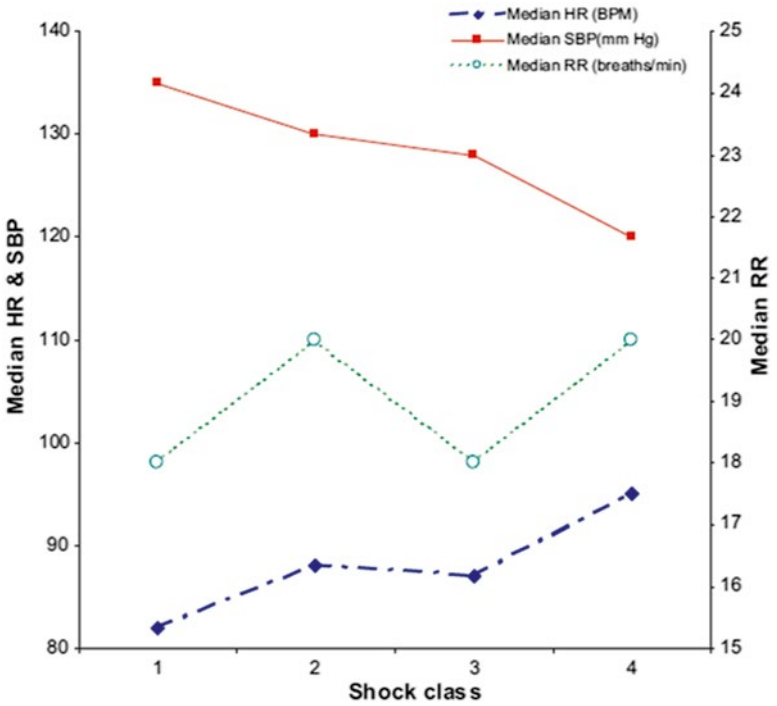

Fig. 14.8 Vital signs in each ATLS class of hemorrhagic shock. Reproduced with permission from Elsevier

Table 14.2 Individual vital sign thresholds indicating potential trouble

Vital Sign	Threshold
SBP mmHg	<100
MAP mmHg	<75
HR/min	>110 or <40
RR/min	>20 or <12
SaO_2 on room air	<90
SVI mL/m2	<30

Putting the Vital Signs Together

The vital signs of BP, HR and RR have traditionally been used in trauma triage. A combination of these signs is likely to perform better than each vital sign alone. Indeed the Shock Index (SI) defined by the HR/SBP (normal 0.5–0.7) has been shown to have a high sensitivity and specificity for predicting poor outcomes and performs better than any of the vital signs alone [95]. Bleyer et al. evaluated the prognostic implications of individual patient vital signs during 27,722 patient hospitalizations [1].

The presence of a solitary critically abnormal vital sign was associated with a mortality of 0.92 % vs. a mortality of 23.6 % for three simultaneous critical vital signs. Furthermore, the *trio of critical vital signs* was highly predictive of patient mortality whether these events occurred on admission or at other times during the hospitalization. The threshold values for the "6 vital signs" are provided in Table 14.2.

Early Warning Scoring Systems and Rapid Response Teams

The use of early warning scoring systems (EWS) to recognize and respond to patient deterioration in a non-ICU setting have been widely recommended. These systems allocate points in a weighted manner to vital signs based on their degree of abnormality. The sum of the allocated points—the early warning score (EWS)—is used then used to direct care. The measurement of vital signs and the use of EWS systems are essential components of the 'Chain of Prevention', a paradigm for structuring the early recognition and response to patient deterioration. There are currently over 30 early warning scoring systems. The Royal College of Physicians recommends the use of a National Early Warning Score (NEWS) for the routine clinical assessment of all adult patients (see Table 14.3). Using a large vital signs database (n = 198,755 observation sets) collected from 35,585 consecutive acute medical admissions, Smith et al. demonstrated that NEWS had a high discriminant ability (AUC between 0.72 and 0.89) and performed better than 33 other EWS [96].

Hospitalized patients often exhibit abnormal vital signs in the hours before they suffer a cardiopulmonary arrest. It has therefore been suggested that in most cases of cardiac arrest there is sufficient lead-time to identify patients at risk and to intervene medically thereby preventing further physiological deterioration. This concept led to the birth of the Rapid Response Team (RRT) [97]. A RRT is typically a multidisciplinary team of medical, nursing, and respiratory therapy staff charged with the prompt evaluation, triage, and treatment of patients with signs of clinical deterioration not treated in the ICU. RRTs became widely adopted by hospitals around the world. Although RRTs have broad appeal, robust evidence to support their effectiveness in reducing hospital mortality is lacking. A major multicenter, cluster-randomized, controlled trial (published in 2005), the Medical Early Response

Table 14.3 The National Early Warning Score (NEWS)

Vital Sign	3	2	1	0	1	2	3
Resp. Rate	≤8		9–11	12–20		21–24	≥ 25
SpO_2	≤91	92–93	94–95	>96			
Suppl. O_2		Yes		No			
Temp (C)	≤35		35.1–36.0	36.1–38	38.1–39	≥39.1	
SBP	≤90	91–100	101–110	111–219			≥220
Heart rate	≤40		41–50	51–90	91–110	111–130	≥131
Mentation				Alert			Not alert

Intervention and Therapy (MERIT) study failed to demonstrate a benefit from RRT's. More recent meta-analyses have likewise failure to demonstrate a mortality benefit from RRT's [98, 99].

RRT activation depends on the accuracy of staff observations, judgment about the patient's condition, diligence in the measurements of vital signs and willingness to call for help in a timely fashion. Non-activation and delayed activation of RRT are associated with increased mortality [97]. A system that assists in the acquisition, interpretation and display of vital signs and provides prompts to escalate the level of care might improve the identification of deteriorating patients. Bellomo et al. performed a multicenter controlled before-and-after study to test this hypothesis [100]. Automated vital signs monitors recorded patient temperature, BP, HR, and pulse oximetry. Respiratory rate was entered manually (newer monitors can measure this parameter). This information was then used to automatically calculate an EWS which was displayed as "safe range" in white; "observe range" in yellow; "warning range" in orange, and "urgent range" in red. Deployment of this system was associated with increased survival of patients receiving RRT calls. With the enhanced capabilities of bed-side monitors and the ubiquitous availability of WiFi and smart devices there is no reason that such monitoring systems should not become ubiquitous in the modern hospital.

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Chapter 15
Management of Pain, Agitation and Delirium

"Today we will be mixing ... the Draught of Peace, a potion to calm anxiety and soothe agitation. Be warned: if you are too heavy-handed with the ingredients you will put the drinker into a heavy and sometimes irreversible sleep, so you will need to pay close to what you are doing," admonished potions teacher Severus Snape as he addressed Harry Potter and his classmates at Hogwarts School of Witchcraft and Wizardry.

From Harry Potter and the Order of Phoenix, JK Rowling

Pain and anxiety are almost universal feature of ICU patients. Clinically significant pain and anxiety have been reported in up to 70 % of ICU patients. Anxiety is often caused or exacerbated by uncontrolled pain. Severe anxiety is not limited to mechanically ventilated patients; indeed Treggiari-Venzi and colleagues demonstrated that up to 30 % of non-intubated SICU patients had severe anxiety [1]. Anxiety has numerous adverse effects, consequently, the control of anxiety is an integral component of the management of the ICU patient. Traditionally, the liberal use of sedatives was recommended in order to treat anxiety, with ventilated patients being heavily sedated with continuous infusions of sedative agents. The traditional approach to sedation in the ICU was one of deep sedation in which the patient was "snowed". We now know that is approach to harmful and associated with numerous complications. Furthermore, ICU patients can be effectively managed with minimal or no sedation. Indeed, Strom et al. performed a RCT in which 140 mechanically ventilated patients were randomized to standard sedation or no sedation [2]. In this study patients were randomized to receive no sedation or sedation with propofol for 48 h. After 48 h the sedative was change to an infusion of midazolam. Both groups were treated with bolus doses of morphine (2·5 or 5 mg) as required for pain control. In cases in which delirium was suspected, intravenous haloperidol was given as bolus doses. Patients who received no sedation had greater ventilator and ICU free days with no apparent adverse events. This study dispels the common myth that all patients who require mechanical ventilation should receive sedative medications [3].

The primary objective of sedation is too allay anxiety, enhance patient comfort, promote sleep and facilitates mechanical ventilation. The first step in this process is to treat pain (see Fig. 15.1). Prospective studies confirm that the majority of patients who are treated in ICUs have pain, which makes the assessment of pain and provision of adequate analgesia essential components of ICU care [4]. Studies on ICU-

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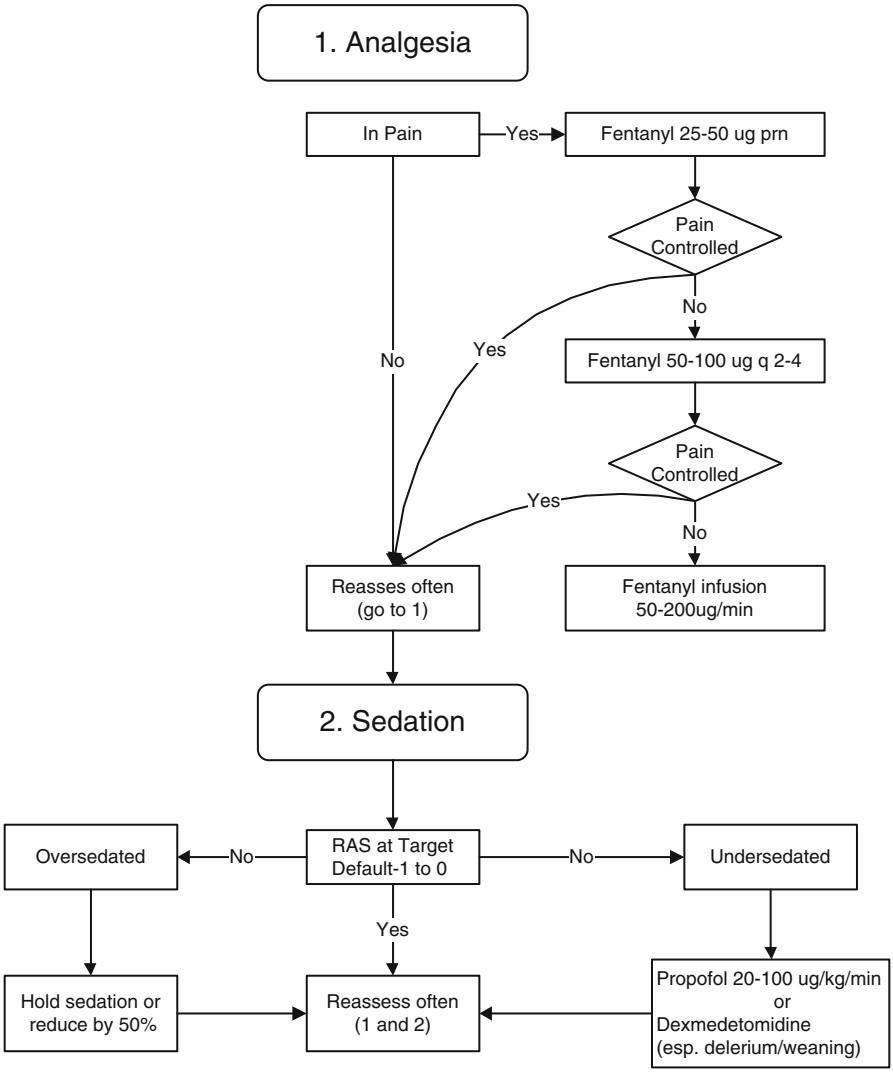

Fig. 15.1 Analgesia/sedation protocol for mechanically ventilated patients. Adapted with Permission from Vanderbilt University, Drs Girard, Pandharipande and Ely

discharged but still-hospitalized patients showed that 82 % remembered pain or discomfort associated with the endotracheal tube and 77 % remembered experiencing moderate to severe pain during their ICU stay [5, 6]. The negative physiologic and psychological consequences of unrelieved pain in ICU patients are significant and long-lasting [7]. Pain management is best achieved with boluses of fentanyl (25–50 μg). In patients in whom pain is poorly controlled with bolus doses of analgesia a continue infusion of fentanyl is recommended. Thoracic epidural anesthesia/analgesia be considered for postoperative analgesia in patients undergoing abdominal aortic

aneurysm surgery. Likewise, thoracic epidural analgesia should be considered for patients with traumatic rib fractures. Sedative agents should be considered in patients who continue to display anxiety once pain control is achieved. Maintaining light levels of sedation in adult ICU patients is associated with improved clinical outcomes (e.g., shorter duration of mechanical ventilation, shorter ICU length of stay, less delirium). In 251 critically ill patients, Shehabi et al. identified deep sedation within 4 h of commencing ventilation as an independent negative predictor of the time to extubation, hospital death, and 180-day mortality [8]. Similarly, in a study of 259 patients ventilated for greater than 48 h these authors demonstrated that the depth of sedation in the first 48 h was independently associated with longer time to extubation, hospital death and 180-day mortality [9]. A minority of ICU patients have an indication for continuous deep sedation, for reasons such as the treatment of intracranial hypertension, severe respiratory failure, refractory status epilepticus, and prevention of awareness in patients treated with neuromuscular blocking agents

Strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) are preferred over sedation with benzodiazepines. A meta-analysis which compared a benzodiazepine sedative strategy with a nonbenzodiazepine sedative strategy, demonstrated that the nonbenzodiazepine strategy was associated with a shorter ICU length of stay and duration of mechanical ventilation without a mortality difference [10]. Patients who have been receiving prolonged infusions of benzodiazepines at high doses in the acute setting are at risk of withdrawal on discontinuation. In mechanically ventilated ICU patients managed with individualized targeted sedation, Pandharipande et al. demonstrated that the use of a dexmedetomidine infusion resulted in more days alive without delirium or coma and more time at the targeted level of sedation than with a lorazepam infusion [11]. The 28-day mortality in the dexmedetomidine group was 17 vs. 27 % in the lorazepam group ($P=0.18$).

Based on these data three sedative strategies are currently recommended:

- Propofol infusion titrated to the lowest possible dose
- Dexmedetomidine infusion
- Bolus doses of lorazepam (1–5 mg)

Infusions of benzodiazepines are best avoided as they are associated with a higher incidence of delirium. None of the sedative agents have analgesic properties, hence opiates are required for pain control. Opiates are also associated with an increased risk of delirium. However, opiates act synergistically with sedative agents allowing lower doses of each agent to achieve the desired effect.

An essential component of the pain, agitation and delirium pathway (PAD) is the regular bedside assessment of pain, agitation and delirium using validated scoring tools [12]. Assessing the degree of sedation and titrating the drug regimen to predetermined end-points is essential as both over sedation and inadequate sedation are associated with significant complications. Complications of under-sedation include severe anxiety with delusional behavior, interference with medical and nursing care, sympathetic over-activity with increased myocardial oxygen consumption, self-injury and self extubation. Severe anxiety with inadequate sedation has been

reported to be the most important factor leading to unplanned extubations. Oversedation is associated with significant morbidity including prolonged intubation with an increased risk of pulmonary complications and disorientation and delirium. In addition, oversedation may mask significant neurological and neuromuscular complications.

In anxious patients it is important to exclude treatable causes of anxiety and not just increase the amount of sedative drugs being used. Treatable causes of anxiety include:

- uncontrolled pain (NB)
- ventilator settings inappropriate (esp inadequate flow rate)—respiratory incoordination
- drug or alcohol withdrawal syndrome,
- increased work breathing, e.g. pneumothorax, kinked/blocked tube
- pulmonary edema
- Loud ventilator alarms and monitors
- Poor communication with patient as regards diagnosis, therapy etc.

"Doctor, doctor, my patient is very agitated!"
What is your next step?

a. Give 2 mg Ativan to the nurse
b. Give 5 mg Haldol to the patient
c. Take 5 mg morphine for yourself
d. *Look at your patient*.

Assessing the Level of Pain and Sedation

A patient's self-report of pain is considered the "gold standard," and clinicians should always attempt to have a patient rate his or her own pain first [12]. Chanques and colleagues demonstrated that a 0–10 visually enlarged horizontal numeric rating scale was the most valid and feasible of five pain intensity rating scales tested in over 100 ICU patients [13]. The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain scales for monitoring pain in medical, postoperative, or trauma adult ICU patients who are unable to self-report and in whom motor function is intact and behaviors are observable [12, 14–17]. Vital signs (or observational pain scales that include vital signs) should not be used alone for pain assessment in adult ICU patients.

Ongoing clinical evaluation is the most effective method of assessing sedation. In order to provide a more consistent and objective means of assessing the degree of sedation a number of sedation scales have been developed. Reliable sedation scales can enhance communication among caregivers, improve consistency in drug administration,

be used in sedation protocols and improve precision of medication titration as patient needs change over time. The routine use of a sedation scale, including frequent adjustments of the sedation target as needed, is strongly endorsed by evidence-based guidelines [12].

The Glasgow Coma Scale (GCS) was developed to assess the level of consciousness of trauma patients. This scale is commonly used in neurosurgical ICU's. The GCS is however essentially a measure of pathologic obtundation and cannot be recommended for monitoring the level of sedation in ICU patients. The Ramsay Sedation Scale and variations of this scale are frequently used method of assessing and documenting sedation in the ICU. The Ramsay scale was reported by Ramsey and colleagues in 1974 in a study which assessed the use of alphaxalone-alphadolone (Althesin) in 30 ICU patients [18]. The Ramsey scale has a number of significant limitations when used to assess the level of sedation in ICU patients and is not recommended

The Ramsey Sedation Scale

I. Anxious and agitated
II. Cooperative, orientated and tranquil
III. Drowsy, responds to verbal commands
IV. Asleep, responds briskly to light stimulation
V. Asleep, sluggish response to stimulation
VI. Asleep, no response to stimulation

Over 25 instruments have been developed to measure consciousness in the ICU [18, 19]. The Richmond Agitation-Sedation Scale (RASS) which was specifically designed to assess sedation in the ICU, is that scale which has been most extensively tested for reliability and validity in adult ICU patients and is currently recommended as the sedation scale of choice [20, 21]. RASS is a 10-point scale, with four levels of anxiety or agitation (+1 to +4 [combative]), one level to denote a calm and alert state (0), and 5 levels of sedation (−1 to −5) culminating in unarousable (−5).

The Richmond Agitation-Sedation Scale (RASS)

+4 Combative
+3 Very agitated
+2 Agitated
+1 Restless
0 Alert and calm
−1 Drowsy
−2 Light sedation

−3 Moderate sedation
−4 Deep sedation
−5 Unarousable

Sedation Vacations

Observational and randomized trials have demonstrated that protocols directed at minimizing the use of sedative infusions shorten the weaning process. Specifically, approaches intended to avoid over-sedation by limiting the use of continuous infusions either through sedation assessment scoring or by daily cessation of sedation, decreases duration of mechanical ventilation and duration of ICU stay [22–24].

Girard et al. published the results of a trial that employed a "wake up and breathe" strategy (the ABC trial) [25]. Patients randomized to a daily awakening trial followed by a SBT (versus SBT alone) experienced increased time off of mechanical ventilation, decreased time in coma, decreased ICU and hospital length of stay and improved survival at 1 year. Based on this data, the sedation should be stopped (or the dose significantly reduced) each morning; this allows for neurological assessment of the patient, performance of a SBT, reassessment of the goals of sedation, and an individualized exercise/occupational program. Schweickert and colleagues performed a RCT in which patients who remained ventilator dependant for more than 3 days were randomized to early physical and occupational therapy which was coupled with daily awakenings [26]. Patients in the intervention group had shorter duration of delirium and more ventilator-free days with significantly more patients returning to an independent functional status.

Non-pharmacologic Interventions

- Minimize sleep deprivation related to noise and light
- Establish a "normal" day-night cycle
- Orient the patient (place, day, time) as frequently as possible
- Communicate goals of treatment with patient (if possible)
- Music therapy
- Ensure comfort by turning and positioning
- Ensure ventilator synchrony

Delirium

Delirium is characterized by a disturbance of consciousness with accompanying change in cognition. Delirium typically manifests as a constellation of symptoms with an acute onset and a fluctuating course. Delirium in the ICU is very common,

the incidence ranging from 45 to 87 %. The incidence appears to vary according to whether the studied population is composed exclusively of mechanically ventilated patients. The symptoms of delirium have been organized into cognitive and behavioral groups. Common cognitive symptoms include disorientation, inability to sustain attention, impaired short-term memory, impaired visuospatial ability, reduced level of consciousness, and perseveration. Common behavioral symptoms include sleep-wake cycle disturbance, irritability, hallucinations, and delusions. The manifestations of delirium can vary widely among patients. While some patients may manifest somnolence and even coma, others appear anxious, disruptive, or combative. Recognition of this symptom variability has led to the classification of delirium into motoric subtypes. One such subtype is hyperactive delirium, of which the manifestations include agitation, hypervigilance, irritability, lack of concentration, and perseveration. One the other hand, hypoactive delirium manifests as diminished alertness, absence of or slowed speech, hypokinesia, and lethargy. Mixed delirium, as the name implies, includes manifestations of both hyperactive and hypoactive delirium. The mixed and hypoactive forms of delirium are the most common in the ICU. Hypoactive delirium tends to occur more frequently in older patients and carries worse prognosis. While multiple clinical risk factors have been identified and numerous pathophysiologic pathways have been hypothesized, the pathophysiology of delirium remains poorly understood [27]. Studies using magnetic resonance imaging have shown a positive association between the duration of delirium in the ICU and both cerebral atrophy and cerebral white-matter disruption [28, 29]. These preliminary investigations indicate either that delirium in the ICU gives rise to alterations in brain structure or that the presence of such cerebral atrophy and white-matter disruption renders patients more susceptible to delirium. The major predisposing factors include respiratory failure, older age, alcohol abuse, dementia and medications. Classes of medications commonly associated with delirium include anticholinergic agents, benzodiazepines, and opiates. Benzodiazepines appear to be strongly associated with delirium in ICU patients [11].

Delirium is associated with increased ICU and hospital length of stay. The presence of delirium has important prognostic implications; in mechanically ventilated patients it is associated with a 2.5 fold increase in short-term mortality and a 3.2 fold increase in 6-month mortality. Furthermore, delirium is associated with the development of post-ICU cognitive impairment. Delirium is frequently undiagnosed unless specific diagnostic instruments are used. Therefore routine monitoring of delirium in all ICU patients is recommended [12]. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools (see Fig. 15.2) [30]. Gusmao-Flores et al. performed a metaanalysis comparing the CAM-ICU with the ICDSC [31]. The CAM-ICU had a high sensitivity and specificity with a diagnostic odds ratio of 103.3 and a ROC of 0.97. The ICDSC has moderate sensitivity and good specificity (ROC 0.89). The available data suggest that both CAM-ICU and the ICDSC can be used as a screening tool for the diagnosis of delirium in critically ill patients. It is however not clear that the use of these scales is more sensitive than unstructured assessments made by trained bedside nurses who are prompted to look for delirium [32].

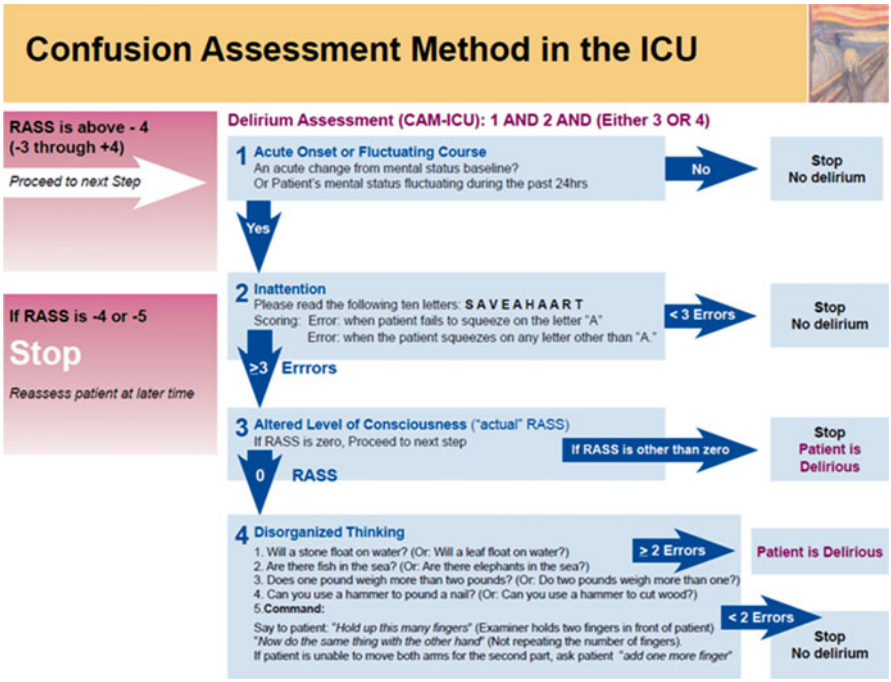

Fig. 15.2 Confusion assessment method for the ICU (CAM-ICU)

Non-pharmacological approaches such as physical and occupational therapy decrease the duration of delirium and should be encouraged. The use of pharmacologic agents to prevent delirium is not recommended, as there is no compelling data to demonstrate that this reduces the incidence or duration of delirium. Page and colleagues randomized 141 mechanically ventilated patients to receive haloperidol 2·5 mg or placebo intravenously every 8 h, irrespective of coma or delirium status [33]. Patients in the haloperidol group spent the same number of days alive, without delirium, and without coma as did patients in the placebo group.

Traditionally haloperidol has been used to treat delirium in the ICU. There is however no published evidence that treatment with haloperidol reduces the duration of delirium. Girard et al. randomized 101 mechanically ventilated patients with delirium/coma to receive haloperidol, ziprasidone, or placebo every 6 h for up to 14 days [34]. Treatment with antipsychotics did not improve the number of days alive without delirium or coma, nor did it increase adverse outcomes. Devlin et al. performed a double-blind, placebo controlled, multicenter study which evaluated the efficacy and safety of quetiapine in 36 ICU patients diagnosed with delirium [35]. Rescue intravenous haloperidol was allowed to be used in both groups. The results showed that quetiapine was associated with quicker resolution of delirium, reduced time of delirium and agitation, and reduced haloperidol requirement compared to placebo. There was however no difference in the duration of ICU stay, length of hospitalization, and

Table 15.1 Dosages and side effects of the atypical antipsychotics

	Starting dose	Sedation	EPS	NMS	QTc prolong
Olanzapine	5 mg daily	Moderate	Low	Low	Low
Quetiapine	25 mg bid	Moderate	Very low	Very low	Low
Risperidone	0.5 mg bid	Low	Low to mod	Low to mod	Low
Ziprasidone	40 mg q6	Low	Low	Unknown	Moderate

EPS extrapyramidal symptoms, *NMS* neurolept malignant syndrome

hospital mortality. Two clinical trials have found that antipsychotics, compared with placebo, hasten the resolution of delirium in hospitalized patients without critical illness. Hu et al. found that haloperidol and olanzapine each led to earlier improvements in Delirium Rating Scales scores among 175 elderly patients, compared with placebo [36]. Similarly, Kalisvaart et al. found that haloperidol reduced the severity and duration of delirium among elderly patients undergoing hip surgery, compared with placebo [37]. These data suggest haloperidol has a limited role in the treatment of delirium. Atypical antipsychotics may reduce the duration of delirium (see Table 15.1). Dexmedetomidine has been demonstrated to reduce the duration of delirium and may be the agent of choice in these patients [38].

Melatonin, a pineal gland hormone that plays a central role in sleep/wake regulation could provide the link between delirium and disruption of the sleep/wake cycle. Melatonin supplementation has therefore been suggested as a treatment option for delirium. Melatonin supplementation might reduce delirium by decreasing the breakdown of both tryptophan and serotonin through negative feedback. Alternatively, melatonin may reset the sleep/wake cycle or may play a direct role in the prevention of delirium. Al-Aama et al. randomized 145 elderly patients admitted to a medical service to receive 0.5 mg melatonin or placebo [39]. In this study, melatonin was associated with a lower risk of delirium (12.0 % vs. 31.0 %, P = 0.014; OR 0.19, CI: 0.06–0.62). Ramelteon is a potent agonist of the melatonin M1 and M2 receptor that has been approved by the FDA for the treatment of insomnia. Small clinical trials have demonstrated the efficacy of ramelteon in the prevention and treatment of delirium. Ramelteon is given as a dose of 8 mg at night. The agent may hold promise in the prevention and management of patients with delirium in the ICU [40, 41].

Sedative and Analgesics Agents

Lorazepam

- Kinetics: Half-life of 10–20 h; less lipid soluble than diazepam; slower onset of action (2–5 min) with peak effect at 30 min; metabolized in liver to inactive metabolites by glucuronide conjugation; least affected by liver and renal disease; longer duration of action due to smaller volume of distribution (10–20 h)

- Dose: 1–2 mg up to 5 mg q 4–6 hourly IV.
- Continuous infusion of lorazepam is not recommended except in patients with severe alcohol withdrawal syndrome. Start at 5 mg/h and then titrate to effect, increasing by 1–2 mg/h not more frequently than every 15 min.
- Rarely, propylene glycol, the solvent in which lorazepam is delivered, can cause toxicity. This causes a constellation of symptoms, including a hyperosmolar metabolic acidosis, high lactate, hypotension, and arrhythmias [42]. This syndrome seems to be most strongly correlated to higher infusion rates and higher 24-h cumulative doses

Midazolam

- Kinetics: Half-life of 4–6 h (shortest); hepatic transformation to active metabolite which is renally cleared; Rapid onset (1–3 min), peak 5 min, duration 1–2.5 h. Accumulates with prolonged infusion.
- Dose: boluses of 1–5 mg every 5 min until desired effect achieved.
- Half-life prolonged in
  - Elderly
  - CHF
  - Liver disease
  - Renal disease
  - MOF

Midazolam is not recommended for sustained sedation because prolonged administration results in extended pharmacologic activity, caused by accumulation of parent drug, especially in patients who are obese, have low serum albumin, or have renal impairment. Prolonged sedative activity from midazolam may also be related to accumulation of its active metabolite, alpha-hydroxymidazolam, especially in patients with renal insufficiency. In addition, because it is metabolized by cytochrome P450 3A4, this drug is subject to significant interactions with several inhibitors and substrates of this enzyme system, including fluconazole, fentanyl, and propofol.

Benzodiazepines should be avoided in

- Patients with liver failure
- Non-intubated COPD patients

Propofol

- Kinetics: Half-life of 30–60 min. Onset 30 s; offset few minutes (does not accumulate). Even when the drug is used for several days, the return to a conscious state occurs within 10–15 min. Propofol is metabolized by glucuronide and

sulfate conjugation. Dose reduction is not required in patients with hepatic or renal disease.

- Dose: Produces stable and predictable levels of sedation. The starting dose of propofol is 5 μg/kg/min. The dose should be increased by 5 μg/kg/min every 15 min until desired effect is achieved (RASS-level). Normal dose range is between 15 and 75 μg/kg/min (depends on desired effect and co-administered drugs)
- Propofol has no analgesic properties and therefore analgesics may be required.
- The emulsion in which propofol is contained represents approximately 0.1 g of fat (1.1 kcal) for every milliliter. This high lipid load may result in excessive CO_2 production, as well as hyperlipidemia when used for prolonged periods of time in the ICU. Significant elevation of serum triglyceride levels have been reported with prolonged infusions of propofol. It is currently recommended that the lipid profile be monitored closely if patients receive the drug for more than 72 h and that appropriate adjustments be made to the enteral nutritional formulation.
- Propofol should not be used in non-intubated patients as the patient may rapidly lose control of their airway (VERY NB).

Dexmedetomidine

- Dexmedetomidine is a selective alpha2-adrenergic receptor agonist with anxiolytic, analgesic, sedative and sympatholytic properties.
- Dexmedetomidine results in a state of "cooperative sedation" and is associated with EEG changes commensurate with natural sleep.
- Kinetics: About 94 % protein bound, but this has been reported to be significantly decreased in patients with hepatic impairment. Dexmedetomidine is almost completely metabolized by direct glucuronidation or by cytochrome P450 isoenzymes. It is excreted mainly as metabolites in the urine and faeces. The terminal elimination half-life is about 2 h.
- Dose: Loading dose of 1 μg/kg over 10 min, followed by a maintenance infusion of 0.2–0.7 μg/kg/min
  - Reduced doses may be necessary in patients with hepatic impairment and in the elderly
- Does not depress the respiratory drive
- The most frequently observed adverse effect with dexmedetomidine is hypotension. Other adverse effects include bradycardia, nausea and vomiting, and fever.
- Unlike clonidine, cessation of administration does not appear to be associated with rebound hypertension or agitation.
- Dexmedetomidine is associated with less delirium than other sedative agents and may also be the drug of choice for the treatment of delirium.

Haloperidol

- Kinetics: Half-life 18–54 h; Onset 5–30 min; duration 4–8 h
- Dose: 2–5 g IV. The dose can be repeated with 5 mg increments every 15 min, up to 25 mg.
- Useful for the treatment of delirium
- AVOID in patients with prolonged QTc
  - Procainamide, quinidine, amiodarone, azithromycin, etc.
  - Monitor QTc with prolonged use

Fentanyl

- Kinetics: Half-life 2–4 h; Onset 1–2 min; Duration 30–60 min. Fentanyl is a potent opiate which has a rapid time to onset, short duration of action (compared to morphine), is easily titratable and has minimal hemodynamic effects. These properties make fentanyl the agent of choice for pain control in the ICU.
- Dose: 25–100 μg boluses q 2–4 hourly or an infusion starting at 5 μg/h titrate up to 200 μg/h in 20 μg increments every 30 min.
- Transdermal fentanyl patches (which deliver 25, 50, 75 or 100 μg/h) may provide excellent pain control.

Morphine

- Kinetics: Half-life 2–3 h; Onset 1–2 min, peak effect 20 min, Duration 1–2 h
- Dose: 2–5 mg boluses or an infusion starting at 2 mg/h, titrate up to 10 mg/h in 2 mg increments every 30 min.
- Morphine should be AVOIDED in patients with renal failure. Morphine has active metabolites (morphine 3-glucuronide and morphine 6-glucuronide) which are renally excreted; these accumulate in renal failure causing "delayed" respiratory depression.

Meperidine

Meperidine should generally be avoided in ICU patients. This drug has an active metabolite, normeperidine, which is a CNS stimulant and causes seizures particularly in patients with renal impairment and patients with a history of seizures. This agent can be used in patients with pancreatitis as it does not cause contraction of the sphincter of Oddi.

Neuromuscular Blockade

The use of neuromuscular blocking agents' has fallen out of favor because of evidence that they may contribute to prolonged neuromuscular weakness; however, a study by Papazian and colleagues demonstrated that neuromuscular blockade may be useful in a select population of patients with early severe acute respiratory distress syndrome when used for a limited timeframe of 48 h [43]. Expert guidelines suggest that neuromuscular blocking agents should be titrated to train of-four twitch monitoring [44], although results of clinical trials are conflicting when train-of-four (TOF) monitoring is compared with "clinical judgment" alone [45]. TOF monitoring was probably appropriate with the use of "older" neuromuscular blocking agents which tended to accumulate with long term use. However, this appears unnecessary with cisatracurium. Cisatracurium is currently the preferred neuromuscular blocking agent, because it undergoes spontaneous metabolism by Hofmann degradation. In the rare circumstances in which neuromuscular blocking agents are administered in the ICU, there seems little reason to justify the use of any drug other than cisatracurium. A bolus vecuronium or rocuronium may be used in situations were "emergent" neuromuscular paralysis is required.

Neuromuscular Blocking Agents

Cisatracurium

- Duration of action 30–90 min
- Intubation: initial, 0.15–0.20 mg/kg IV bolus
- Maintenance: 2–3 μg/kg/min (infusion range of 0.5–10.2 μg/kg/min)
- The metabolism and excretion of cisatracurium is not dependent upon renal function, but rather upon organ-independent Hofmann elimination, and dosing reductions are not required in renal failure and hepatic failure

Vecuronium

- Duration 60–75 min
- Intubation: 0.07–0.1 mg/kg
- Maintenance: 4–10 mg/h

Rocuronium (for intubation only)

- Duration: Acts within 1 min with duration of action up to 30 min.
- Intubation: 0.6–1.2 mg/kg

Succinylcholine (for intubation only)

- Duration 5–15 min.
- Intubation 1 mg/kg
- Beware bradycardia with repeated doses

- CONTRAINDICATIONS to the use of Succinylcholine include:
  - renal failure
  - burns
  - severe trauma with muscle injury
  - severe sepsis
  - ocular injuries

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Chapter 16
Hospital Acquired Infections and Their Prevention

"We can't solve problems by using the same kind of thinking we used when we created them."

Albert Einstein, Theoretical Physicist (1879–1955)

This chapter will review Central Line Associated Blood Stream Infection (CLABSI), Catheter Associated Urinary Tract Infections (CAUTI), Ventilator associated pneumonia (VAP), *Clostridia difficile* enterocolitis and Nosocomial Rhinosinusitis (NS) as well as measures to prevent these infections.

Hospital acquired infections (HAIs) are infections developing in the hospital setting and are a worldwide problem occurring both in developed and in developing countries. It was estimated that in 2002 a total of 1.7 million HAIs (4.5 per 100 admissions) occurred in the US and that almost 99,000 deaths resulted from or were associated with a HAIs; similar data have been reported from Europe [1–3]. These facts have been widely publicized in the lay press and attracted the attention of hospital administrators and governmental agencies, whose stated goals are to *eliminate HAIs*. It is however likely that these estimates are inflated. More recent data suggest that there are approximately 440,000–640,00 HAIs annually in the US [4, 5]. In a recent point prevalence study conducted in 183 acute care hospitals in 10 "geographically diverse states" in the US, 4 % of patients developed one or more HAIs [5]. In this study the most common infections were pneumonia (21.8 %), surgical site infections (21.8 %) and gastrointestinal infections (17.1 %). *C. difficile* was the most commonly reported pathogen, causing 12.1 % of all HAIs. Device-associated infections (CLABSI, CAUTI and VAP) which have traditionally been the major focus of infection control programs accounted for only 25.6 % of HAIs.

HIAs increase length of stay and hospital costs. The annual excess costs of HAIs in the US is estimated to be $9.8 billion [4]. The per case excess cost of a CLABSI is been estimated to be $45,814, while that for a VAP is estimated to be $40,144, a surgical site infection $20,785, *C. difficile* infection $11,285 while a CAUTI is estimated to cost $896 [4]. The effects of HAIs on attributable mortality are less clear. Nosocomial infections are more common in those patients with higher acuity illnesses who have a higher mortality and length of stay than less sick patients. It has therefore been unclear as to whether nosocomial infections independently contribute to adverse outcomes. Lambert and colleagues evaluated the clinical

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impact of HAIs on the risk of ICU death and excess length of stay [6]. Complex statistical modelling was used to answer this question. In addition, the authors evaluated the interaction of bacterial resistance with these outcome variables. This study included 119,699 patients from 537 ICU's. During their ICU stay 7 % of patients developed hospital acquired pneumonia (HAP) and 4 % had a blood stream infection. For all pathogens the hazard ratio for excess ICU death was 2.3 for pneumonia and 3.1 for blood stream infection. The time-adjusted excess length of stay was 7.2 and 1.1°days for these diagnoses respectively. The hazard ratios for resistant organisms were only slightly larger than for non-resistant organisms. As will be reviewed below (see section. "Ventilator Associated Pneumonia"), the mean attributable mortality for VAP's is about 13°%. The attributable mortality for the other HAIs has not been studied. It is likely that "CAUTI's" have a negligible attributable mortality while that for surgical site infections is quite low.

In response to the widespread information generated by HAIs, governmental agencies (in the US) have introduced non-payment policies to punish healthcare providers whose patients' develop a HAI. The position of the Federal Government, Centers for Medicare and Medicaid Services (CMS), the Agency for Health Care Quality and Improvement (AHQI), the Institute for Healthcare Improvement (IHI), and other health care organizations in the US is that HAIs should never happen (a never event) and that physicians/nurses have failed in their duty to their patient should a HAI occur. This is clearly an absurd and counter-productive approach to a very complex issue. There is no question of doubt that HAIs are associated with significant morbidity and an increase in the length and cost of hospitalization and all reasonable efforts should be taken to avoid such infections. However, the reality of critical care medicine is that HAIs are an inevitable consequence of managing very sick patients in the ICU. This does not mean that ICU managers/directors should not track HAIs. This data is vital to identify trends and to determine the microbiology of the infecting pathogens. In the study by Climo et al., despite strict adherence to comprehensive infection control measures, 4.78 hospital acquired blood stream infections occurred per 1,000 patient days [7]. It is therefore critically important to recognize that while evidence based interventions reduce the risk of HAIs ***they cannot be totally eliminated*** and therefore healthcare workers should not be punished for factors beyond their control. By the very nature of their illness, host defense mechanisms are impaired (cough reflex, muco-ciliary clearance, skin and mucosal barrier, innate and acquired immunity) which predispose the critically ill and injured ICU patient to infection. The only way to "completely eliminate" HAIs, is by not recording them accurately (i.e. to cheat) or by admitting low acuity (healthy) patients to the ICU. Nevertheless, in October 2008, CMS discontinued additional payments for HAIs (CLABSI, CAUTI and mediastinitis following CABG) that were deemed preventable. These punitive measures are likely to have a number of adverse effects (unintended consequences), including "*If you don't look, you don't find and don't report*" (and? don't treat). Furthermore surveillance bias and data quality bias influence reporting results [8]. Illustrated in Fig. 16.1 is the rate of CLABSI before and after public reporting was mandated in the State of Pennsylvania

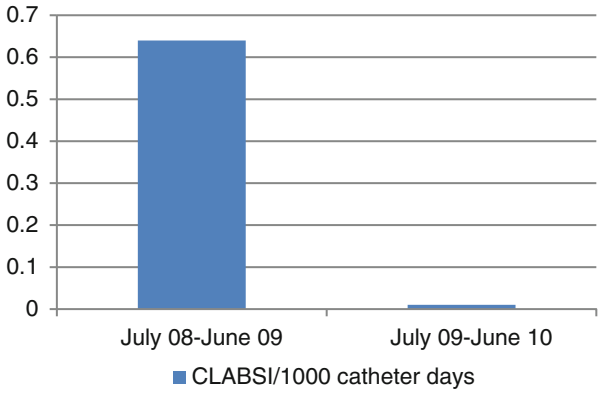

Fig. 16.1 CLABSI before and after mandatory reporting in the state of Pennsylvania

in 2007 [9]. Common sense would suggest that both rates are incredibly low and not believable… *if it looks good to be true… it's probably not true*. Using Medicare impatient claims following 638,761 CABG procedures in 1,234 hospitals in the US, Calderwood and colleagues demonstrated that at the exact time that CMS adopted the withholding of payments for mediastinitis there was a sudden and precipitous fall in the coding (reporting) of mediastinitis [10]. However, mediastinitis rates using National Healthcare Safety Network surveillance data showed no change in mediastinitis infection rates, i.e. if it looks like a duck and quacks like a duck it must be coded as a camel.

By the very nature of "the beast" critically ill patients will develop HAI's, and the sicker the patient the greater the likelihood they will develop an infection.

Colonization with Multidrug Resistant Organisms

The sequence of events leading to HAIs has been well characterized. The vast majority of HAIs are due to bacteria and fungi (Candida spp.) which the patients' acquire while in the hospital and ICU. Colonization of the patient' skin and upper respiratory tract is the first step in the chain of events leading to a HAI. For example, HAP including ventilator associated pneumonia (VAP) results from the aspiration of colonized oropharyngeal material. It is now well recognized that the most important mode of transmission of nosocomial pathogens are through direct-contact between an infected or colonized person and a susceptible host [11]. This occurs predominantly by means of transmission through the hands of health care providers; i.e. health care providers transfer potential pathogens from infected or colonized patients to other patients. Less commonly, infection occurs by contaminated medical devices, from the patient's own flora and via airborne particles. In addition, contaminated hard surfaces (bed-rails, bedside tables) and soft surfaces (sheets,

pillowcases or gowns) may be a source of microbes contributing to indirect-contact and aerosol transmission of nosocomial-related pathogens [12, 13].

The colonizing pathogens are usually multidrug resistant organisms (MDR) [6, 14]. The most common nosocomial pathogens are *Clostridium difficile*, Staphylococci (especially *Staphylococcus aureus*), *Klebsiella* species, *Escherichia coli*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Streptococcus* species and Acinetobacter species [5]. The prevalence rates of pathogens that cause HAIs have a high level of resistance to antibiotics such as MDR *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, MDR *Acinetobacter baumannii*, Carbapenem Resistant Enterobacteriaceae (CRE), Methicillin Resistant Staphylococcus Aureus (MRSA), and vancomycin resistant enterococci (VRE).

Handwashing and Infection Control Measures

Handwashing

Measures which reduce the colonization rate of hospitalized patients with potentially pathogenic organisms reduce the risk of HAIs. Colonization of ICU patients occurs predominantly by means of indirect patient-to-patient transmission through the hands of health care providers. Common sense would therefore suggest that the most effective means to break this cycle is a rigorous program and enforcement of adequate hand hygiene. This seminal observation was made by Dr. Ignac Semmelweis in 1847 when he demonstrated that puerperal fever could be prevented by ***hand antisepsis*** (with a chlorine lime solution) [15]. While no randomized controlled trials comparing hand-antisepsis to no hand-antisepsis have been (or are likely to be) conducted, multiple lines of evidence suggest that hand-antisepsis is the single most important intervention to reduce HAIs [16, 17].

ICU managers must enforce strict policies of hand antisepsis of all health care workers on both entry and exit from the ICU room [16]. Alcohol-based hand-hygiene products have excellent in vitro germicidal activity against gram-positive and gram-negative bacteria including multi-drug resistant pathogens [16]. Alcohol-based gels or foam products should therefore be provided outside every ICU room. As hand antisepsis products have very poor activity against bacterial spores, the use of gloves and hand washing with soap-and water should be mandated in all patients with *Clostridia difficile* infection [16].

Chlorhexidine Bathing

Climo and colleagues demonstrated that daily bathing with chlorhexidine-impregnated washcloths reduces the risk of acquisition of MDR organisms and the development of hospital acquired blood stream infections [7]. The use of chlorhexidine-impregnated

washcloths did not alter chlorhexidine susceptibly of clinical isolates collected during the study. This approach is therefore strongly recommended to reduce colonization of ICU patients.

Gloves and Gowns and Healthcare Provider Apparel

The use of "gloves and gowns" has been popularized as a method of reducing the transmission of potential pathogens from the clothes of health care workers. It has however remained rather speculative and unproven that the clothes of health care workers may play a role in the transmission of such organisms. Harris and colleagues demonstrated no benefit from universal "gown and glove" use when compared to usual care [18]. This findings is supported by the study of Huskins et al. who provided convincing evidence that in the setting of a MRSA/VRE screening protocol, barrier precautions are no more effective in preventing the transmission of potential pathogens than "adequate" hand hygiene alone [19].

The Society of Healthcare Epidemiology (SHEA) of America has recently released an official statement regarding heath care workers attire and infection control measures [20]. This policy statement emphasized that "*no clinical studies have demonstrated cross-transmission of healthcare-associated pathogens from a health care provider to a patient* via *apparel*". They further state that "*priority should be placed on evidence-based measures to prevent HAIs* (*e.g.*, *hand hygiene*, *appropriate device insertion and care*, *isolation of patients with communicable diseases*, *environmental disinfection*)." Studies which have assessed patient's preferences for certain types of attire, indicate a strong preference for formal attire, including a white coat. Formal attire and white coats inspire confidence in the physician and is associated with an increased degree of professionalism [20–22]. A "*Bare below the elbows*" (BBE) mandate has been issued in the UK. BBE is defined as healthcare providers wearing short sleeves, no wristwatch, no jewelry, and no ties during clinical practice. Patients have shown general disapproval of BBE attire [22]. Furthermore, there is no evidence that BBE has any impact on the transmission of pathogens and the acquisition of HAI [23]. SHEA does not recommend limiting the use of specific HCP apparel including neckties and jewelry [20].

Universal Screening for MDR's and "Protective Isolation"

Screening all ICU admissions for nasal MRSA carriage and isolating those colonized or previously colonized/infected with MRSA has been widely adopted as a method to reduce spread of MRSA. Previous studies have demonstrated that this "vertical" approach has limited or no benefit. More recent prospective, cluster controlled studies have confirmed this finding. Derde et al. performed a large multiphase, time series, cluster randomized controlled trial comparing usual infection

control measures with universal chlorhexidine body-washing combined with enforced hand hygiene (best standard precautions) [17]. They then compared best standard precautions with conventional screening for MRSA and VRE, and with rapid screening (PCR testing for MRSA) with contact precautions for all identified carriers [17]. In this study, improved hand hygiene plus unit-wide chlorhexidine body-washing reduced acquisition of MDR's. In the context of a sustained high level of compliance to hand hygiene and chlorhexidine bathing, screening and isolation of carriers did not reduce acquisition rates of MDR, whether or not screening was done with rapid testing or conventional testing. In a similar study, Huang et al. compared (1) screening and protective isolation, with (2) screening, protective isolation and decolonization of MRSA with (3) a strategy of universal decolonization using daily chlorhexidine bathing and intranasal mupirocin for 5 days (without screening and isolation) in a very large cohort of patients (76,256 patients and 74 ICU's) [24]. The strategy of universal decolonization was significantly more effective in preventing infection with MRSA as well as bloodstream infection from any pathogen. These studies in composite now suggest that the screening and isolating patients with MRSA is an ineffective intervention in preventing HAI and should abandoned. Not only is this strategy ineffective but it has many downstream negative consequences. Apart from the costs and time expended, this strategy "isolates" patients from both their health care providers and their family. In the study by Harris et al. universal use of "gowns and gloves" significantly reduced the number of times heath care provides entered the room of their patients. Previous research has demonstrated that patients isolated for infection control precautions experience more preventable adverse events, express greater dissatisfaction with their treatment, and have less documented care [25–27]. Families of patients in "protective isolation" find the procedures involved burdensome and distressing and interfere with their ability to provide emotional support to their loved ones. Protective isolation should however be reserved for patients with *C. difficile* infection

Oropharyngeal and Gastrointestinal Decolonization

Interventions such as chlorhexidine mouth wash and selective decontamination of the digestive tract with non-absorbable antibiotics kill colonizing pathogens before they can be aspirated and thereby theoretically reduce the risk of VAP [28, 29]. The use of chlorhexidine mouth washes is however controversial, as this intervention has only been demonstrated to reduce this risk of VAP in cardiac surgery patients. A recent metaanalysis demonstrated that chlorhexidine mouth washes had no effect the risk of VAP, duration of mechanical ventilation or ICU LOS in non-cardiac surgery patients and was associated with a trend towards increased mortality in these patients (see Sect. "Ventilator Associated Pneumonia") [30]. Nevertheless, meticulous oral hygiene is recommended in all intubated ICU patients.

Selective decolonization of the digestive tract (SDD) was popularized in Europe over 30 years ago [31]. SDD regimens typically include oropharyngeal and enteral

antimicrobials (usually tobramycin, polymyxin E, and amphotericin B) throughout the period of endotracheal intubation in combination with parenteral antimicrobials (usually cefotaxime) for the first few days. Various modifications of the "full SDD" protocol have been studied including selective digestive decontamination (without parenteral antibiotics) and selective oropharyngeal decontamination. The goal of SDD is to prevent patient colonization with potentially pathogenic organisms. Since the original study by Soutenbeek et al. in 1984 [31], over 50 RCT's have been performed in medical-surgical, medical, surgical, pediatric and burn ICU's. In general these studies have shown a reduction in HAIs particularly VAP as well as a reduction in the duration of mechanical ventilation and duration of ICU stay [32–34]. The effect of SDD on mortality has been somewhat inconsistent [33–35]. However, a meta-analysis which included 21 "full SDD" studies demonstrated a significant reduction in mortality (OR 0.71; 95 % CI 0.61–0.82, $p<0.001$) [36]. While SDD is "popular" in Europe this technique has not been adopted in the US for fear of increasing bacterial resistance. However, this fear appears unfounded. In a review of 64 studies, Daneman and colleagues detected no relation between the use of SDD and the development of antimicrobial resistance, and concluded that the "*perceived risk of long-term harm related to selective decontamination cannot be justified by available data*" [37]. Oostdijk et al. performed a cost effective analysis of the use of SDD/SOD in 13 Dutch ICU's [38]. In this analysis SDD/SOD were associated with relative risk reductions of mortality at day 28 of 13 % and 11 %, respectively, as compared with standard care with total patient costs being lower with SDD/SOD.

Private Rooms and Environmental Control

Teltsch and colleagues demonstrated a reduction in colonization rates following ICU room privatization (single patient rooms) [39]. This finding is likely explained by the fact that it is difficult to operationalize and enforce hand hygiene when patients are in close proximity in a multi-bed ICU room.

ICU rooms should be cleaned (terminal cleaning) once a patient has been discharged from the room and prior to the admission of the next patient; this is particularly important in patients with a *C. difficile* infection. A novel approach to environmental control of MDR organisms involves the use of copper impregnated hard and soft surfaces within the ICU. Metallic copper has intrinsic broad-spectrum antimicrobial activity. In vitro, copper surfaces reduce bacterial concentration by at least seven logs within 2 h, including bacteria commonly encountered in the ICU. Schmidt et al. demonstrated that copper limits the concentration of bacteria on bed rails within the ICU [40]. Salgado et al. demonstrated that patients cared for in ICU rooms with copper alloy surfaces had a significantly lower rate of incident HAIs and colonization with MRSA or VRE than did patients treated in standard rooms [41].

An aggressive policy of hand washing together with chlorhexidine body bathing appears to be the most effective method of limiting colonization of ICU patients with

MDR organisms and thereby reducing the risk of HAI's. Although the data supporting SDD appears compelling, the use of this technique remains controversial.

Central Line Associated Blood Stream Infection

Central venous catheters (CVC's) are ubiquitous in the ICU. In the US alone 15 million CVC days occur in ICU's each year [42]. CVC's are not without risk during both placement and while in situ. The most important complication associated with use of CVC's are central line associated blood stream infections (CLABSIs). Approximately 250,000 cases of CLABSI (80,000 in the ICU) occur in hospitals in the US annually; an estimated 30,000–62,000 of these patients die as a result of this infection [42, 43]. In response to this problem, a number of healthcare organizations in the US and Europe have published "Clinical Practice Guidelines" with the aim of reducing the incidence of CLABSIs [43–49]. In common, these guidelines recommend "bundles of care" which include selection of catheter type, method of placement, care of the catheter and timely removal of the catheter. With the institution of these "bundles" the incidence of CLABSI has been reduced to less than 3 per 1,000 catheter-days in most hospitals in the US and Europe [50]. Current data demonstrates a mean CLABSI rate of between 1.1 and 1.8/1,000 catheter days in non-burn ICU's in the US [51].

Central Line Associated Blood Stream Infection (CLABSI) may be caused by:

- non-tunneled central venous catheters (CVC's)
- tunneled CVC's
- peripherally inserted central venous catheters (PICC)
- arterial lines
- non-tunneled hemodialysis catheters
- tunneled hemodialysis catheters
- subcutaneous ports

Generally tunneled/cuffed CVCs and PICC catheters (out-patients) have a lower risk of CLABSI than non-tunneled CVCs. Tunneled hemodialysis catheters have a

lower risk of CLABSI than non-tunneled hemodialysis catheters. Similarly, the risk of CLABSI is lower for arterial lines as compared to non-cuffed CVCs. However, it should be noted that the simultaneous placement of multiple CVC's significantly increases the rate of CLABSI [52]. The incidence of CVC related blood stream infection is reported to vary from about 1 to 5 per 1,000 catheter-days (mean about 2/1,000 catheter days); for arterial lines the incidence varies from about 1 to 3 per 1,000 catheter-days [51, 53–55]. While the risk of CLABSI with PICC lines is generally believed to be less than those of CVC's, this may not be so in hospitalized patients. A prospective cohort study by Safdar and Maki reported that ICU patients with PICCs had rates of CLABSI that were similar to those in patients with non-tunneled central catheters and higher than infection rates for PICCs in the outpatient setting [56]. Pongruangporn et al. reported a PICC CLABSI rate of 3.13/1,000 catheter days in hospitalized patients [57]. In this study the risk of infection was greater for double lumen (OR 1.89) and triple lumen PICC's (OR 2.87). Similarly, Baxi et al. reported a PICC CLABSI rate of 2.69/1,000 catheter days [58]. In this study double and triple lumen PICCs as well as "Power PICCS" had an increased risk of CLABSI. It should be noted that PICCs are associated with an increased risk of thrombosis and pulmonary emboli. In a single-center study of hospitalized patients, the incidence of PICC thrombosis was 4.9 % with those patients with a history of prior venous thromboembolism having an extremely high risk for this complication (OR 10.83). The size and shape of the tip of the PICC influences the risk of thrombosis; Power PICCs appear to be associated with an increased risk of thrombosis [58].

The pathogenesis of non-tunneled CVC infections is usually due to extraluminal colonization of the catheter by skin commensal flora with hub colonization playing a lesser role. In comparison, tunneled CVC's or implantable devices, contamination of the catheter hub and intraluminal infection is the most common route of infection [59]. A number of factors have been identified as increasing the risk of CLABSI including, length of time in situ, the number of lumens in the CVC, the number of stopcocks, the transfusion of blood and blood products, parenteral nutrition, and an open infusion system. While the risk of CLABSI increases with time the catheter remains in-situ, changing catheters at regularly scheduled interval has not been shown to reduce the risk of CLABSI. Furthermore, guidewire exchanges may increase the risk of infection [60].

The preferred site for placement of a non-tunneled CVC is controversial. The subclavian site is associated with a lower rate of cutaneous colonization, dressing disruption, catheter colonization and infection and is recommended in US and European guidelines [61]. While the subclavian site is the preferred site for CVC placement in most patients, this is not always possible. Many guidelines recommend that the femoral site be avoided due to the perceived higher risk of CLABSI associated with this site. The 2011 recommendations from the "Healthcare Infection Control Practices Advisory Committee" of the Centers for Disease Control (CDC) state "*Avoid using the femoral vein for central access in adult patients*" (Class 1A recommendation) [43]. A meta-analysis by Marik et al. demonstrated no difference in the risk of CLABSI between the subclavian, internal jugular or femoral sites [62]. This study was limited by the fact that the quality of the studies included in the

meta-analysis were generally poor, however the authors found no evidence to support the CDC recommendations [62]. More recently, Timset and colleagues analyzed the risk of colonization and CLABSI in 2,128 patients who had either a femoral ($n = 1{,}301$) or internal jugular (n=1,001) CVC placed as part of two RCT's [63]. As the data were obtained from prospective RCT's specifically studying CLABSI they were able to perform a very detailed analysis from the combined data set. Despite the fact that patients with femoral catheters were sicker than those with an internal jugular CVC's (higher SAPS II score) the risk of CLABSI, catheter-tip colonization, dressing disruption and skin colonization did not differ between the two sites. This very well executed study therefore supports the meta-analysis by Marik et al. Although the meta-analysis by Marik et al. did not show a difference between the internal jugular and subclavian sites, "soft data" suggests that the risk of infection is lowest at the subclavian site [64–67]. In the study by Parienti et al., patients with a BMI > 28.4 kg/m^2 had a higher risk of CLABSI with femoral as compared to jugular placement of a dialysis catheter [68]. Parienti and colleagues have recently completed the *3-SITES Multicenter Randomized Controlled Trial* in which over 3,000 patients were randomized to placement of a CVC at either the internal jugular, femoral or subclavian site (clinTrials.gov NCT01479153). It should be noted that in this study patients with morbid obesity underwent restrictive randomization to the subclavian or internal jugular sites. The results of this study should (hopefully) provide high quality evidence to resolve this ongoing debate.

Based on these data, a pragmatic approach to site selection for central venous cannulation is recommended. The site of preference should depend on the expertise and skill of the operator and the risks associated with placement. In an emergent situation or in high risk patients femoral placement may be preferred. All lines that are placed under less than ideal emergency circumstances should be removed and re-sited within 24–48 h. Lines placed in the internal jugular and femoral site should be placed under direct ultrasound guidance as this technique reduces the risk of placement complications [69–72]. The subclavian site should be avoided in patients with chronic renal failure to preserve the arm veins and subclavian vein for possible fistula placement [48]. The femoral veins should be avoided in renal transplant patients. The femoral site should be avoided in morbidly obese patients (BMI > 40 kg/m^2). Another potential reason to avoid the femoral site is to allow early mobilization; this is particularly true for dialysis catheters. The internal jugular site is associated with a higher risk of CLABSI in patients with tracheotomy and this site should therefore be avoided in these patients [73, 74].

Coagulase-negative staphylococci (CNS) account for up to 40 % of cases. Methicillin resistant *S. aureus* (MRSA) and vancomycin resistant Enterococci are becoming important causes of CLABSI [75]. The implicated pathogens vary somewhat with the site of catheter placement, with the incidence of Candida species and gram-negatives being higher for femoral catheters [76, 77].

The diagnosis of CLABSI can be challenging. Routine culture of blood withdrawn from the catheter is not recommended, however, the catheter exit site should be inspected daily for evidence of erythema or pus. The absence of local infection, however, does not exclude CLABSI. In a patient with an indwelling CVC who

develops a fever two sets of peripheral blood cultures should be drawn. If the patient has systemic signs of infection and no other identifiable source of infection, the catheter should be removed and empiric antibiotics commenced, pending culture results (see Chap. 18; Fever in the ICU). In patients with limited venous access the central catheter may be replaced with a new catheter over a guidewire, however, both the catheter tip as well as the intracutaneous portion of the catheter should be sent for culture. If the catheter culture returns positive (>15 cfu) or the blood cultures are consistent with a CLABSI, the line that was changed over a guidewire must be removed and replaced with a new catheter at a clean site. Followup blood cultures should be obtained in patients with CLABSI. If blood cultures remain positive a thorough investigation for septic thrombosis, infective endocarditis, and other metastatic infections should be pursued.

Staphylococcus epidermidis is the most commonly isolated CNS. Currently, there are more than 40 recognized species of CNS. These organisms typically reside on healthy human skin and mucus membranes, rarely cause disease, and are most frequently encountered by clinicians as contaminants of microbiological cultures. Other important CNS include *Staphylococcus lugdunensis*, *Staphylococcus saprophyticus*, and *Staphylococcus haemolyticus*. The pathogenic potential of CNS lies in their ability to colonize and proliferate on biomaterials. As CNS account for the majority of CLABSI it is often difficult to distinguish a true CLABSI from a "contaminant." A single positive culture should be regarded as a contaminant while multiple positive cultures suggest a CLABSI. When in doubt cultures should be repeated. The Infectious Diseases Society of America consider the following criteria to indicate probable or definite CNS CLABSI [78]:

- At least two positive blood cultures
- At least one blood culture should yield a quantitative count of ≥ 15 colony-forming units (CFU)/m
- The blood samples that yielded positive culture results should have been collected within a 72-h period.

This issue is further complicated by the fact that the biotype cultured from the blood may not be the same biotype as cultured from the catheter [79]. Furthermore, it would appear that CNS strains that cause CLABSI may be genetically distinct from common skin colonizers [80]. It is therefore likely that genetic biotyping may assist in distinguishing true "pathogens" from colonizers. Procalcitonin (PCT) assays may be useful in distinguishing true infection from contamination. Scheutz and colleagues demonstrated that patients with CNS blood stream infection had higher PCT concentration than those with blood contamination [81]. At a cutoff of 0.1 ng/dL, PCT had a sensitivity of 100 %, and a specificity of 80 % for the diagnosis of BSI.

In a number of patients the fever is noted to defervesce after removal of the catheter, yet the blood cultures remain negative. These patients are considered to have "culture-negative" CLABSI; presumably the bacteremia was intermittent or below the threshold required for a positive culture. Antibiotics are generally not required in these cases.

The usual approach to patients' with suspected CLABSI involves removal of the catheter. However, only about 20 % of patients who have a CVC removed due to suspected CLABSI are proven to have CLABSI. This subjects patients with negative cultures to the added risk of line placement. To avoid this problem a number of methods have been investigated for the diagnosis of CLABSI which do not require removal of the CVC [82]. Comparison of blood cultured from the CVC with that from a peripheral venous site is currently the most widely used technique. In patients' with CLABSI time to positivity is shorter (more than 2 h) for blood withdrawn from the catheter as opposed to the peripheral site. However, Kaasch et al. demonstrated that the differential time to positivity was not useful in diagnosing CRBSI in routinely obtained blood cultures [83]. This study raises doubt about the utility of this technique.

Management of CLABSI's

In patients with suspected CLABSI all indwelling catheters should be removed and empiric antibiotic therapy commenced. Vancomycin is usually recommended because of its activity against coagulase negative staphylococci and *S. Aureus*. Additional empiric coverage for enteric gram-negative bacilli and *Pseudomonas aeruginosa* with the use of a third or fourth-generation cephalosporin, such as ceftazidime or cefepime, may be needed for severely ill or immunocompromised patients.

Patients with CLABSI should be classified into those with uncomplicated bacteremia or those with complicated infections, in which there is:

- Septic thrombosis
- Endocarditis
- Osteomyelitis
- Possible metastatic seeding

If there is a prompt response to initial antibiotic therapy, most patients who are not immunocompromised without valvular heart disease or an intravascular prosthetic device should receive 10–14 days of antimicrobial therapy. A more prolonged course of therapy (4–6 weeks) should be considered if there is persistent bacteremia or fungemia after catheter removal or if there is evidence of endocarditis or septic thrombosis, and 6–8 weeks of therapy should be considered for the treatment of osteomyelitis. Echocardiography including transesophageal ECHO should be considered in patients with persistent bacteremia/fungemia or lack of clinical improvement to exclude endocarditis.

CNS are the most common cause of CLABSI. CLABSI due to coagulase-negative staphylococci usually present with fever alone, rarely developing "frank sepsis" [84]. While coagulase-negative staphylococci CLABSI may resolve with removal of the catheter and no antibiotic therapy, most experts believe that such infections should be treated with antibiotics (vancomycin) [84]. Furthermore, it has been suggested that catheter removal is not required with CNS CLABSI and that

treatment with antibiotics alone is adequate. This approach has been endorsed by international guidelines [78]. However, Raad and colleagues demonstrated that while this approach was effect in the resolution of infection within 48 h of commencing antimicrobial therapy, it was associated with an unacceptably high rate of recurrence [85]. This is probably related to the fact that CNS develop a multilayered biofilm matrix on the catheter in which they embed themselves and that eradication of catheter colonization is difficult without removal of the catheter.

Antibiotics Lock Therapy

In patients with CLABSI removal of all indwelling vascular catheters is recommended. This may be problematic in patients with tunneled catheters and infusion ports; this necessitates removal of the device and re-insertion once the infection has cleared. A potential solution to this problem is based on the fact that the majority of infections in tunneled catheters originates in the catheter hub and then spreads to the catheter lumen. This fact has prompted the "antibiotic-lock" technique, where the catheter lumen is filled with pharmacologic concentrations of antibiotics where they are allowed to dwell for hours or days. Antibiotic lock therapy, with concomitant parental therapy has a reported response with a catheter salvage rate between 60 and 82 % [84, 86, 87].

Prevention of CLABSI

The best way to avoid a CLABSI is to avoid placement of a central line. While entrenched dogma suggests that vasopressor agents should never be administered using a peripheral venous catheter, this appears to be incorrect (see Chap. 12) [88]. The administration of vasoactive agents using a peripheral catheter in selected patients should reduce the need for central venous catheterization.

While CLABSI is an inevitable complication of critically ill patients who require a central venous catheter, the risks can be significantly reduced by specific interventions [49, 89]. When inserting a new catheter the following precautions should be followed:

- Full drapes and strict sterile precautions
- Use of a line cart
- Skin cleansing with chlorhexidine
- ICU nurse for observation (sterility not broken) and assistance

Additional measure include:

- Clear adhesive dressings
- Limit blood draws from CVC's
- Limits "breaks" in the circuit

- Remove the catheter when no longer required
- All catheters inserted in clinically urgent situations without maximal sterile barrier precautions should be replaced as soon as possible
- Before accessing catheter hubs or injection ports, clean them with an alcoholic chlorhexidine preparation or 70 % alcohol to reduce contamination
- Replace administration sets not used for blood, blood products, or lipids at intervals not longer than 96 h
- Povidone-iodine or polysporin ointment should be applied to hemodialysis catheter insertion sites in patients with a history of recurrent *Staphylococcus aureus* CLABSI
- Guidewire exchanges are strongly discouraged [60]

Antimicrobial coated/impregnated CVC's have been demonstrated to reduce the risk of colonization and CLABSI [90, 91]. These catheters should be considered in ICU's when

- the incidence of CLABSI > 3/1,000 catheter/days despite all the precautions listed above
- Patients who have limited venous access and a history of recurrent CLABSI.
- Patients who are at heightened risk for severe sequelae from a CLABSI (*e.g.*, patients with recently implanted intravascular devices, such as a prosthetic heart valve or aortic graft).

The use of strict aseptic techniques, chlorhexidine skin cleansing and antimicrobial impregnated catheters reduce CLABSI by reducing extraluminal colonization of the catheter. These measures however do not address CLABSI caused by hub colonization. Wright et al. demonstrated that the use of disinfection caps with 70 % alcohol reduced the rate of CLABSI in patients with central lines [92]. The disinfection cap is a plastic threaded cap that houses a small sponge saturated with 70 % isopropyl alcohol. The disinfection cap is threaded onto any lumen not actively in use and remains in place until the lumen is accessed, at which time the disinfection cap is removed and discarded. After the lumen is accessed, a new disinfection cap is threaded on to the lumen. In patients receiving hemodialysis through a catheter, routine interdialytic use of an antimicrobial lock solution has been demonstrated to reduce the risk of CLABSI and is strongly recommended especially in high risk patients [93, 94]. Timset and colleagues demonstrated that disruption of catheter dressings is a common problem and an independent risk factor for CLABSI [67]. In this study dressing disruption occurred less frequently with subclavian catheters, which may largely explain the lower risk of CLABSI that has been reported at this site [64–66].

Do not routinely replace CVCs or arterial catheters. As the risk of infection is less with tunneled dialysis catheters, a tunneled catheter should be placed as soon as feasible (patients with ARF generally will require 2–6 weeks of renal replacement therapy). The role of PICCs in the ICU is unclear. PICCs should be considered in patients who will require prolonged venous access.

Catheter Associated Urinary Tract Infection

It is widely quoted that catheter related urinary tract infections (CAUTI) are the most common HAIs in the ICU, accounting for approximately 23 % of HAI infections among adult ICU patients in the US [95]. It is however likely that this data is wrong and that most ICU patients who are treated for CAUTI have "asymptomatic" bacteriuria which does not require treatment. The treatment of patients with "asymptomatic bacteriuria" is based on a single study performed in the early 1980s that may not be applicable today [96]. Platt and colleagues demonstrated that in hospitalized patients bacteriuria with greater than $>10^5$ colony forming units (CFU) of bacteria per milliliter of urine during bladder catheterization was associated with a 2.8-fold increase in mortality. Based on this study hundreds of thousands (if not millions) of hospitalized patients with urinary tract colonization have been treated with antibiotics. In patients with indwelling urinary catheters, colonic flora rapidly colonizes the urinary tract. Stark and Maki have demonstrated that in catheterized patients bacteria rapidly proliferate in the urinary system to exceed 10^5 cfu/mL over a short period of time [97]. Bacteriuria develops at an average daily rate of 3–10 % per day of catheterization. Almost 26 % of patients with a catheter in place for 2–10 days develop bacteriuria while virtually all patients who have been catheterized for 1 month develop bacteriuria.

The terms bacteriuria and UTI are generally although *incorrectly* used as synonyms. Indeed, most studies in ICU patients (at least prior to 2009) have used bacteriuria to diagnose a UTI. Bacteriuria implies colonization of the urinary tract without bacterial invasion and an acute inflammatory response. Urinary tract infection implies an infection of the urinary tract. However, criteria have not been developed for differentiating asymptomatic colonization of the urinary tract from symptomatic infection. Furthermore, the presence of white cells in the urine is not useful for differentiating colonization from infection, as most catheter-associated bacteriurias have accompanying pyuria [98].

According to National Healthcare Safety Network (NHSN) data from 2006 to 2007, rates CAUTI ranged from 2.6 to 6.5/1,000 catheter days in non-burn ICU's with an average rate of about 2.9/1,000 catheter days [99]. Rates on general care wards were higher, ranging from 4.7/1,000 catheter days in adult step-down units to 16.8/1,000 catheter days in rehabilitation units. In January 2009, the NHSN and the CDC made a significant change to the definition of CAUTI: asymptomatic bacteriuria was removed, leaving only ***symptomatic and bacteremic cases of CAUTI*** to be counted [51]. This change likely affected the reported incidence of CAUTI. According to NHSN data for 2009, CAUTI rates ranged from 1.2 to 2.3/1,000 catheter days in non-burn ICUs [51]. Similarly, Press and Metlay reported that the incidence of CAUTI at their institution fell from 12.5 ± 0.4/1,000 catheter days to 5.3 ± 0.5 following the change in definition [100].

The distinction between asymptomatic bacteruria and "symptomatic CAUTI" is very important, as asymptomatic catheter associated bacteriuria or candiduria is rarely associated with adverse outcomes and generally does not require treatment

with antimicrobials. The diagnosis of "symptomatic CAUTI" is however exceedingly problematic (if not impossible) in ICU patients. The diagnosis of a symptomatic CAUTI requires one or more symptom of a UTI and a positive urine culture growing $>10^5$ cfu/mL with no more than two microorganisms. Symptoms associated with a UTI include urinary frequency, urgency, dysuria, and suprapubic tenderness, symptoms that are unlikely to be volunteered by any ICU patient. Indeed, if an ICU patient is able to volunteer these symptoms he/she does not need a Foley catheter and is unlikely to require continued treatment in an ICU. Furthermore, while fever is common in the ICU, a CAUTI is rarely the cause (see Chap. 18). Tambyah and Maki assessed 1,497 newly catheterized hospitalized patients for evidence of "CAUTI" [101]. In this study, 235 new cases of CAUTI were diagnosed. There was no difference in the signs and symptoms between the patients with and without CAUTI. Only 1 of the 235 (0.42 %) episodes of CAUTI that were prospectively studied was equivocally associated with secondary bloodstream infection. i.e. less than 0.01 % of catheterized patients are likely to develop a significant infection (which is easily treated with antibiotics). Similarly, in a study of 4,465 patients who were admitted to the ICU for a least 48 h, 6.5 % developed a UTI (most were likely asymptomatic bacteruria) with an overall incidence of 9.6 per 1,000 ICU days [102]. However, the incidence of bacteremia and fungemia was only 0.1 per 1,000 catheter days.

Foley catheters are essential in critically ill ICU patients to monitor volume status and renal function and in sedated and comatose patients who have lost voluntary control over micturition. The benefit of these devices clearly outweighs the very low risk of a true CAUTI (approx. 1 in 1,500 patients), which it itself is easily treated with antibiotics and very rarely associated with adverse outcomes. Once the ICU patient has recovered the Foley should be removed. This data suggests that with very few exceptions (patients with urological surgery, stones, stents, renal transplant, etc.,) the urine of ICU patients should NEVER BE cultured… as thousands of patients without an infection (asymptomatic bacteruria) will be treated needlessly with antibiotics (akin to giving antibiotics to sterilize the gut). Catheterized patients with a fever and systemic signs of sepsis should have blood cultures performed and treated with broad-spectrum antibiotics pending culture data (see Chap. 18). Avoiding treatment of asymptomatic bacteriuria should reduce the risk of development of antibiotic resistance and is consistent with the Infectious Diseases Society of America and US Preventive Services Task Force guidelines on bacteriuria [103].

While true CAUTI's are uncommon in ICU patients, Foley catheters should only be placed by adequately trained healthcare professionals using sterile precautions. The Foley should be connected to a closed system and removed when no longer required. Despite the fact that anti-infective urinary catheters seem to reduce bacteriuria in patients with short-term urinary catheterization, there is no convincing evidence that use of these catheters prevents CAUTI, UTI-related bloodstream infection, or mortality.

The National Anti-Foley Obsession is a CONSPIRACY that must be vigorously challenged.

Ventilator Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as a pneumonia which develops after 48 h of mechanical ventilation. VAP is believed to be the commonest nosocomial infection in the ICU and an important cause of morbidity. While the incidence varies according to the diagnostic criteria used and the patient population, it complicates the hospital course of about 20 % of patients receiving mechanical ventilation or about 5 episodes per 1,000 ventilator days [104]. More recent data however suggests an incidence rate of 1.33 per 1,000 ventilator days [4]. VAP has been *associated* with higher mortality, increased length of ICU stay, and greater hospitalization costs. The diagnosis of VAP is extremely difficult as there is no "Gold Standard" diagnostic test. The usual clinical signs of fever, elevated white cell count, change in quality of endobronchial secretions and the presence of a new infiltrate on a portable chest radiograph lack sensitivity and specificity. It is therefore likely that many patients who are diagnosed with VAP don't have VAP and many patients have an undiagnosed VAP. The misdiagnosis of VAP will lead to unnecessary, prolonged and harmful antibiotic treatment. Nussenblatt and colleagues evaluated patients treated for a VAP in 6 ICUs over a 1 year period [105]. A multidisciplinary adjudication committee determined whether the ICU team's VAP diagnosis and therapy were justified, using clinical, microbiologic, and radiographic data. In this study 58.4 % of cases treated for VAP were determined not to have VAP by the committee. Surveillance definitions for VAP have been used by the Centers for Disease Control (CDC) to compare rates between hospitals in the United States. New surveillance definitions for VAP were developed by the CDC in 2013 [106, 107]. These surveillance definitions have little clinical utility (discussed below).

While it is clearly evident that almost all CAUTIs have no clinical significance, what about the clinical significance of VAPs? Do critically ill patients with multiorgan failure who develop a VAP die from the VAP or is the VAP just an epiphenomena

of critical illness. In a cohort of 2,873 patients of whom 434 developed VAP, Nguile-Makao and colleagues estimated an attributable mortality of 8.1 % [108]. In this study, attributable mortality was higher in surgical patients and patients with an intermediate severity of illness score (SAPS II) at ICU admission. Melsen and colleagues determined the attributable mortality of VAP by performing a meta-analysis of individual patient data from randomized prevention studies [109]. Individual patient data were available for 6,284 patients from 24 trials. The overall attributable mortality was 13 %. Most importantly the attributable mortality was *close to zero* in trauma, medical patients, and patients with low or high severity of illness scores. Highest cumulative risks for dying from VAP were noted for surgical patients and patients with midrange severity scores at admission (APACHE II Score between 20 and 29). This study suggests that in medical and trauma patients VAP occurs as part the multi-organ dysfunction syndrome and is merely a concomitant epiphenomena. However, in patients undergoing surgery, VAP is an important complication which contributes to excessive mortality. This finding has important implications for the adoption of measures to "prevent" VAP and for the treatment of VAP.

Pathogenesis of VAP

In mechanically ventilated patients colonization of the oropharynx with potentially pathogenic organisms (PPO) occurs within 36 h of intubation with colonization of the endotracheal biofilm within 96 h [110]. Furthermore, endotracheal intubation compromises the patient's natural anatomic barriers (glottis, larynx, ciliated epithelium and mucus). Subglottic pooling of colonized oropharyngeal secretions with subsequent leakage of secretions around the endotracheal cuff allows PPO to gain entry to the lower respiratory tract [111]. Patients are unable to cough and the mucociliary escalator is rendered ineffective by endotracheal intubation. Intubated patients are therefore unable to clear these colonized secretion from the lower respiratory tract predisposing to both infection and atelectasis. The "aspiration" of colonized oropharyngeal secretions is therefore believed to be the major pathogenic mechanism causing VAP [112]. Using molecular bio-typing Bahrani-Mougeeot and colleagues demonstrated that 88 % of patients with VAP had the same bacteria isolated from the lung (by bronchoalveolar lavage) as their oral cavity [113].

The major risk factors for VAP include factors that increase oropharyngeal colonization, increase the risk or degree of aspiration as well as factors that impair local defense mechanisms. The major risk factors include:

- Supine positioning
- Previous antibiotics (esp. broad spectrum)
- Ventilation lasting greater than 7 days
- Reintubation
- Intra-hospital patient transport
- Chronic obstructive pulmonary disease
- ARDS

- Thoraco-abdominal surgery
- Trauma
- Burns
- Central nervous system disease

The common pathogens causing VAP include:

- *Pseudomonas aeruginosa*
- Methicillin resistant *Staphylococcus aureus* (MRSA)
- *Klebsiella pneumonia*
- Acinetobacter species
- *Stenotrophomonas maltophilia*
- *Streptococcus pneumoniae* (early VAP)
- *Haemophilus influenzae* (early VAP)

Less common pathogens include:

- *Escherichia coli*
- *Enterobacter* spp.
- *Citrobacter* spp.
- *Serratia* spp.
- *Legionella* spp.

Colonization (often extensive) of the respiratory tract with Candida species is common in mechanically ventilated patients [114]. However, invasive Candida pneumonia is extremely rare. Respiratory tract colonization with Candida species has been reported to be an independent predictor of mortality; this is likely related to the fact that colonization is associated with severity of illness and prior use of broad-spectrum antibiotics rather than being a direct contributor to excess mortality [115]. There is no data to suggest that colonization of the respiratory tract with Candia species, nor its presence in high concentration in quantitative culture requires treatment with anti-fungal agents. *Aspergillus fumigatus* may occur in organ transplant, immunocompromised and neutropenic patients; an environmental source such as contaminated air ducts or hospital construction should be suspected.

Polymicrobial infection is common. Importantly, the incidence of VAP caused by MDR organisms is increasing [116]. VAP caused by MDR organism(s) is associated with increased mortality [111, 117, 118]. Risk factors for infection by MDR organisms include:

- Intubation for longer than 7 days
- Previous broad spectrum antibiotics
- Hemodialysis
- Hospitalization for 2 days or more (in the last 90 days)
- Prior to admission to the ICU
- Immunosuppression
- Poor functional status

Taking these factors into account, patients with suspected VAP should be divided into two groups; namely those at high or low risk of having an infection

with multi-resistant pathogens [119]. This is similar to the approach for treating patients with other types of pneumonia (see Chap. 17) This classification is more useful that the traditional distinction between early and late VAP [120, 121].

Diagnosis of VAP

The clinical criteria that have "traditionally" been used to diagnose VAP include: a new or progressive pulmonary infiltrate, fever, leukocytosis and purulent tracheabronchial secretions. These clinical criteria are however non-specific and of little clinical utility in the diagnosis of VAP [122, 123]. An autopsy investigation demonstrated that only 52 % of patients with pneumonia at autopsy had a localized infiltrate on their chest radiograph and that 40 % did not have a leukocytosis close to their death [124]. The Clinical Pulmonary Infection Score (CPIS) was developed as a "non-invasive" method to diagnose VAP, and uses a combination of clinical features together with the culture of a tracheal aspirate to diagnose pneumonia [125]. The CPIS assigns 0–12 points based on six clinical criteria:

- Fever
- Leukocyte count
- Oxygenation
- Quantity and purulence of secretions
- Type of radiographic abnormality
- Results of sputum (tracheal aspirate) gram stain and culture.

Both the original CPIS and the modified CPIS have, however, proven unreliable for the diagnosis of VAP, with a low sensitivity and specificity with considerable inter-observer variability in the calculation of the score [123, 126–128]. It should be emphasized that the upper respiratory tract of intubated patients are rapidly colonized with PPO and that gram stain and culture of tracheal aspirates are unable to distinguish between upper airway colonization and lower respiratory tract infection (pneumonia).

As the clinical criteria of VAP lack specificity, a number of diagnostic techniques have been reported which attempt to distinguish between patients with lung infection as opposed to those colonized with potentially pathogenic organisms or those with a tracheo-bronchitis. Lower respiratory tract sampling is based on the premise that the lower respiratory tract is normally sterile, that there is a good correlation between the concentration of bacteria in the lung and the severity of the pulmonary inflammatory process and that bronchoalveolar lavage (BAL) quantitative culture closely correlates with the concentration of bacteria in the lung [129, 130]. BAL specimens may be obtained bronchoscopically or blindly using the mini-BAL technique [125, 131]. The advantages of m-BAL is that bronchoscopy is not required and that sampling can readily and safely be performed by trained respiratory care practitioners [132, 133]. Effective antibiotic therapy causes a rapid decline in the BAL bacterial load within 24 h. BAL sampling should therefore be *performed prior*

to the initiation of antibiotics. False negative results are therefore more common in patients who have had a new antibiotic instituted within 72 h of sampling. To lower the risk of not treating patients with VAP (false negatives) we suggest a diagnostic threshold of 10^4. While this "quantitative" diagnostic approach appears to be logical and is supported by experimental studies it has not been proven to have a major impact on clinical outcomes [134]. Furthermore, procalcitonin (PCT) appears to have a poor diagnostic accuracy for VAP (for reasons that are unclear), PCT may be used to guide the duration of antibiotic therapy [135, 136].

To complicate issues further the Centers for Disease Control and Prevention (CDC) convened a VAP Surveillance Definition Working Group to ***simplify and standardize*** the diagnosis of VAP [106, 107]. This group coined a number of new terms including *Ventilator Associated Condition* (VAC) and *Infection Related Ventilator Associated Complication* (IVAC). IVACS' were further subdivided into *Possible Ventilator Associated Pneumonia* or *Probable Ventilator Associated Pneumonia* with diagnostic criteria provided for each category.

The CDC document states "*The Working Group's surveillance definition algorithm, which is referred to as the ventilator-associated events or VAE surveillance definition algorithm, represents a purposeful departure from VAP toward more general, objective measures of conditions and complications occurring in patients on mechanical ventilation*" (you figure what this means).

The stated benefit of these "new" definitions is to improve public reporting and performance evaluation [137]. From the perspective of the beside intensivist managing critically ill patients, this word-soup appears to be of little value… except for confusing administrators to the point that they are totally clueless!

Treatment

Multiple studies have demonstrated that the most important factor determining the outcome of VAP is the early initiation of appropriate antibiotic therapy [138–141]. In order to initiate appropriate initial antimicrobial coverage two factors are crucial:

- Is the patient at risk of infection with a MDR organism
- Local ICU bacteriology

Due to the spectrum of potential pathogens and the increasing prevalence of MDR organisms a broad spectrum, multi-drug, empiric antibiotic protocol is required in most patients with suspected VAP (except those at low risk of infection with a MDR organism). BAL and quantitative culture allows for the de-escalation of antibiotics once a pathogen(s) is identified. Furthermore, negative lower respiratory tract cultures can be used to stop antibiotic therapy in a patient who had cultures obtained in the absence of an antibiotic change in the past 72 h [119]. A low PCT provides further evidence for stopping antibiotics in these patients [135, 136].

General Concepts for the Antimicrobial Treatment of VAP

- An empiric therapy regimen should include agents that are from a different class than the patient has recently received.
- Linezolid should be considered the drug of choice for proven MRSA infection. The role of vancomycin for the initial empiric coverage until microbiological data is available is controversial.
- De-escalation of antibiotics should be considered once data are available on the results of lower respiratory tract cultures and the patient's clinical response. Once a pathogen has been isolated and its sensitivity determined, monotherapy is appropriate for most patients with VAP (including Pseudomonas) except for those patients who are neutropenic or bacteremic [142].
- In patients with negative quantitative lower respiratory tract cultures strong consideration should be made for discontinuing antibiotics, particularly in non-surgical patients. This decision should take into account the patient's clinical status, as well as changes in the chest radiograph and clinical features of infection as well as the PCT level.
- Aerolized antibiotics have not been proven to have value in the therapy of VAP
- An 8 day course of antibiotics is recommended for patients with uncomplicated VAP who have received initially appropriate therapy and have had a good clinical response, with no evidence of infection with non-fermenting gram-negative bacilli. A short course of antibiotics has been shown to reduce the risk of recurrence of VAP with no adverse outcomes. However,

for cases of VAP due to non-fermenting Gram-negative bacilli, recurrence is greater after short-course therapy, and 14 days of treatment is suggested in these patients [143].
- There is enormous variability of bacteriology from one hospital to another, specific sites within the hospital and from one time period to another. Current site specific data must be used to guide the choice of antibiotics.

Empiric Antibiotic Choices

No risk factors for MDR pathogens (single agent Rx) [119]

- Ceftriaxone
- Levofloxacin or moxifloxacin
- ampicillin/sulbactam
- piperacillin/tazobactam

Risk factors for MDR pathogens (combination Rx) [119]

- Antipseudomonal cephalosporin (Cefepime, Ceftazidime)
- Antipseudomonal carbapenem (Imipenem or Meropenem) or
- Piperacillin/tazobactam

Plus

- Anti-pseudomonal fluoroquinolone (ciprofloxacin or levofloxacin)
- Aminoglycoside (amikacin, gentamicin, or tobramycin)

Plus

- Linezolid
- Vancomycin

"Specific" Interventions for Prevention of VAP

As discussed above, it may not be possible to completely prevent VAP, however a number of interventions have been demonstrated to reduce the incidence of VAP. Intubated critically ill patients have impaired local defense mechanisms, predisposing these patients to VAP and the only way to prevent VAP with a high degree of certainty is removal of the endotracheal tube.

The Institute for Healthcare Improvement (IHI) has developed "*a ventilator bundle*" that incorporates several strategies that supposedly prevent VAP. This "ventilator bundle" has been widely adopted throughout the world and is considered by many to be the standard of care. However, many of the elements of the "ventilator bundle" are not evidence based and remarkably one of the "preventive measures" has been conclusively demonstrated to increase the risk of VAP (you figure!). Moreover, it is not clear that institution of "the bundle" predictably reduces the risk of developing VAP [144]. Furthermore, the concept of "bundling" in severely flawed and devoid of scientific evidence [145]. Remarkably, those interventions that have been demonstrated to reduce the risk of VAP, were not included in the bundle, namely SDD (as discussed above) and subglottic secretion drainage (discussed below) … . Quite Bizarre! (see Table 16.1).

Table 16.1 Elements of the IHI ventilator bundle

Bundle element	Comment
Elevation of the head of the bed to 45°	No better than elevation to 10°
Daily sedation vacations and assessment of readiness to extubate	Hastens extubation but has not been shown to reduce the risk of VAP.
Daily oral care with chlorhexidine	Reduces risk of VAP in cardiac patients only; no effect on duration of mechanical ventilation or ICU LOS. Trend towards increased mortality in non-cardiac patients
Proton pump inhibitors or H2 receptor antagonists	Increase risk of VAP (see Chap. 33)
Anticoagulants or compression devices preventing venous thromboembolism	Likely to be beneficial. No evidence that this intervention reduces risk of VAP

Elevation of Head of Bed

In a paper published in 1999, Drakulovic and colleagues demonstrated a lower frequency of clinically suspected VAP in 39 intubated patients randomized to the semirecumbent (45°) as opposed to the supine body position (47 patients) [146]. In this study the risk of pneumonia was highest for patients receiving EN in the supine body position. Based on this small, single center study it became standard of care to nurse all ICU patients in a semirecumbent 45° position particularly when receiving tube feeds. Indeed the Centers for Disease Control and Prevention (CDC) [147], the Agency for Healthcare Research and Quality (AHRQ) [148], and the Institute for Healthcare Improvement (IHI) [149] all suggest elevating the head of the bed to 45° above horizontal to reduce gastroesophageal reflux and the incidence of nosocomial pneumonia. The results of the study by Drakulovic et al. have however not been reproduced. Nieuwenhoven et al. randomized 112 intubated patients to the semirecumbent position with a target backrest elevation of 45° and 109 patients to a supine position with a backrest elevation of 10° [150]. Average elevations were 9.8° and 16.1° at day 1 and day 7, respectively, for the supine group and 28.1° and 22.6° at day 1 and day 7, respectively, for the semirecumbent group. The target semirecumbent position of 45° was not achieved for 85 % of the study time, and these patients more frequently changed position than supine-positioned patients. There was no difference in the risk VAP or any other outcome variable between groups. In an observational study of 66 ventilated patients, Grap et al. reported a mean backrest elevation of 21.7° with no association between backrest elevation and the Clinical Pulmonary Infection Score [151]. Rose and colleagues performed 2,112 backrest elevation measurements in 371 patients in 32 ICU's. Backrest elevation ≥45° was recorded in 5.3 % of instances and elevation of between 30° and 45° in 22.3 % of instances [152]. In this study the mean backrest elevation was 23.8°. These studies suggest that nursing a patient semirecumbent at 45° is not feasible and attempts to do so may not reduce the risk of VAP. When the head of the bed is inclined at 45°, the patient often slides down; most of the weight of the upper body is applied on the sacral area and this position becomes uncomfortable for the patient. Furthermore, experimental models suggest that the semirecumbent position may enhance the flow of mucous into the lungs with an increased risk of bacterial colonization and pneumonia [153]. While maintaining a patient supine (0°) probably increases the risk of pneumonia there is no strong evidence that elevation of the head of the bed between 10 and 30° is associated with a greater risk of pneumonia than a semirecumbent 45° position.

Chlorhexidine Mouth Wash

Because the pathophysiology of VAP involves aspiration of contaminated secretions into the respiratory tract, efforts have been made to decontaminate the mouth with chlorhexidine to prevent VAP. A meta-analysis by the Cochrane group demonstrated that oral care that includes either chlorhexidine mouthwash or gel is

associated with a 40 % reduction in the odds of developing VAP [154]. There was no evidence of a difference between oral hygiene including toothbrushing (+chlorhexidine) compared to oral hygiene without toothbrushing (+chlorhexidine) for the outcome of VAP. Furthermore, there was no evidence of a difference in the outcomes of mortality, duration of mechanical ventilation or duration of ICU stay in patients' receiving oral care with vs. without chlorhexidine. A more recent meta-analysis stratified studies into cardiac surgery and non-cardiac surgery studies [30]. This stratification is appropriate as cardiac surgery patients are intubated on average for only 1 day and therefore by definition do not develop VAP but rather HAP. In this meta-analysis chlorhexidine reduced this risk of HAP in cardiac surgery patients but had no effect on the risk of VAP in non-cardiac surgery patients. There was no difference in the duration of mechanical ventilation or ICU-LOS in either group. However there was a strong trend towards an increased risk of death in the non-cardiac surgery patients (RR 1.13; 0.99–1.29). The authors of this study suggest that the 13 % increased risk of death in the non-cardiac surgery patients may be related to the aspiration of chlorhexidine with the subsequent development of acute lung injury. Based on the results of this study, the role of chlorhexidine mouth washes needs to be re-evaluated. However, this does not imply the oral care should be abandoned.

Subglottic Suctioning

Secretions in the upper airways of intubated patients pool above the ETT cuff, allowing for leakage of contaminated secretions into the lower airway. In several studies, the effect of using an ETT with a separate dorsal lumen, which allows continuous aspiration of the subglottic secretions, was compared with that of a conventional ETT. A meta-analysis of 10 RCTs conducted by Wang and colleagues demonstrated that subglottic suctioning significantly reduced the incidence of VAP (RR 0.56, 95 % CI 0.45–0.69, $p < 0.00001$) and reduced duration of mechanical ventilation by 1.55 days (95 % CI 2.40–0.71 days, $p = 0.0003$) [155]. Subgroup analyses suggested a significant reduction in incidence of VAP when stratified by intermittent (RR 0.49) vs. continuous (RR 0.61) subglottic suctioning.

Acid Suppressive Therapy

For reasons that remain "shrouded in mystery" the IHI VAP prevention bundle includes stress ulcer prophylaxis with an H2-blocker or proton pump inhibitor. As discussed in Chap. 33, these agents increase the risk of VAP. Indeed, acidification of tube feeds has been suggested as a method to reduce the risk of VAP [156].

Probiotics

A number of studies have investigated the use of probiotics for the prevention of VAP. A meta-analysis which included 7 RCTs showed no beneficial effect [157]. Considering the potential harm associated with probiotics (see section of *C. difficile* treatment) these agents are best avoided.

While it may be impossible to completely eliminate VAP's institution of the measures listed below have associated with a reduction in the incidence of VAP [158].

Recommended Measures to Limit the Development of VAP

- Head up 10–30°
- Oral care
- Use orogastric rather than nasogastric tubes
- Subglottic secretion drainage
- Avoid unnecessary changes of ventilator circuit
- Routinely empty condensate in ventilator circuit
- Maintain endotracheal cuff pressure >20 cm H_2O
- Limit use of proton pump inhibitors and H2 blockers
- "Prophylactic PEEP" of 5 cm H_2O [159]
- Chest therapy [160]
- Avoid gastric overdistention
- Avoid unplanned extubation and reintubation
- Kinetic/rotating beds in high risk patient [161]

Clostridium difficile *Infection*

Clostridium difficile is the leading cause of hospital associated infectious diarrhea, and *C. difficile* infection (CDI) is now considered a public health emergency in the US, Canada, and Europe [162]. CDI is increasing in prevalence and severity. Data from the US Nationwide Inpatient Sample demonstrated that 348,950 patients were diagnosed with CDI in 2008 [163]. More recent data suggest an annual incidence of 133,657 cases in the US [4]. The burden on the US health-care system is substantial, with attributable costs ranging from $2,871 to $4,846 per case of primary CDI and from $13,655 to $18,067 for recurrent or relapsing infection [163]. Increased use of antibiotics and immunosuppressive agents, aging of the population and increased exposure to *Clostridium difficile* in health care settings have contributed to the sharp increase in cases of CDI. In addition, it should be noted that acid-suppressive therapy has been reported to increase the risk of colonization and infection with *C. difficile* [164–166]. The combination of broad-spectrum antibiotics and acid suppressive therapy (common in most ICU patients) appears to be an effective iatrogenic method of causing CDI. Furthermore, the use of acid suppressive therapy during an incident

CDI has been demonstrated to increase the risk of relapse [167]. It should be noted that patients with inflammatory bowel disease are also at an increased risk of CDI. The recent increase in the virulence and incidence of CDI is also attributed to the emergence of an epidemic strain termed North American pulsed-field gel electrophoresis type 1 or NAP1 [168].

C. difficile is a ubiquitous, anaerobic, Gram-positive spore-forming bacterium. Individuals who ingest spores of this bacterium from the environment can become colonized. Successful colonization usually relies on disruption of normal gut flora with the use of broad-spectrum antibiotics (and acid suppressive therapy). *Clostridium difficile* can be cultured from the stool of 1–3 % of healthy adults and from the stool of 30 % of infants aged <12 months. The ability of *C. difficile* to form spores that resist many common disinfectants and can survive for months on environmental surfaces makes it particularly prone to nosocomial transmission. The primary mode of *C. difficile* transmission is believed to be person-to-person via the fecal-oral route. Environmental contamination and transmission via fomites and the hands of health care workers are the major mechanism of leading to nosocomial CDI [169]. Infected patients' with diarrhea, especially those who are incontinent, lead to significant shedding of spores in the environment [168]. Prevention of transmission is essential in reducing nosocomial outbreaks.

Traditionally, pathogenic strains of *C. difficile* have been shown to produce toxin B and in most cases toxin A. However, toxin B is much more potent than toxin A, thought to be the reason why some strains of *C. difficile* remain pathogenic despite producing only toxin B. Both toxins damage the intestinal mucosa by a direct effect on enterocyte cytoskeletons. Damage to enterocytes result in an inflammatory response in the bowel mucosa with resulting clinical symptoms. *C. difficile* is recognized to cause a spectrum of disease in humans. This may include short-term colonization, acute diarrhea, fulminant diarrhea (often with pseudomembranous colitis and marked leukocytosis), or recurrent *C. difficile* infection.

CDI should be considered in every ICU patient that develops diarrhoea (an increase in the number of stools or change in the consistency of the stool). The cardinal symptom of CDI is watery diarrhea, which can be up to 10–15 stools per day. The diarrhea is rarely bloody. The stool from patients with *C. difficile* has a unique smell, is liquid and is green-yellow in appearance; ICU nurses can usually diagnose *C. difficile* by the "smell and eye test" (sensitivity and specificity unknown). Other clinical features include fever (which can be high), an increased white cell count (including a severe leukemoid reaction) as well as abdominal distention and pain. *Leukocytosis may precede diarrhea*. A retrospective review of 60 patients with unexplained leukocytosis reported 35 (58 %) with *C. difficile* toxin in their stool. Of these patients, 30 (86 %) eventually had symptoms consistent with colitis, but for 16 (53 %) leukocytosis was noted before onset of colitis symptoms [170]. Marked leukocytosis (WBC > 50,000/mL) and lactic acidosis are worrisome signs and should prompt surgical consultation. Fulminant CDI may lead to the development of toxic megacolon, perforation, and death. These patients typically have ileus and absence of diarrhea or minimal diarrhea, and the diagnosis can only be made if there is a high index of suspicion. A stool specimen (single specimen) should be send to

the lab in all patients suspected of having *C. difficile* enterocolitis. Plain abdominal radiography or computed tomography may be indicated in patients with severe pain, severe illness, or distention. The decision of whether or not to begin empiric treatment depends on the degree of suspicion of CDI and the severity of illness.

Laboratory Diagnosis

Testing of stool from asymptomatic patients and tests of cure are discouraged, as tests can remain positive indefinitely. The diagnostic tests for CDI have evolved over the last decade. A number of laboratory tests have been developed to diagnose CDI including the Cell Culture Neutralization Assay, Anaerobic Stool Culture, Enzyme Immunoassays (EIA) for toxin A/B, enzyme immunoassay for Glutamine dehydrogenase (GDH) and most recently polymerase chain reaction (PCR) tests for the detection of *C. difficile* toxin A or B gene. Stool cultures are tedious and time consuming and are currently rarely performed. Modern diagnostic protocols use a combination of tests as outlined in Fig. 16.2. It is important to recognize the diagnostic sensitivity of "modern" algorithms is only about 90 %. If the testing algorithm is negative, a clinical decision should be made whether to treat based on the likelihood of disease.

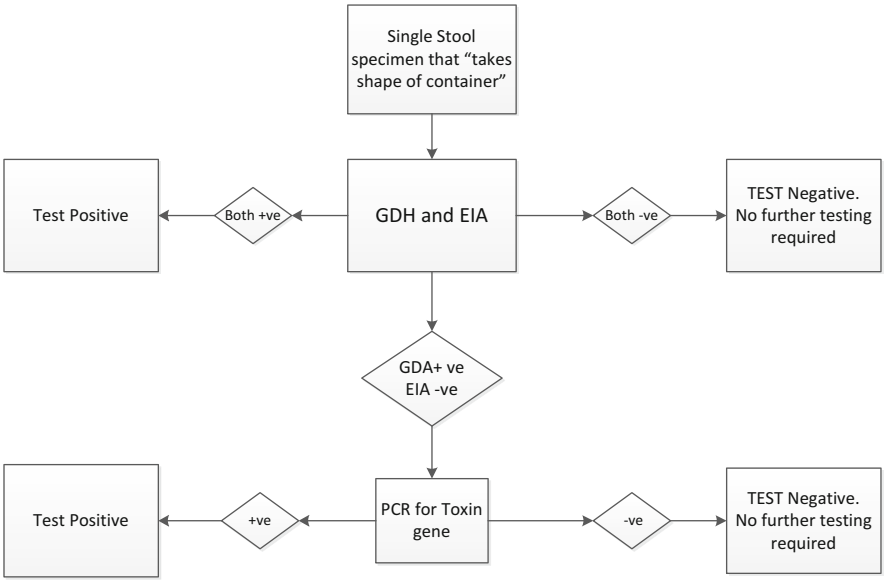

Fig. 16.2 A laboratory diagnostic algorithm for *C. difficile* infection

Enzyme Immunoassays for Toxin A/B

For the past two decades, EIA for *C. difficile* toxin A and B has been the most commonly used test for detection of CDI. The EIA is easy to perform and results are available very rapidly. However, sensitivity of the test is only between 60 and 80 % which has led to delays or absence of treatment [171].

Enzyme Immunoassay for Glutamine Dehydrogenase

EIA for glutamine dehydrogenase (GDH), a metabolic enzyme that is produced almost exclusively by *C. difficile*, has been increasingly used as part of the testing algorithm for suspected CDI. The benefits of this test are rapid completion and good sensitivity; however, the test has poor specificity because it also detects colonization by *C. difficile*. The poor positive predictive value (PPV) and high negative predictive value (NPV) of the EIA for GDH make it a useful test for screening, but requires additional testing for confirmation after a positive test result.

Nucleic Acid Amplification for Toxin A/B Gene

The newest testing methodologies are nucleic acid amplification tests, including polymerase chain reaction (PCR) and loop-mediated isothermal amplification tests. These tests detect genes residing within the pathogenicity locus of the *C. difficile* genome such as the toxin A gene (tcdA), toxin B gene (tcdB), and the toxin regulatory gene (tcdC). Overall performance for gene amplification assays shows sensitivities of 90–100 % with specificities of 94–100 % [172]. In a head-to-head comparison, gene amplification significantly outperformed EIA-based testing [173]. A further advantage of these tests is that it may allow identification of the *C. difficile* strain which carries both prognostic and public health implications.

Sigmoidoscopy

Sigmoidoscopy and colonoscopy are useful in patients with atypical presentations, such as ileus (aids in obtaining stool) and those with nonresponse to clinical therapy, and when there is a high index of suspicion with negative laboratory test results. Direct visualization of pseudomembranes by these tests is very specific, but pseudomembranes are only seen in about 55 % of CDI cases [169].

Treatment

The first step in the treatment of patients with CDI is discontinuation of concomitant antibiotic therapy, if possible. In some patients, this strategy alone is sufficient to resolve symptoms without requiring additional pharmacological therapy [169]. The successful treatment of *C. difficile* infection relies on reducing or eliminating the burden of *C. difficile* bacteria and toxin in the gastrointestinal tract. Both resolution of acute infection and prevention of recurrence are linked to reestablishing normal bacterial flora within the gastrointestinal tract. Reducing the burden of toxin is typically accomplished by administration of antibacterial agents with activity against toxin-producing *C. difficile*, although other strategies aimed at reconstituting colonic flora have also been used. Antimotility agents for the treatment of CDI has traditionally been discouraged as it has been postulated that such treatment may mask symptoms and promote the development of paralytic ileus and toxic megacolon [169]. However, in a review by Koo et al. these authors were unable to find evidence supporting the hypothesis of worsened outcomes with the use of antimotility agents [174]. Nevertheless, experts in the field caution against the use of antimotility agents in patients with CDI [175]. Should antimotility agents be used, the patient should be closely monitored (abdominal examination, lactate, etc.) and this therapy should be avoided before effective *C. difficile* has been instituted.

There is no data to support the use of antimicrobial therapy in asymptomatic patients. In patients with diarrhea, but without complications or systemic illness, the decision to treat prior to receiving results from diagnostic testing should be made on an individual basis. Ultimately, this is determined by the clinician's index of suspicion and the clinical condition of the patient. Due to the high incidence of *C. difficile* infection in the hospitalized setting, starting treatment for *C. difficile* infection in severely ill patients with diarrheal illness should be immediate. The recommended course of therapy is 10–14 days in most published guidelines and clinical trials. Following the first course of therapy, up to 25 % of patients will experience a recurrence The use of longer and/or tapering courses of antimicrobial therapy has been reported in the treatment of refractory or recurrent cases.

Oral vancomycin and metronidazole are the most commonly used agent's to treat *C. difficile* infection. Eleven prospective clinical trials have been performed assessing the effectiveness of these agents [176]. For mild to moderate cases the efficacy of these agents appears to be equivalent; due to the higher costs for prescribing PO vancomycin and ready accessibility of metronidazole, metronidazole is considered as first line therapy. Recent studies suggest that the efficacy of vancomycin may be better than metronidazole in patients with severe infection and that the rate of recurrence in these patients may be higher with metronidazole. Consequently, the 2010 Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) guidelines recommend the following [177]:

Mild-moderate infection:

– Metronidazole 500 mg 3×/day for 10–14 days

Severe infection (Creatinine 1.5× normal or WBC > 15 $\times 10^3/mm^3$):

– Vancomycin 125 mg po 4×/day for 10–14 days

Severe, ***complicated infection*** (pressor requiring, ileus, toxic megacolon):

– Vancomycin 500 mg 4×/day po or by NG tube plus IV metronidazole 500 mg 3×/day

First recurrence: Treat like first episode
Second recurrence: Vancomycin taper and/or pulse *as follows*

– Vancomycin in standard dose (125 mg po 4×/day × 10–14 days) then 125 mg po 2×/day × 7 days, then 125 mg po 1 × 7 days, then 125 mg every 2–3 days for 2–8 weeks.

Fidaxomicin

Fidaxomicin, a macrocyclic antibiotic, is more active in vitro than vancomycin against clinical isolates of *C. difficile*, including NAP1 strains [178]. This activity, in combination with minimal systemic absorption, high fecal concentrations, and limited activity in vitro against components of the normal gut flora, makes fidaxomicin a promising agent for the treatment of *C. difficile* infection. A double-blinded, randomized-controlled trial comparing oral vancomycin and fidaxomicin showed similar efficacy for treatment of acute infection, however, patients treated with fidaxomicin had a statistically significant decrease in recurrence of infection [178].

Adjunctive Treatment Options

IVIG at 200–500 mg/kg for 1–3 doses has been used in patients with fulminant colitis. A RCT published by Lowey et al. demonstrated that the addition of monoclonal antibodies against *C. difficile* toxins to antibiotic agents significantly reduced the recurrence of *C. difficile* infection [179]. Anion-exchange resins, such as cholestyramine and colestipol have been used for recurrent CDI based on notion that these agents my bind free toxin. However, these agents have been found to be no better than placebo for the treatment of CDI [163]. Fecal microbiota transplantation is the introduction of stool from a healthy donor into the GI tract of a patient. Fecal transplantation has been reported to be associated with improved response or clinical cure in up to 80 % in anecdotal studies [163].

Probiotics

The evidence supporting the use of probiotics in the prevention and treatment of CDI is inconclusive. A randomized, double blind, placebo-controlled study examining the efficacy of preventing antibiotic-associated diarrhea and CDI in hospitalized patients receiving antibiotics demonstrated that consumption of a probiotic drink containing *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* led to a decreased incidence of antibiotic associated diarrhea and CDI [180]. A meta-analysis concluded that "*moderate-quality*" evidence suggests that probiotic prophylaxis results in a reduction in CDI without an increase in clinically important adverse events [181]. However, Allen and colleagues performed a large multicentre, randomized, double-blind, placebo-controlled trial using a multi-strain preparation of lactobacilli and bifidobacteria in 1,470 inpatients aged 65 years and older and exposed to one or more oral or parenteral antibiotics [182]. In this study the risk of antibiotic-associated diarrhoea and CDI was not different between groups. It should be noted that probiotics contain "live Bacteria" and both Lactobacillus sepsis and *Saccharomyces cerevisiae* fungemia have been reported following the use of probiotics; the risk of this complication is increased in immunocompromised critically ill patients [183, 184]. In addition, in a randomized controlled trial in patients with severe pancreatitis (the PROPATRIA trial) an unexpected increase in mortality was reported in the probiotic-treated patients [185]. These data suggest that probiotics should probably be avoided critically ill ICU patients.

Surgical Intervention

In patients with complicated *C. difficile* entero-colitis as manifested by hypotension, ileus, megacolon, severe leukocytosis or leukopenia, elevated serum lactate, altered mental status or end-organ failure early surgical consultation is suggested. Several case series have demonstrated better outcomes with early surgery in patients with fulminant colitis [186]. The standard operation for fulminant colitis is subtotal colectomy but the high mortality of the operation, and the long-term morbidity even in survivors combine to act as deterrents to early surgical consultation and operation [186]. CT of the abdomen may be valuable in assessing disease severity and the need for surgical intervention. CT signs of fulminant colitis include evidence of colonic thickening, pericolonic stranding, and the "accordion sign" (oral contrast material in the colonic lumen alternating with an inflamed mucosa with low attenuation) [186]. A "double-halo sign" or "target sign" is often seen with intravenous contrast representing varying degrees of attenuation of the mucosa secondary to hyperemia and submucosal inflammation.

Nosocomial Rhinosinusitus

Nosocomial rhinosinusitis (NS) is an underappreciated cause of fever and sepsis in the ICU [187]. NS is diagnosed in up to 30 % of intubated patients and is associated with VAP, septicemia and fever of unknown etiology [188]. The diagnosis is usually not made until other more common infectious causes of fever have been excluded. If NS is not diagnosed and treated in timely fashion it can lead to nosocomial pneumonia and sepsis. Nasal colonization with enteric gram negative rods, mechanical ventilation, nasotracheal tubes, nasoenteric tubes, illness severity, recumbent position (lying flat), deep sedation and a Glasgow coma scale of <7 are all risk factors for NS [187, 189]. Pathologic antral changes, identified with CT are reported to occur in 75 % of patients with an orotracheal tube within 48 h after their admittance in the ICU. After 1 week in the ICU, pathologic changes are found in 90–100 % of the patients with initial normal sinus radiology [190]. The reported rates of NS vary greatly from 0.7 to 30 % of the patients in ICU depending to a large extent on the diagnostic criteria [187, 188]. Zaten and colleagues reported that NS was the sole cause of fever in 16 % of patients and one of several causes in an additional 14 %; i.e. 30 % of febrile patients had evidence of NS. Elwany et al. diagnosed NS in 40 of 51 ICU patients (78 %) with occult fever [191].

The diagnosis of NS is difficult. CT scan of the sinuses is considered the gold standard; however this requires transportation of the patient to the radiology suite. Radiologic maxillary sinusitis is defined as complete opacification of the sinus or as the presence of an air-fluid level. In patients with radiologic evidence of sinusitis, aspiration of the sinuses is required to confirm the diagnosis and to identify the causative pathogen [192, 193]. If a patient is too critically ill to be transported out of the ICU plain films of the sinuses can be obtained. In order to maximize the chances of making the diagnosis multiple views of the sinuses are required.

Bedside ultrasound has been gaining popularity and studies have suggested that it is at least equivalent to CT scanning. Due to aeration of the normal maxillary sinus, a normal image results in an acoustic shadow arising from the anterior wall of the sinus (see Fig. 16.3a) Opacification of the sinus results in visualization of the hyperechogenic posterior wall of the sinus or visualization of posterior wall and the internal wall of the sinus outlining the hypoechogenic sinus cavity (see Fig. 16.3b) [194, 195]. Using these criteria, Hilbert et al. reported a concordance of 97 % between B-mode ultrasound and CT scanning [194].

When the sinus ultrasound is normal the diagnosis of sinusitis can be excluded [195]. When a sinus ultrasound shows a partial sinogram, it could be due to air-fluid level or a mucosal thickening. Vargas et al. used the ultrasonic disappearance of a partial sinogram in the maxillary sinus with a postural change (to supine position) as an indicator of an air-fluid level rather than mucosal thickening [196]. This postural maneuver increased the positive predictive value of ultrasound examination from 61 to 91.2 %.

Nasal endoscopy allows visual inspection of the nasal cavity, especially the area of the middle meatus where the frontal, anterior ethmoid and maxillary sinuses

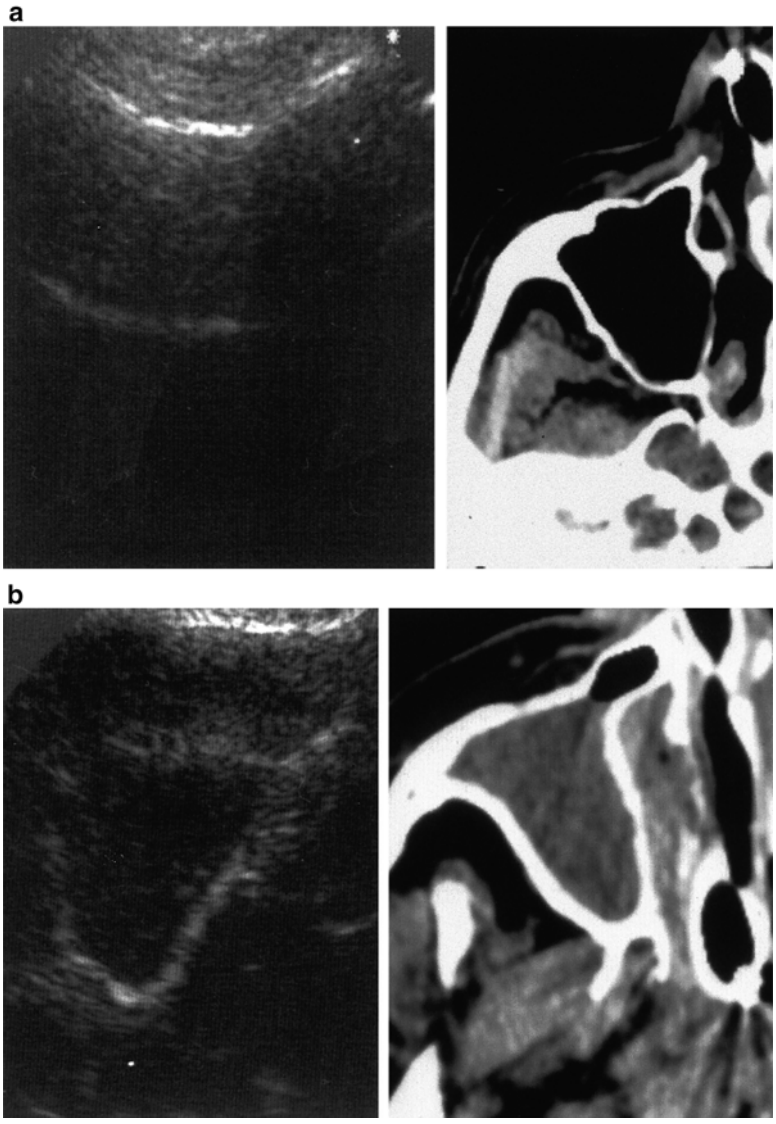

Fig. 16.3 (**a**) Normal maxillary sinus. CT (*right panel*) and ultrasound equivalent (*left panel*) with complete acoustic barrier. (**b**) Radiological maxillary sinusitis with total opacity of the sinus (computed tomography) (*right panel*), compared with B-mode ultrasound visualization of the posterior and internal walls of the sinus (*left panel*) [194]. Reproduced with permission from Lippincott Williams and Williams

drain and allows for directed cultures to be obtained from the middle meatus. Using this technique Elwany and colleagues demonstrated that middle meatal cultures had a sensitivity of 92.8 %, a specificity of 80.0 %, and an accuracy of 90.2 % in comparison with CT scans [191].

Once sinusitis is diagnosed, all nasal tubes should immediately be removed with early sinus drainage. Broad spectrum antibiotics should be commenced with coverage that includes Pseudomonas and MRSA. The antibiotics should then be de-escalated once culture data is available. Topical decongestants and vasoconstrictors are also recommended. Early detection and treatment is important because delays can lead to the development of VAP, sepsis, and life-threatening complications such meningitis, mastoiditis, intra-cranial abscesses and venous thrombosis of the sinus cavernosus [187].

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Part II
Pulmonary

Chapter 17
The Bacterial Pneumonias: A New Treatment Paradigm

Pneumonia—The old man's best friend—Captain of the Men of Death

Sir William Osler, Physician (1849–1919)

Pneumonia is a common disease and a leading cause of death. Indeed, William Osler recognized that most old people die from pneumonia rather than from old age itself [1]. Pneumonia is therefore a leading cause of hospitalization and amongst the most common reasons for admission to the ICU. Indeed, over 50 % of patients with severe sepsis have pneumonia. Most bacterial pneumonias, with the notable exception of Legionella Pneumonia, Tuberculosis and Leptospiral Pneumonia are caused by the aspiration of oropharyngeal material colonized with the causative pathogen. This implies that the "causative" pathogen together with low-virulence oral flora are aspirated in most pneumonia. *Appropriate initial antimicrobial therapy*, defined as the use of at least one antibiotic active *in vitro* against the causative bacteria, is associated with reduced length of hospitalization, reduced morbidity and reduced mortality when compared with patients receiving initial inappropriate therapy [2–4]. As inappropriate initial antibiotic therapy is usually associated with infection with a drug-resistant pathogen (DRP), and as DRPs are usually acquired in specific settings, the treatment of pneumonia has traditionally been based on the setting in which the pneumonia develops. The number of individuals receiving health care outside the hospital setting, including home wound care and infusion therapy, dialysis, nursing homes and long-term acute care (LTAC) facilities is increasing. One of the most frequent causes of hospitalization and mortality in these patients is pneumonia. Hence a new class of pneumonia was identified; healthcare associated pneumonia (HCAP). Consequently, the 2005 and 2007 guidelines for the management of pneumonia by the *American Thoracic Society* and the *Infectious Diseases Society of America* recommend that pneumonia should be classified into one of three categories at diagnosis: (1) community-acquired pneumonia (CAP), (2) healthcare-associated pneumonia (HCAP), and (3) hospital-acquired pneumonia (HAP) [5, 6]. These three categories of pneumonias are further subdivided into the following "word-soup" subtypes according to the setting where the pneumonia develops, the severity of illness and the risk of aspiration, namely:

- Community Acquired Pneumonia (CAP)
- Severe Community Acquired Pneumonia (S-CAP)

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- Healthcare Associated Pneumonia (HCAP)
- Nursing-Home acquired pneumonia (NHP)
- Long Term Acute Care Associated Pneumonia (LTAC-P)
- Hospital Acquired Pneumonia (HAP)
- Early Ventilator Associated Pneumonia (E-VAP)
- Late Ventilator Associated Pneumonia (L-VAP)
- Aspiration pneumonia (AP)

The mortality of patients with HCAP is higher than that of patients with CAP (about 30 % vs 5 %); this is likely related to the comorbidities and poor-functional status of patients with HCAP rather than the virulence of the pathogen or the prescription of initial inappropriate antibiotic therapy [7–9].

It has been argued that patients with HCAP and HAP are at a higher risk of infection with DRP's such as *Pseudomonas aeruginosa* and methicillin–resistant Staphylococci (MRSA) and therefore require an initial broad spectrum multidrug antibiotic regimen. It has been assumed that the three major categories of pneumonia are distinct clinical entities that require specific antimicrobial regimens. However, increasing evidence suggests that there is much overlap between these conditions and that a more unified approach to the treatment is more practical. In essence these pneumonias differ by the spectrum of colonizing organisms which are aspirated and it may therefore be more useful to risk stratify patients according to the likelihood of developing infection with gram-negative and DRPs. The traditional approach assumes that patients with HCAP are infected with DRPs while CAP patients are infected with multi-sensitive organisms (MSO). However, a small percentage of patients with CAP are infected with DRPs while a significant percentage of patients with HCAP are infected with MSO (see Fig. 17.1). Indeed, only 10–30 % of patients with HCAP are infected with DRPs [7, 10, 11]. A more useful schema is to assess the risk of infection with a pathogen not susceptible to ceftriaxone, ampicillin-sulbactam, macrolide or a respiratory fluoroquinolone; these known as CAP drug-resistant pathogens (CAP-DRPs) [8]. In a large prospective observational study Shindo et al. reported infection with CAP-DRPs in 26.6 % of patients with HCAP and 8.6 % of patients with CAP. Remarkably, the risk factors for

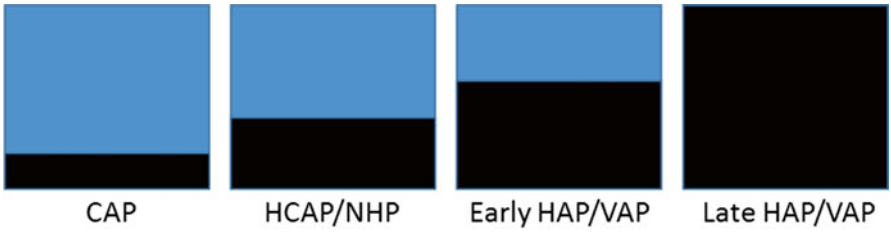

Fig. 17.1 Traditional classification of bacterial pneumonias with percentage of ***CAP-DRPs*** (in *black*)

CAP-DRPs were almost identical in patients with CAP and HCAP. Based on this concept, the following have been identified as risk factors for infection with a CAP-DRPs in both community and healthcare associated pneumonia [8, 10, 12]:

- Hospitalization for >2 days during the previous 90 days
- Antibiotic use during the previous 90 days
- Non-ambulatory status
- Tube feeds
- Immunocompromised status
- Use of acid suppressive therapy
- Chronic hemodialysis during the preceding 30 days
- Positive MRSA history within previous 90 days
- Present hospitalization >2 days

The risk of a CAP-DRPs increases with the number of risk factors being about 3 % with no risk factors, 10 % with one risk factor and greater than 80 % for 5 or more risk factors [8]. According to this revised treatment approach a patient with pneumonia and one or more risk factors for a CAP-DRP (irrespective of where the patient develops the pneumonia) should receive broad spectrum antibiotics, while all others should be treated with narrow spectrum antibiotics (traditional CAP antibiotics) [8, 9]. It may be also reasonable to tailor the "aggressiveness" of the CAP-DRPs regimen according to the number of risk factors for a CAP-DRP. Poor functional status (Barthel Index score <50) is a major factor increasing the risk of infection with a CAP-DRP; these patients usually have multiple other risk factors for infection with a CAP-DRP [9, 13, 14]. The antibiotic regimen for those likely to be infected with a CAP multi-sensitive organism (CAP-MSO) is further stratified according to severity of illness (see algorithm below). In patients risk stratified to treatment with a CAP-DRP regimen, monotherapy is adequate once a known pathogen is identified. This strategy of initiating broad spectrum cover with two or more antibiotics and then narrowing the spectrum to a single agent when a pathogen is identified is known as "antimicrobial de-escalation" [15]. The de-escalation approach has been demonstrated to be associated with a reduction in mortality [16]. The exception to this "monotherapy" rule is patients with "severe-CAP" in whom combination therapy with ceftriaxone and a macrolide is recommended (see below)

Unified Treatment Algorithm

No Risk Factors for a CAP-DRP

Low Acuity of illness

- Macrolide
- Fluoroquinolone

- Ampicillin-sulbactam
- Doxycycline

High Acuity of illness (*ICU admission*)

- Ceftriaxone and macrolide

Risk Factors for CAP-DRPs

- Piperacillin/Tazobactam + vancomycin + ciprofloxacin
- Carbapenem + vancomycin
- Cefepime + vancomycin
- Piperacillin/Tazobactam + vancomycin + aminoglycoside (once daily)
- Etc, etc…

Influenza (Co-Existent or Influenza Pneumonia)

- Early treatment (within 48 h of the onset of symptoms) with oseltamivir or zanamivir is recommended for influenza A.
- Use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 h, but these drugs may be used to reduce viral shedding in hospitalized patients or for influenza pneumonia.
- *S. pneumoniae* and *S. aureus*, the most common causes of secondary bacterial pneumonia in patients with influenza.

Patients with severe pneumonia are best managed in the ICU. Patients with the following criteria require ICU admission [6].

Major Criteria

- Requirement for mechanical ventilation or
- Septic shock (SBP < 90 despite fluids)

Minor Criteria (3 or More)

- 30 < white blood cell count < 4×10^9/L
- Blood urea nitrogen > 20 mg/dL
- PaO2/FiO_2 < 250
- Multilobe involvement

- Respiratory rate >30/min
- Platelet count $< 100{,}000 \times 10^9$/L
- Confusion/disorientation
- Hypothermia (temperature <36°)
- Hypotension requiring fluid resuscitation

The classically described "atypical" pathogens that cause CAP include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* species. The "atypical" moniker is an inaccurate description of the clinical features of the pneumonia associated with these organisms and is retained more as a classification than a specific descriptor of the disease process or clinical presentation. *M. pneumoniae* has been shown to be the most common of the atypical pathogens and accounts for 17–37 % of outpatient CAP and 2–33 % of CAP requiring hospitalization. *C. pneumoniae* is more common than *Legionella* species; however, *Legionella* species can lead to rapidly progressive and fatal pneumonia.

Diagnostic Testing of Hospitalized Patients with Pneumonia

- Blood cultures
- Urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumonia*
- Expectorated sputum for culture
- Intubated patients require endotracheal aspirate or m-BAL with quantitative culture
- Screening for HIV in at risk patients
- Nasopharyngeal swab for influenza during seasonal influenza (rapid Ag test and viral PCR)

Non-Infectious Diseases Masquerading as Pneumonia

- Cryptogenic organizing pneumonia (COP)
- Eosinophilic pneumonia
- Hypersensitivity pneumonia
- Drug induced pneumonitis: methotrexate, nitrofurantoin, gold, amiodarone
- Pulmonary vasculitis
- Pulmonary embolism/infarction
- Pulmonary malignancy
- Radiation pneumonitis
- Tuberculosis

Special Considerations

Severe CAP with no MDR Risk Factors

Streptococcus pneumoniae remains the most common and important pathogen causing "Classic CAP". Although monotherapy is considered standard for "classical CAP", a survival benefit of combination β-lactam and macrolide has been suggested. Waterer et al. found that patients with bacteremic pneumococcal CAP who receive at least two effective antibiotic agents within the first 24 h after presentation had a significantly lower mortality than patients who received only one effective antibiotic agent [17]. The most common combination was a third generation cephalosporin with a macrolide or quinolone. Using a large hospital database Brown et al. demonstrated a lower mortality, shorter LOS and lower hospital charges for patients with CAP treated with dual therapy using macrolides as the second agent [18]. Rodriguez et al. undertook a secondary analysis of data obtained from a prospective observational cohort study of cases in 33 ICUs in Spain. Overall, 270 patients required vasoactive drugs and were characterized as having shock. In the cases with shock, combination antibiotic therapy was associated with a significantly higher adjusted 28-day in-ICU survival (hazard ratio 1.69: 95 % CI 1.09–2.60; $P=0.01$) [19]. Another study investigated outcome of patients with severe CAP, comparing patients treated with β-lactam/macrolide combination versus those treated with fluoroquinolone monotherapy [20]. Lower 30-day mortality rates were seen for those treated with β-lactam/macrolide combination (18.4 versus 36.6 % ($P=0.05$). In a systemic review by Sligl et al. which included almost 10,000 critically ill patients with CAP macrolide use was associated with a significant 18 % relative reduction in mortality compared with non-macrolide therapies [21].

The possible explanations for the benefits of dual coverage (esp. with a macrolide) include antibiotic synergy, coverage of unrecognized atypical pathogens, immunomodulating effects and the effect on bacterial quorum sensing. Macrolides, at sub-minimum inhibitory (MIC) concentrations, are potent inhibitors of the production of pneumolysin (a potent virulence factor) by macrolide-susceptible strains of the pneumococcus, whereas the beta-lactam agent, ceftriaxone, as well as amoxicillin, ciprofloxacin, moxifloxacin, and tobramycin are relatively ineffective [22]. Although they also antagonize various pro-inflammatory activities of neutrophils, macrolides primarily target the synthesis of interleukin (IL)-8 by bronchial epithelial cells, eosinophils, monocytes, fibroblasts and airway smooth muscle cells [23].

Community-Acquired MRSA Pneumonia (CA-MRSA)

In the United States, some patients with CAP have been affected by a severe necrotizing bilateral pneumonia caused by community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA), a pathogen that seems more common in the

United States than in Europe [24]. Initially reports of CA-MRSA were of patients with severe pneumonia and a high mortality, but more recently the spectrum of illness caused by this pathogen has expanded to include patients with milder illness [24–26]. CA-MRSA is resistant to fewer antimicrobials than are hospital acquired MRSA strains and often contain a novel type IV SCCmec gene. In addition, most contain the gene for Panton-Valentine leukocidin, a toxin associated with the clinical features of necrotizing pneumonia, shock, as well as formation of abscesses and empyemas [27]. Because the clinical presentation of this infection is disproportionately exotoxin-mediated, treatment is recommended with antibiotics that suppress toxin production, such as linezolid or clindamycin (added to vancomycin); these regimens have been associated with reduced mortality [28, 29].

Clinical Features suggesting CA-MRSA [30]

- Cavitary infiltrate or necrosis
- Rapidly increasing pleural effusion
- Gross hemoptysis
- Neutropenia
- Erythematous rash
- Skin pustules
- Young, previously healthy patient
- Severe pneumonia during summer months
- Severe pneumonia complicating influenzae

Aspiration Pneumonia

Aspiration pneumonia refers to the development of a radiographic infiltrate in the setting of patients with risk factors for increased oropharyngeal aspiration [31]. Dysphagia is the major risk factor leading to aspiration pneumonia. Aspiration pneumonia is probably the final common pathway by which most chronically ill patients die. It has been estimated that over 16 million senior citizens in the US suffer from dysphagia [32]. Furthermore, an additional 300,000–600,000 patients develop dysphagia each year in the US from neurological disorders [33]. Dysphagia affects more than 30 % of patients who have had a cerebrovascular accident; 52–82 % patients with Parkinson's disease; 84 % of patients with Alzheimer's disease, up to 40 % of adults aged 65 years and older, and more than 60 % of elderly institutionalized patients [34]. The efficiency of the swallow mechanism decreases with aging increasing the risk of aspiration and pneumonia in the elderly [35, 36].

Risk factors for dysphagia and aspiration pneumonia

- Cerebrovascular disease
  - ischemic stroke
  - hemorrhagic stroke
  - subarachnoid hemorrhage

- Degenerative neurological disease
  - Alzheimer's dementia
  - Multi-infarct dementia
  - Parkinson's disease
  - Amyotrophic lateral sclerosis (motor neuron disease)
  - Multiple sclerosis
- Head and neck cancer
  - Oropharyngeal malignancy
  - Oral cavity malignancy
  - Esophageal malignancy
- Other
  - Scleroderma
  - Diabetic gastroparesis
  - Reflux esophagitis
  - Presbyesophagus
  - Achalasia

There is no "gold standard" test to diagnose aspiration. Furthermore, in patients with aspiration pneumonia, unlike the case of aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient with known risk factors for aspiration has an infiltrate in a characteristic bronchopulmonary segment. In patients who aspirate in the recumbent position the commonest sites of involvement are the posterior segments of the upper lobes and the apical segments of the lower lobes. Patients who aspirate in the upright or semi-recumbent position the basal segments of the lower lobes are favored. The usual picture is that of an acute pneumonic process, which runs a course similar to that of a typical CAP. Untreated, however, these patients appear to have a higher incidence of cavitation and lung abscess formation [37].

Antimicrobial therapy is indicated in patients with aspiration pneumonia. The choice of antibiotics depends on the patients risk for infection with a DRP (as indicated above). Classic teaching suggests that "aspiration pneumonia" is caused by anaerobic bacteria and that drugs with specific anaerobic activity are required [38, 39]. However, it should be recalled that almost all bacterial pneumonias are caused by aspiration of oropharyngeal contents (which contain oral anaerobes) and that these "typical" pneumonias are not treated specifically with drugs with anaerobic activity. The anaerobic bacteria that colonize the oropharynx are intrinsically of low virulence. In an experiment dating back to 1930, Smith introduced bacteria isolated from patients with Vincent's Angina into the lungs of rabbits [40]. Cultures of a single organism failed to produce pneumonia; only when multiple different organisms were instilled into the lungs did the animals develop pneumonia (synergistic anaerobic infection). In the most rigorous study to date, El-Sohl and colleagues performed protected quantitative bronchial sampling in 95 patients with severe aspiration pneumonia [41]. Out of the 67 pathogens identified, gram-negative enteric bacteria were the predominant organisms isolated (49 %), followed by anaerobic bacteria (16 %) and *Staphylococcus aureus* (12 %). A single anaerobic bacterium

was isolated from 11 patients usually in association with a gram-negative pathogen. Although seven cases with anaerobic isolates received initially inadequate antimicrobial therapy, 6 had effective clinician response. This data suggests that treatment with antimicrobial agents with specific anaerobic activity may not be required in all patients with aspiration pneumonia. However, antimicrobials with specific anaerobic activity are indicated in patients with periodontal disease, patients expectorating putrid sputum and patients with a necrotizing pneumonia or lung abscess on chest radiograph [5, 31, 42, 43].

All elderly patients with pneumonia and chronic idiopathic lung disease as well as patients' with a recent cerebrovascular accident and those with degenerative neurological diseases should be referred to a speech and language pathologist (SLP) for a formal swallow evaluation [44, 45]. Those patients with dysphagia require the formulation and implementation of an individualized management strategy. A clinicians' bedside assessment of the cough and gag reflex is unreliable in screening for patients at risk of aspiration. Because objective swallowing evaluation can be performed with an NG tube (or feeding tube) in place, it is not necessary to remove the NG tube (and interrupt enteral feedings) to evaluate dysphagia. Similarly, there is no contraindication to leaving an NG tube in place to supplement oral alimentation [46]. The neurotransmitter, Substance P, in believed to play a major role in both the cough and swallow sensory pathways. Angiotensin converting enzyme (ACE) inhibitors prevent the breakdown of Substance P and may theoretically be useful in the management of patients with aspiration pneumonia. A number of studies have demonstrated a lower risk of aspiration pneumonia in stroke patients treated with an ACE inhibitor compared to other antihypertensive agents [47, 48].

Nursing Home-Acquired Pneumonia

Nursing home-acquired pneumonia is a leading cause of hospitalization, morbidity, and mortality among nursing home residents, accounting for 13–48 % of infections in this setting [49]. Many of these patients have risk factors for DRP and should be treated accordingly. Furthermore, many of these patients have aspiration pneumonia and should undergo screening for dysphagia. As described by William Osler over 100 years ago, aspiration pneumonia is commonly the terminal event in old frail people… these patients should not be admitted to the ICU (see Chap. 48, Management of the Elderly Patient).

Persistent Temperature/Failure to Respond to Rx

A common misconception is that the patient's temperature should settle within 24 h of commencing antibiotic therapy. It has been demonstrated that it may take up to 72 h for the temperature to normalize in a patient with pneumococcal pneumonia.

However, in a patient with a widely swinging temperature it would be prudent to exclude a complication within this time frame. The following are the major reasons for a failure to respond to antimicrobial agents:

- Wrong antibiotic; wrong spectrum or drug resistance
- Exclude masquerader
- Wrong dosage
- Viral, fungal or opportunistic pathogen
- Unusual pathogens (see below)
- Superadded complication
- Complicated pleural effusion/empyema
- Endocarditis
- Purulent pericarditis
- Septic arthritis
- Meningitis, etc.

Unusual Pathogens

- *Coxiella burnetii*
  - Cats, goats, sheep, cattle
- Tularemia
  - Rabbits, ticks
- Leptospirosis
  - Rats (water exposure/rafting)
- Hantavirus
  - rats
- SARS
- Psittacosis
  - birds
- Nocardia
  - steroids
- Aspergillus
  - Steroids/neutropenia
- *Pneumocystis jiroveci*
  - immunosuppression
- Dimorphic fungi
  - Recent travel
- *Burkholderia pseudomallei*
  - Recent travel
- TB

Complicated Pleural Effusion/Empyema

When pleural fluid is detected in a patient with pneumonia, a diagnostic thoracocentesis should always be performed to rule out pleural space infection (except if the effusion is very small). Pleural fluid studies differentiate between a benign parapneumonic effusion and an early empyema (complicated pleural effusion). Drainage is necessary when the pleural fluid is grossly purulent or if pleural fluid studies show any of the following:

- pH < 7.2 (most sensitive indicator)
- Glucose < 40 mg/dL
- White blood cell count > 10,000/mL
- +ve gram stain

Complicated pleural effusions and empyema require chest tube drainage. Surgical intervention is required in those patients who have an inadequate response to tube drainage alone (VATS). The addition of intra-pleural fibrinolytic agents has been advocated to break down fibrin bands that cause loculations and thereby reduce the need for subsequent surgical debridement of the pleural space. A Cochrane review published in 2008 was unable to demonstrate a benefit with fibrinolytic therapy [50]. A more recent study by Rahman and colleagues randomized patients with an infected pleural effusions using a 2 × 2 factorial design to double-placebo, intrapleural tissue plasminogen activator (t-PA) and DNase, t-PA and placebo, or DNase and placebo [51]. Intrapleural t-PA–DNase therapy improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or t-PA alone was however ineffective. A systematic review by Janda and Swiston recommended the use of fibrinolytic therapy in patients with loculated pleural effusions as this therapy reduced the need for surgical intervention [52].

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Chapter 18
Fever

Humanity has but three great enemies: fever, famine and war;
of these by far the greatest, by far the most terrible, is fever…

—Sir William Osler, Physician (1849–1919)

Common Misconception and Fables [1]

- Normal body temperature is fairly constant and is usually 37 °C (98.6 °F)
  - Normal oral temperature ranges from 35.6 °C (96.1 °F) to 38.2 °C (100.8 °F) with marked diurnal variations [2]
- Fever is a bad thing and suppressing a fever will eliminates its bad effects
- Fever should be treated because fever makes patients uncomfortable
- Fever should be treated empirically with antibiotics
- Reducing core temperature in febrile patients has no ill effects
- Atelectasis is the most common cause of fever in the first few postoperative days

Fever is a common problem in the ICU. A prospective observational study in a general ICU reported fever (core temperature >38.3 °C) in 70 % of patients, caused equally by infective and non-infective processes [3]. In a large retrospective cohort study (24,204 ICU admission), Laupland et al. reported that 44 % of patients developed a fever of >38.2 °C during their ICU stay; 17 % of these patients had positive cultures [4]. The discovery of fever in an ICU patient has a significant impact on health care costs, as blood cultures, radiologic imaging and antibiotics routinely follow. It is therefore important to have a good understanding of the mechanisms and etiology of fever in ICU patients, how and when to initiate a diagnostic workup and when initiation of antibiotics is indicated.

The *Society of Critical Care Medicine* and the *Infectious Disease Society of America* considers a temperature of 38.3 °C or greater (101 °F) a fever in an ICU patient which warrants further evaluation [5]. This does not necessarily imply that a temperature below 38.3 °C (101 °F) does not require further investigation, as many variables determine a patient's febrile response to an insult. In addition, it should be recognized that there is a daily fluctuation of temperature by 0.5–1.0 °C, with women having wider variations in temperature than men. Furthermore, with aging the maximal febrile response decreases by about 0.15 °C per decade.

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Accurate and reproducible measurement of body temperature is important in detecting disease and in monitoring patients with an elevated temperature. A variety of methods are used to measure body temperature, combining different sites, instruments and techniques [2, 6]. Infrared ear thermometry has been demonstrated to provide values that are a few tenths of a degree below the temperature in the pulmonary artery and brain. Rectal temperatures obtained with a mercury thermometer or electronic probe are often a few tenths of a degree higher than core temperatures. However, patients perceive having rectal temperatures taken as unpleasant and intrusive. Furthermore, access to the rectum may be limited by patient position with an associated risk of rectal trauma. Many tachypneic patients are unable to keep their mouth closed to obtain an accurate oral temperature. Axillary measurements substantially underestimate core temperature and lack reproducibility. Body temperature is therefore most accurately measured by an intravascular thermistor; however, measurement by infrared ear thermometry or with an electronic probe in the rectum is an acceptable alternative.

Pathogenesis of Fever

Cytokines released by monocytic cells play a central role in the genesis of fever [7, 8]. The cytokines primarily involved in the development of fever include interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These cytokines bind to their own specific receptors located in close proximity to the preoptic region of the anterior hypothalamus. Here the cytokine receptor interaction activates phospholipase A2, resulting in the liberation of plasma membrane arachidonic acid as substrate for the cyclooxygenase pathway. Some cytokines appear to increase cyclooxygenase expression directly, leading to the liberation of prostaglandin E2 (PGE2).

Fever appears to be a preserved evolutionary response within the animal kingdom [9, 10]. With few exceptions, reptiles, amphibians, fish and several invertebrate species, have been shown to manifest fever in response to challenge with microorganisms. Increased body temperature has been shown to enhance the resistance of animals to infection. Although fever has some harmful effects, it appears to be an adaptive response which has evolved to help rid the host of invading pathogens. Temperature elevation has been shown to enhance several parameters of immune function including antibody production, T-cell activation, production of cytokines and enhanced neutrophil and macrophage function. Furthermore, some pathogens such as *Streptococcus pneumoniae* are inhibited by febrile temperatures.

Treatment of Fever

Data from a retrospective study of 636,051 patients showed that although the presence of fever in the first 24 h after ICU admission was associated with an increased risk of mortality in patients without infection, it was associated with a decreased

risk of mortality in those with an infection [11]. In this study the adjusted in-hospital mortality risk progressively decreased with increasing peak temperature in patients with infection. Similarly, Weinstein and colleagues reported that patients with spontaneous bacterial peritonitis had improved survival if they had a temperature greater than 38 °C [12]. While fever is generally regarded as a beneficial response to infection, up to 70 % of ICU patients with a fever are treated with antipyretic agents [13]. Yet, the preponderance of data suggest that treating a fever in this setting is harmful. Schulman et al., investigated the benefit of fever control in patients admitted to a trauma ICU [14]. Patients were randomized to an active treatment group in which acetaminophen and cooling blankets were used to aggressively cool patients as compared to a permissive group in which fever was only treated once it reached 40 °C. In this study there was a strong trend towards increased mortality in the active treatment group; all the patients who died in the aggressive treatment group had an infectious etiology as the cause of the fever. Lee et al. performed a prospective observational study to determine the association between antipyretic treatment of fever and mortality in 1,425 critically ill patients with and without sepsis [15]. These authors demonstrated that that treatment with non-steroidal anti-inflammatory drugs or acetaminophen independently increased 28-day mortality for septic patients (OR: NSAIDs: 2.61, $p=0.028$, acetaminophen: 2.05, $p=0.01$), but not for non-septic patients. Doran et al. demonstrated that children with varicella who were treated with acetaminophen had a more prolonged illness [16]. Bernard and colleagues conducted a randomized, double-blind, placebo-controlled trial of intravenous ibuprofen given every 6 h for 8 doses in 455 patients who had severe sepsis [17]. In this study treatment with ibuprofen decreased fever, tachycardia, oxygen consumption, and lactic acidosis, but it did not prevent the development of shock or ARDS and did not improve survival Against this background of convincing evidence demonstrating the harm of antipyresis in patients with sepsis, Schortgen and colleagues performed a multicenter, RCT in which vasopressor dependent febrile patients with septic shock were randomized to external cooling to achieve normothermia for 48 h or no external cooling [18]. In this study, there was a greater reduction of pressor use, more rapid shock reversal and a lower mortality at 14 days (19 vs. 34 %; $p=0.013$) in the cooling group. However, the difference in mortality was no longer significant at ICU or hospital discharge. Based on the results of this single study and the fact that fever is widely believed to be beneficial in the setting of infection external cooling cannot be recommend at this time. This study however does raise the possibility that external cooling may be beneficial in vasodilatory shock while anti-pyretic agents may be harmful. The HEAT trial is an ongoing prospective, multicentre, concealed, RCT comparing the administration of acetaminophen for antipyresis with a permissive temperature strategy in critically ill patients with known or suspected infection [19]. The results of this study should hopefully help resolve this controversial issue.

In contrast to patients with infectious disorders, patients with acute cerebral insults (ischemic stroke, hemorrhagic stroke, SAH, head injury, post cardiac arrest) have worse outcomes with increased temperature. For these patients the current recommendation is to maintain the patient's temperature in the normothermic range.

Antipyresis must always include an anti-pyretic agent, as external cooling alone increases heat generations and catecholamine production [20]. Furthermore, acute hepatitis may occur in ICU patients with reduced glutathione reserves (alcoholics, malnourished etc.) who have received regular therapeutic doses of acetaminophen.

Fever from an infectious cause should not be treated unless the patient has limited cardio-respiratory reserve or the temperature exceeds 40 °C (104 °F).

Causes of Fever in the ICU

Any disease process that results in the release of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α will result in the development of fever. While infections are common causes of fever in ICU patients, many non-infectious inflammatory conditions cause the release of the pro-inflammatory cytokines and induce a febrile response. Similarly, it is important to appreciate that not all patients with infections are febrile. Approximately 10 % of septic patients are hypothermic and 35 % normothermic at presentation. Septic patients who fail to develop a fever have a significantly higher mortality than febrile septic patients. The reason that patients with established infections fail to develop a febrile response is unclear, however, it appears that this aberrant response is not due to diminished cytokine production [21]. The approach to a patient who presents to hospital with a fever is different from that of a patient who develops a fever in the ICU. This chapter reviews fever that develops in the ICU; Chap. 12 summarizes the approach to the patient who presents to hospital with sepsis. As reviewed in Chap. 12 any one of the following features alone or in combination should alert the clinician to the increased likelihood of infection as a cause of fever:

- Fever >38.9 °C
- Systolic BP <90 mmHg
- PCT >0.5 ng/mL
- Bandemia >5 %
- Lymphocytopenia $<0.5 \times 10^3$ μL
- Thrombocytopenia $<150 \times 10^3$ μL
- Lactate >1.6 meq/L

The diagnosis of the cause(s) of a fever which develop in the ICU patient can be a daunting task. Consequently, the presence of a fever in the ICU patient frequently triggers a battery of diagnostic tests that are costly, expose the patient to unnecessary risks and often produce misleading or inconclusive results. It is therefore important that fever in ICU patients be evaluated in a systematic, prudent, clinically appropriate and cost effective manner.

Infectious Causes of Fever in the ICU

The prevalence of nosocomial infection in ICUs has been reported to vary from 3 to 31 %. The most common nosocomial infectious disorders are listed below [22, 23]:

- Ventilator associated pneumonia (VAP)
- Central Line Assocaited Blood Stream Infection (CLABSI)
- Primary septicemia
- Sinusitis
- *Clostridia difficile* enterocolitis
- Surgical site/wound infection
- Cellulitis
- Infected decubitus ulcer
- Suppurative thrombophlebitis
- Endocarditis

Note: Catheter Associated Urinary Tract Infection (CAUTI) is an exceedingly uncommon cause for a patient developing a fever in the ICU (see Chap. 16—Hospital Acquired Infections)

Non-Infections Causes of Fever in the ICU

A large number of non-infectious conditions result in tissue injury with inflammation and a febrile reaction. Those non-infectious disorders which should be considered in ICU patients are listed below. For reasons that are not entirely clear most non-infectious disorders usually do not lead to a fever in excess of 38.9 °C (102 °F); therefore, if the temperature increases above this threshold the patient should be considered to have an infectious etiology as the cause of the fever [24]. However, patients with drug fever may have a temperature >102 °F. Similarly, fever secondary to blood transfusion may exceed 102 °F. In patients with a temperature above 40 °C (104 °F) neuroleptic malignant syndrome, malignant hyperthermia, the serotonin syndrome and subarachnoid hemorrhage must always be considered. Most of the clinical conditions listed below are clinically obvious and do not require additional diagnostic tests to confirm their presence. However, a few of these disorders require special consideration.

Non-Infectious Causes of Fever

- Drug related
  - Drug fever
  - Neuroleptic malignant syndrome
  - Malignant hyperthermia

  - Serotonin syndrome
  - Drug withdrawal (including alcohol and recreational drugs)
  - IV contrast reaction
- Post-transfusion fever
- Neurologic
  - Intracranial hemorrhage
  - Cerebral infarction
  - Sub-arachnoid hemorrhage
  - Seizures
- Endocrine
  - Hyperthyroidism
  - Pheochromocytoma
  - Adrenal insufficiency
- Rheumatologic
  - Crystal arthropathies
  - Vasculitis
  - Collagen vascular diseases
- Hematologic
  - Phlebitis
  - Hematoma
- Gastrointestinal/hepatic
  - Acalculous cholecystitis
  - Ischemic bowel
  - Cirrhosis
  - Hepatitis
  - Gastrointestinal bleed
  - Pancreatitis
- Pulmonary
  - Aspiration pneumonitis
  - Acute respiratory distress syndrome
  - Thromboembolic disease
  - Fat embolism syndrome
- Cardiac
  - Myocardial infarction
  - Dressler's syndrome
  - Pericarditis
- Oncologic
  - Neoplastic syndromes

The most common non-infectious causes of a fever in ICU patients include drug fever, transfusion of blood and blood products, alcohol withdrawal, postoperative fever and thromboembolic disease. Acalculous cholecystitis is a relatively uncommon cause of fever in ICU patients; however, as it may be associated with severe morbidity and mortality it should always be considered in the differential diagnosis.

Drug Fever

Most ICU patients receive numerous medications. All drugs have side effects, including fever. It is estimated that about 10 % of inpatients develop drug fever during their hospital stay [25]. The diagnosis of drug fever in ICU patients is challenging as the onset of fever can occur immediately after administration of the drug or it can occur days, weeks, months, or even years after the patient has been on the offending medication. Furthermore, once the implicated medication is discontinued the fever can persist in excess of 4–5 days. Associated rashes and leukocytosis occur in less than 20 % of cases. An eosinophilia is suggestive of drug fever. Penicillins, cephalosporins, anticonvulsants, heparin and histamine 2-blockers are commonly used medications in the ICU that are associated with drug fevers.

Alcohol and Drug Withdrawal

Withdrawal from alcohol and medications is a common cause of non-infectious fever in hospitalized patients and usually presents within the first few days of hospital admission (see Chap. 46).

Postoperative Fever

Surgery alone can cause fever which is self-limited and resolves spontaneously [26–28]. In the early postoperative period a patient's temperature may increase up to 1.4 °C with the peak occurring approximately 11 h after surgery [26]. Fifty percent of postoperative patients will develop a fever greater than or equal to 38 °C with 25 % reaching 38.5 °C or higher. The fever typically lasts for 2–3 days. Postoperative fever is believed to be caused by tissue injury and inflammation with associated cytokine release [26]. The invasiveness of the procedure, as well as genetic factors, influences the degree of cytokine release and the febrile response. A good physical examination and history of the timing and sequence of events is crucial to help to differentiate postoperative fever from other infectious and noninfectious causes of fever. Reactions to medications (especially anesthesia), blood products and infections that might have existed prior to the surgery should also be considered during a patient's early postoperative course. Nosocomial and surgical site infections usually develop 3–5 days following surgery.

Atelectasis is commonly implicated as a cause of postoperative fever [27]. Standard ICU texts list atelectasis as a cause of fever, although they provide no primary source. Indeed a major surgery text states that "*fever is almost always present* (*in patients with atelectasis*)" [29]. During rounds, many medical students and house-staff have been taught that atelectasis is one of the "five" main causes of postoperative fever. However, there is very little data to support his widely held belief (myth). Engeron studied 100 postoperative cardiac surgery patients and was unable to demonstrate a relationship between atelectasis and fever [30]. Furthermore,

when atelectasis is induced in experimental animals by ligation of a main stem bronchus, fever does not occur [31]. The role of atelectasis as a cause of fever is unclear, however, atelectasis probably does not cause fever in the absence of pulmonary infection.

Blood Transfusions

A large number of patients in the ICU will receive transfusions of blood products (also see Chap. 38; Transfusion of blood and blood products). Febrile non-hemolytic transfusion reactions are common following transfusion of blood and blood products. This is likely mediated by the transfusion of cytokines such as IL-1, IL-6, IL-8, and TNF-α which accumulate with increasing length of blood storage [32, 33]. Febrile non-hemolytic reactions normally present within the first 6 h after transfusion and are self-limiting. They can present with chills and rigors in addition to fever. It is crucial to differentiate these from febrile acute hemolytic transfusion reactions which can be life threatening. Leukoreduction has been shown to reduce the risk of febrile non-hemolytic transfusion reactions.

Thromboembolic Disease

Fever has been reported in 18–60 % of patients with thromboembolic disease. Typically the fever is low grade (37.5–38 °C) however fever up to 39 °C has been reported [34, 35].

Acalculous Cholecystitis

Acute acalculous cholecystitis (AAC) is a condition of inflammation of the gallbladder in the absence of calculi [36]. AAC most commonly complicates surgery, multiple trauma or burn injuries. However, this disease is not uncommon in medical patients undergoing mechanical ventilation. AAC is a disease with significant morbidity and mortality as it can lead to empyema, gallbladder gangrene and gallbladder perforation. A high index of suspicion is required as this can be a difficult diagnosis to make, especially in the intubated and sedated patient. Initially patients present with very few symptoms. Clinical features include fever, leukocytosis, abnormal liver function tests, a palpable right upper quadrant mass, vague abdominal discomfort and jaundice. Untreated, bacterial superinfection may occur and this can progress to empyema, peritonitis and septic shock.

The pathophysiology of acalculous cholecystitis is complex and involves hypoperfusion and biliary stasis. However, bile stasis appears to be a major factor leading to AAC in both experimental and clinical studies [37]. Risk factors include trauma, surgery, mechanical ventilation, fasting, total parental nutrition, continuous tube feeding, immunosuppression, transfusions of blood products, hypotension, opiates,

diabetes and renal failure [37]. Bolus tube feeding, particularly with a high fat formula, may protect against acute acalculous cholecystitis (see Chap. 32)

The diagnosis acalculous cholecystitis is challenging and is made by a composite of clinical and laboratory findings and abdominal imaging findings. Ultrasound of the gallbladder is the most accurate modality to diagnose AAC in the critically ill patient [37]. Thickening of the gallbladder wall is the single most reliable criterion, with reported specificity of 90 % at 3 mm and 98.5 % at 3.5 mm wall thickness, and sensitivity of 100 % at 3 mm and 80 % at 3.5 mm. Accordingly, gallbladder wall thickness greater than or equal to 3.5 mm is generally accepted to be diagnostic of AAC [37]. Other helpful sonographic findings for AAC include pericholecystic fluid, sludge or the presence of intramural gas. Although technetium 99mTc iminodiacetic acid imaging is approximately 95 % accurate to diagnose calculous acute cholecystitis, false-negative and false-positive hepatobiliary scans make this test unreliable for the diagnosis of ACC in the setting of critical illness [37, 38]. Intravenous morphine (0.04–0.05 mg/kg) given after initial nonvisualization of the gallbladder may increase the accuracy of cholescintigraphy among critically ill patients, by enhanced gallbladder filling caused by increased bile secretory pressure. CT seems to be as accurate as ultrasound in the diagnosis of AAC [37, 39]. Diagnostic criteria for AAC by CT are similar to those described for sonography. As soon as the diagnosis is suspected blood cultures should be drawn, broad spectrum antibiotics initiated and a surgical consult requested. In most ICU patients percutaneous drainage is preferable to surgical intervention [40]. After patients with AAC have recovered from percutaneous cholecystostomy, further treatment such as cholecystectomy might not be needed [41].

Malignant Hyperthermia

Malignant hyperthermia is a rare genetic disorder of the muscle membrane causing an increase of calcium ions in the muscle cells. This can cause a variety of clinical problems, most commonly a dangerous hypermetabolic state after the use of anesthetic agents such as succinylcholine and inhaled anesthetic agents. This reaction typically occurs within 1 h of anesthesia but can be delayed for up to 10 h. Patients present with continually increasing fevers, muscle stiffness and tachycardia. They can rapidly develop hemodynamic instability with progression into multiorgan failure. Since the introduction of dantrolene, the mortality of malignant hyperthermia has decreased from 80 % in the 1960s to < 10 % today.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is characterized by high fevers, a change in mental status, muscle rigidity, extrapyramidal symptoms, autonomic nervous system disturbances, and altered levels of consciousness. Symptoms usually begin within days to weeks of starting the offending drug. Patients typically have very high creatinine

kinase levels. Neuroleptic malignant syndrome is caused by excessive dopaminergic blockade causing a dopamine deficiency in the central nervous system. Agents that most commonly implicated include neuroleptic medications and certain antiemetics. Treatment includes discontinuing the offending drug, aggressive supportive care and close hemodynamic monitoring. Drug treatment of neuroleptic malignant syndrome is controversial. A case controlled analysis and a retrospective analysis of published cases suggested that dantrolene, bromocriptine and amantadine may be beneficial.

Serotonin Syndrome

Serotonin syndrome is characterized by the triad of neuromuscular hyperactivity, autonomic hyperactivity, and change in mental status [42, 43]. It is not an idiosyncratic drug reaction but is a predictable response to serotonin excess in the central nervous system (CNS). It can occur from an overdose, drug interaction, or adverse drug effect involving serotonergic agents. Most severe cases result from a drug combination especially the combination of selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase inhibitors (MAOI). It occurs in approximately 15 % of patients with SSRI overdose. The death of an 18-year old patient named Libby Zion in a New York City hospital more than 20 years ago, which resulted from the co-administration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition [44].

Serotonin syndrome may result from a large number of drugs and drug combinations:

- Selective serotonin reuptake inhibitors
  - fluoxetine, paroxetine, sertraline, citalopram, escitalopram
- Antidepressants
  - venlafaxine, trazodone, nefazodone, clomipramine, St. John's Wort
- Monoamine oxidase inhibitors
  - phenelzine, moclobemide, tranylcypromine, clorgyline, isocarboxazid
- Antibiotics
  - linezolid (a monoamine oxidase inhibitors), ritonavir (acts through inhibition of cytochrome P-450 $3A_4$)
- Serotonin-releasing agents:
  - fenfluramine, methylenedioxymethamphetamine (MDMA or ecstasy), amphetamine
- Analgesics
  - Meperidine, fentanyl, tramadol
- Antiemetic
  - Ondansetron, granisetron, metoclopramide
- Other
  - lithium, tryptophan, sumatriptan

Diagnosis

A history of exposure to drugs known to cause the serotonin syndrome is key to considering the diagnosis, together with the clinical triad of neuromuscular hyperactivity, autonomic hyperactivity, and change in mental status

- Neuromuscular hyperactivity
  - shivering, tremor, hypertonia, rigidity
- Autonomic hyperactivity
  - hyperthermia, flushing, diaphoresis, diarrhea
- Mental status changes
  - confusion, anxiety, agitation, hypomania

Hyperthermia develops in approximately half of cases and results from increased muscle activity due to agitation and tremor. A core temperature as high as 40 °C is common in moderate to severe cases. Tachycardia, hypertension, mydriasis, hyperactive bowel sounds, myoclonus and ocular clonus are common; however not all of these symptoms are present in every patient. Hyperreflexia, clonus, hypertonicity are greater in lower extremities than in upper extremities. Sustained clonus is usually found at the ankles. Most of the laboratory abnormalities are a consequence of poorly treated hyperthermia and include elevated CPK, serum creatinine and aminotransferases as well as a metabolic acidosis.

There are two recognized sets of criteria that are used to confirm the diagnosis of serotonin syndrome.

Sternbach's Criteria [45]

- Recent addition or increase in a known serotonergic agent
- Absence of other possible etiologies (infection, substance abuse, or drug withdrawal)
- No recent addition or increase of a neuroleptic agent
- At least three of the following symptoms:
  - Mental status changes (confusion, hypomania)
  - Agitation
  - Myoclonus
  - Hyperreflexia
  - Diaphoresis
  - Shivering
  - Tremor
  - Diarrhea
  - Incoordination
  - Fever

Hunter Serotonin Toxicity Criteria [46]

A history of exposure to serotonergic agents and the presence of any one of the following is diagnostic of serotonin toxicity

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and hyperthermia (temperature >38 °C) with inducible clonus or ocular clonus

Treatment

Most important step is the removal of the offending drug. Mild cases (e.g., tremors and hyperreflexia) are managed with supportive care and treatment with benzodiazepines. Control of agitation with benzodiazepine is an essential step in the management. 5-HT_{2A} antagonists (cyproheptadine and chlorpromazine) have been used in moderate to severe cases. There are no randomized clinical trials demonstrating the effectiveness of 5-HT_{2A} antagonists

– Cyproheptadine is only available in oral form; the initial dose is 12 mg followed by 2 mg every 2 h until symptoms improve, and patients may require up to 12–32 mg of the drug in 24-h period
– Sublingual olanzapine (an atypical antipsychotic with 5-HT_{2A} antagonist activity) has also been used
– Chlorpromazine is the only 5-HT_{2A} antagonist available in the parenteral form; 50–100 mg of intramuscular chlorpromazine may be administered

An Approach to the Febrile ICU Patient

The word "*pan-culture*" is meaningless and should NEVER be uttered in the ICU

The following approach is suggested in ICU patients who develop a fever in the ICU with two temperature recordings above 38.3 °C, a single temperature above 38.3 °C with signs of sepsis or a single temperature above 39 °C (see Fig. 18.1). Due to the frequency, excess morbidity and mortality associated with bacteremia blood cultures are recommenced in all ICU patients who develop a fever (two sets from different sites). DO NOT SEND URINE CULTURES (except post urologic surgery, stents, etc.) and DO NOT SEND SPUTUM CULTURES. A comprehensive physical examination and review of the chest radiograph is essential. Non-infectious causes of fever should be excluded. In patients with an obvious focus of infection (e.g. purulent nasal discharge, abdominal tenderness, profuse green diarrhoea) a focused diagnostic workup is required. The measurement of serial procalcitonin and lactate levels are recommended (see Chap. 12) [47]. If there is no clinically obvious source

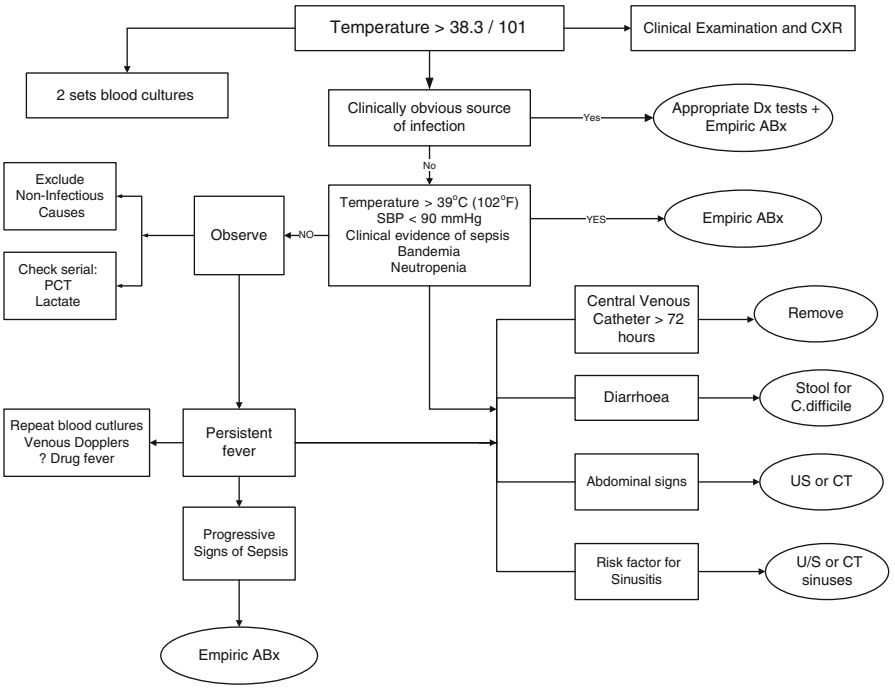

Fig. 18.1 Suggested algorithm for the management of fever

of infection and unless the patient is clinically deteriorating it may be prudent to perform blood cultures and then observe the patient before embarking on the further diagnostic tests and commencing empiric antibiotics. However, the following features should prompt the immediate initiation of broad spectrum antibiotics pending further diagnostic workup:

- Temperature >39 °C (102 °F)
- Fall in blood pressure or SBP <90 mmHg
- Heart rate >120/min
- An increasing lactate or lactate >2.0 meq/L
- PCT >0.5 ng/mL
- Bandemia >5 %
- Lymphocytopenia $<0.5 \times 10^3$ μL
- Fall in platelet count or platelet count $<150 \times 10^3$ μL
- Neutropenia with a neurophil count $<1{,}000 \times 10^3$ μL
- WBC count $>20{,}000 \times 10^3$ μL

In patients whose clinical picture is consistent with infection and in whom no clinically obvious source has been documented, removal of all central lines greater than 72 h old is recommended (USA only: do not culture the catheter tip, else you

will be punished), stool for *C. difficile* toxin (in those patients with loose stools) and an ultrasound examination, CT or plain films of the maxillary sinuses is recommended. If the patient is at risk of abdominal sepsis or has any abdominal signs (tenderness, distension, unable to tolerate enteral feeds) a CT scan of abdomen is indicated. Patients with right upper quadrant tenderness require an abdominal ultrasound or CT examination.

Re-evaluation of the patients' status after 48 h, using all available results and the evolution of the patient's clinical condition in essential. If fever persists despite empiric antibiotics and no source of infection has been identified, empiric antifungal therapy may be indicated in patients with risk factors for candidal infection. Additional diagnostic tests may be appropriate at this time including venous Doppler's, differential blood count for eosinophils (diagnosis of drug fever) and abdominal imaging.

Clinical Pearls

- All patients with a fever >38.3 °C (101 °F) require blood cultures and a clinical evaluation to determine the source of fever
- Urine cultures should not be routinely performed in patients with a fever
- In patients' with suspect VAP, quantitative culture of endobronchial secretions is suggested (see Chap. 17)
- Atelectasis does not cause a fever
- Antibiotics are not antipyretic agents and should therefore only be used in patients with suspected or proven bacterial infection
- As a general rule anti-pyretics should not be used to treat a fever
- A cooling blanket should not be used to treat a fever

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Chapter 19
Mechanical Ventilation 101

The requirement for endotracheal intubation and mechanical ventilation is the most common indication for admission to the ICU. The most common reason for mechanical ventilation is hypoxic respiratory failure (type 1 respiratory failure). In addition, patients with hypercarbic respiratory failure (type II respiratory failure) who have failed non-invasive modes of ventilation (NIV) require mechanical ventilation. With the development, refinement and popularization NIV as a primary mode of ventilatory support (CPAP and Bi-PAP) many patients who previously would have required intubation and mechanical ventilation are now treated with NIV [1–3]. The most common indications for NIV are an acute exacerbation of chronic obstructive lung disease (COPD) and acute cardiogenic pulmonary edema (see Chap. 20). NIV is generally inappropriate for patients with severe respiratory failure due to pneumonia, aspiration pneumonitis, asthma or acute lung injury (ALI).

It should be recognized that intubation eliminates the respiratory protective reflexes (patient cannot cough effectively) and interferes with the mucociliary escalator; these effects significantly increase the risk for the development of pneumonia (ventilator associated pneumonia). In addition, mechanical ventilation is never a curative intervention, but rather provides ventilatory assistance while the underlying disorder improves. Consequently, the decision to initiate mechanical ventilation is often difficult and the clinician should weigh the risks and benefits of the intervention. It is also important to recognize that positive pressure ventilation is potentially lethal in patients with severe pulmonary hypertension (may cause severe RV failure). The decision to intubate and initiate mechanical ventilation is essentially one of clinical judgment and should be based on a number of factors including the respiratory rate, heart rate, blood pressure, signs of respiratory distress (nasal flaring, use of accessory muscles, use of abdominal muscles, grunting, etc), arterial blood gas analysis (ABG-PaO_2, $PaCO_2$, pH) and/or pulse oximetry as well as the patients co-morbidities, acute medical problem and the likely response to medical interventions.

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The most common indications for intubation and mechanical ventilation are listed below:

- Hypoxic respiratory failure
  - Deliver a high FiO_2
  - Reduce shunt
  - Apply PEEP
- Hypercapnic respiratory acidosis
  - Reduce the work of breathing (WOB) and thus prevents respiratory muscle fatigue
  - Maintain adequate alveolar ventilation
- Unprotected and unstable airways (e.g., coma)
  - Secure the airway
  - Reduce the risk of aspiration
  - Maintain adequate alveolar ventilation
- Other
  - To facilitate procedure (bronchoscopy), bronchial suctioning

Think of Respiration as Two Separate Processes

- Oxygenation (assessed by PaO_2 and percent saturation)
- Ventilation (alveolar ventilation is indirectly proportional to PCO_2)

A landmark study published by the ARDSNet group (NIH ARDS Network) in 2000 demonstrated that volume-assisted ventilation (AC) with a low tidal volume (6 mL/kg of predicted body weight) was associated with a significant reduction in 28 day all-cause mortality as compared to AC ventilation with traditional tidal volumes (12 mL/kg of PBW) in patients with ARDS [4]. Such an approach is now considered the standard of care and applies to all mechanically ventilated patients, not just those with ARDS [5–7].

The predicted body weight (PBW) should be calculated on all patients undergoing mechanical ventilation

- Men: PBW = 50.0 + 0.91 (height in centimeters—152.4)
- Women: PBW = 45.5 + 0.91 (height in centimeters—152.4)

Regardless of the mode of mechanical ventilation the tidal volume (Vt) of all patients undergoing mechanical ventilation should target 6 mL/kg PBW and should never exceed 8 mL/kg PBW [4]. Alveolar overdistention has clearly been shown to damage normal as well as injured lungs. It is therefore important that a low Vt (known as a lung protective strategy) be used in all patients undergoing mechanical ventilation. Furthermore, it is important to use the predicted body weight (PBW) and not actual body weight for these calculations. The concept underlying this approach is that it normalizes the Vt to lung size, since lung size has been shown to depend most strongly on height and sex. For example, a person who ideally weighs 70 kg and who then gains 35 kg has essentially the same lung size as he or she did when at a weight of 70 kg and should not receive ventilation with a higher Vt because of the weight gain.

Alveolar Overdistension Damages Normal Lungs

In an observational cohort study, Gajic et al. reported that of patients ventilated for 2 days or longer who did not have ALI/ARDS at the onset of mechanical ventilation, 25 % developed ALI/ARDS within 5 days of mechanical ventilation [8]. In a multivariate analysis, the major risk factors associated with the development of lung injury were the use of a large Vt and transfusion of blood products. Interestingly, female patients were ventilated with larger Vt (per predicted body weight) and tended to develop lung injury more often. Women are generally shorter than men … this may have accounted for this finding. Similarly, in a large prospective observational study, a large Vt and high peak airway pressure were independently associated with development of ARDS in patients who did not have ARDS at the onset of mechanical ventilation [9].

The strongest evidence for the benefit of protective lung ventilation in patients without ALI/ARDS comes from two randomized studies in surgical patients. Intubated mechanically ventilated patients in the surgical ICU randomly assigned to mechanical ventilation with Vt of 12 mL/kg or lower Vt of 6 mL/kg [10]. The incidence of pulmonary infection tended to be lower, and duration of intubation and duration of ICU stay tended to be shorter for non-neurosurgical and non-cardiac surgical patients randomly assigned to the lower VT strategy. Futier and colleagues randomized 400 adults undergoing major abdominal surgery to an intraoperative ventilatory strategy of either 8–10 or 6–8 mL/kg [11]. The primary outcome was a composite of major pulmonary and extrapulmonary complications occurring within the first 7 days after surgery. The mean duration of ventilation was 5.7 h. In the intention-to-treat analysis, the primary outcome occurred 10.5 % assigned to lung-protective ventilation, as compared with 27.5 % assigned to non-protective ventilation (RR 0.40; CI 0.24–0.68; P = 0.001). This remarkable study demonstrates that even short periods of a non-lung protective ventilatory strategy are harmful.

Ventilator Variables and Modes of Ventilation

Current nomenclature related to mechanical ventilation are outdated and confusing. For example, the eighth edition of *Mosby's Respiratory Care Equipment* lists 56 unique names for ventilator mode labels [12]. However, when analyzing the targeting schemes (the feedback control system the ventilator uses to deliver a specific ventilatory pattern) in detail, only about two dozen of these modes are "unique" and identifiable using six basic targeting schemes.

The intensivist should be familiar with a number of modes of ventilation all of which have specific indications. Standard ventilator terminology and variables are listed in Table 19.1 while initial (default) ventilator settings are listed in Table 19.2. Ventilator phase variables are illustrated in Fig. 19.1. Volume Controlled Continuous Mandatory Ventilation (VC-CMV), also termed "Assist/Control Ventilation" is the most common mode of mechanical ventilation in the ICU and can be considered a

"default mode" (see Fig. 19.2). Pressure Controlled Continuous Mandatory Ventilation (PC-CMV), also termed "Pressure Control Ventilation", is equally considered as a default/standard mode in ICUs that have a highly involved Respiratory Therapy Driven Protocol in which the exhaled V_T is closely monitored (Fig. 19.2).

Table 19.1 Ventilator terminology and parameters

Parameter	Explanation
FiO_2	Fraction of inspired oxygen
Rate	Number of breaths per minute
Tidal volume (V_T)	Volume of each breath (usually in mL)
Sensitivity	How responsive the ventilator is to the patient's efforts
Peak flow	The maximum flow rate used to deliver each breath to the patient (usually in L/min)
Inspiratory time	The time spent in the inspiratory phase of the ventilatory cycle
I:E ratio	The inspiratory time compared to the expiratory time; I + E = total cycle time
Flow pattern	The shape of the inspiratory flow profile representing the breath type or patient effort; it can be square wave, sinusoidal, or decelerating
Mode	A predetermined pattern of patient–ventilator interaction. A mode can be described at various levels of detail, e.g., just specifying the control variable (volume or pressure), adding the breath sequence (e.g., VC-CMV, PC-IMV) and finally including the targeting scheme (e.g., PC-CSV with adaptive pressure targeting)
CMV	Continuous mandatory ventilation. A breath sequence that does not allow spontaneous breaths between mandatory breaths
CSV	Continuous spontaneous ventilation. A breath sequence consisting of only spontaneous breaths
Cycling	The change from inspiration to expiration
Expiration	The phase of a breath from the start of expiratory flow to the start of inspiratory flow
Inspiration	The phase of a breath from the start of inspiratory flow to the start of expiratory flow
IMV	Intermittent mandatory ventilation. A breath sequence that allows spontaneous breaths to occur between mandatory breaths
Target	A predetermined goal of ventilator output such as inspiratory pressure, tidal volume, inspiratory flow or minute ventilation
Targeting scheme	A model of the relationship between operator inputs and ventilator outputs to achieve a specific ventilatory pattern. The targeting scheme is a key component of a mode description
Mandatory breath	A breath for which inspiration is machine triggered and/or machine cycled
Spontaneous breath	A breath for which inspiration is both patient triggered and patient cycled
Trigger	To start inspiration. Triggering may be machine initiated (e.g. by a preset frequency) or patient initiated (e.g., by sensing an inspiratory effort using a pressure or flow signal)
PEEP	Positive end-expiratory pressure (usually in cm H_2O)

Table 19.2 Initial ventilator settings

Setting	
Mode	VC-CMV (A/C) or PC-CMV
V_T	6–8 mL/kg-PBW
Rate	12–16 min
PEEP	5 cm H_2O
FiO_2	80 %
Flow rate	40–80 L/min
Waveform	Decelerating

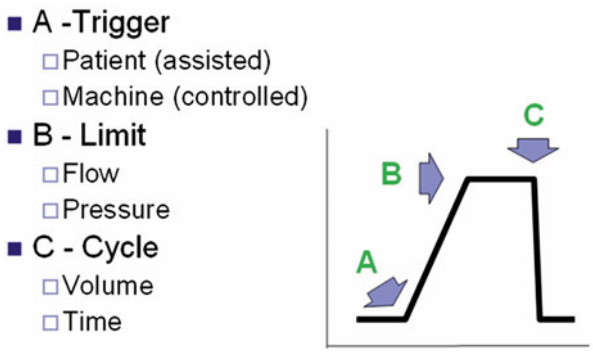

Fig. 19.1 Ventilator phase variables

Continuous Spontaneous Ventilation (CSV), also termed Pressure Support Ventilation (PSV) or Continuous Positive Airway Pressure (CPAP) is considered a Level 1 Evidence Based recommendations for ventilator liberation (weaning) and is commonly used in ventilator dependent patients with chronic respiratory failure (Fig. 19.3) [13]. Because the word "assist" describes the elevation of airway pressure above baseline during inspiration, PSV breath types are assisted, whereas CPAP breaths are unassisted.

These setting should then be dynamically adjusted according to:

- Plateau pressures keep less than 30 cm H_2O (unless stiff chest wall disorder is present, i.e. kyphoscoliosis, morbid obesity, increased abdominal pressures, neuromuscular disease)
- Arterial saturation-pulse oximetry (90–92 %)
- pH and pCO_2
- PEEPi (intrinsic PEEP)
- Flow and Pressure waveforms

Volume Controlled Intermittent Mandatory Ventilation (VC-IMV) otherwise known as, "IMV" or "SIMV" has a limited role; mainly in patients with asthma and those with unresolved respiratory alkalosis. It is the only mode of ventilation not recommended for the ventilator liberation process [13] (Fig. 19.4). Due to the ability of all ventilators to be patient triggered, it is no longer necessary to add the letter "S" to

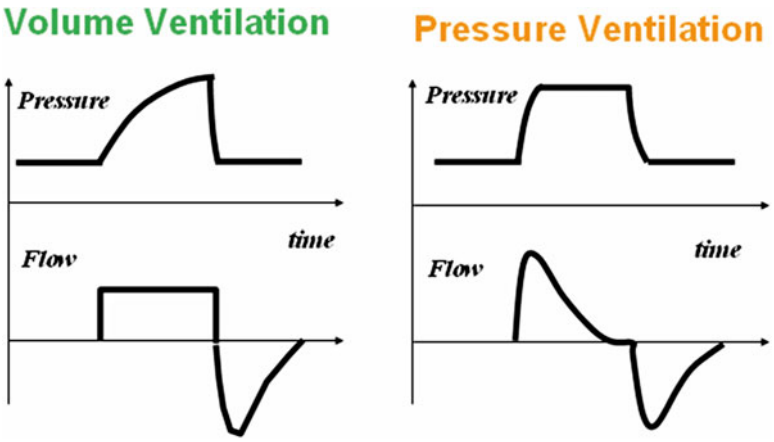

Fig. 19.2 Volume and pressure limited ventilation

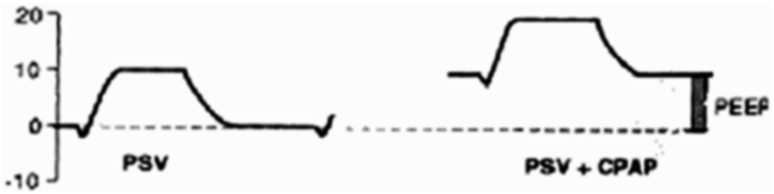

Fig. 19.3 Pressure support ventilation (PSV) and CPAP

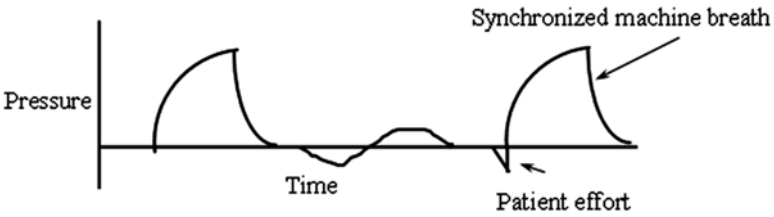

Fig. 19.4 Synchronized intermittent mandatory ventilation (SIMV)

designate "synchronized" [14]. Pressure Controlled Continuous Mandatory Ventilation (PC-CMV) and Airway Pressure Release Ventilation (APRV) should be considered in patients with severe ARDS who have "failed" conventional low V_T ventilation in the VC-CMV mode. In some centers APRV is considered the default mode for ALI/ARDS as well as cardiogenic pulmonary edema [15]. APRV is a useful mode in patients with atelectasis and reduced chest wall compliance.

Ventilator Variables (See Table 19.1)

Cycling

Ventilators have traditionally been classified according to the cycling method (i.e., termination of inspiration). However, modern ventilators have microprocessors, which allow them to function in many different modes with enormous versatility. Therefore cycling is classified as machine or patient cycled. Machine cycling is defined as the inability of the patient to change the inspiratory time with inspiratory or expiratory efforts or changes to the respiratory system time constant, Therefore, examples of machine cycling include volume and time cycling.

- *Volume cycled.* The ventilator delivers fresh gas until the preselected volume of gas is delivered. Alveolar pressure is proportional to respiratory system elastance and inversely proportional to compliance. Airway pressure is a function of volume and flow for a given elastance and resistance.
- *Time cycled.* Inspiration continues for a preset interval, with exhalation beginning when this time interval has elapsed, regardless of airway pressure or volume delivered.

Patient cycling is the influence of the patient to changing inspiratory time by making changes in inspiratory or expiratory effort, or respiratory system time constant. Pressure and Flow cycling are examples of patient cycling.

- *Pressure cycled.* Inspiration continues until a predetermined peak airway pressure is reached. On modern ICU ventilators this normally results in an alarm condition. The tidal volume is variable (from breath to breath) and depends on pulmonary time constant, inspiratory time, and flow rate.
- *Flow cycled.* Inspiration continues until the inspiratory flow decays to a preset value (usually a preset flow rate or a percentage of the peak inspiratory flow rate).

Inspiratory Wave Forms

Ventilators may offer as many as three different types of inspiratory flow patterns in the VC-CMV and VC-IMV modes of ventilation. These include:

- *Square wave:* The inspiratory flow rises to a preset level and is sustained until inspiration is cycled off.
- *Sinusoidal wave:* The flow gradually increases and then decreases until inspiration cycles off according to the first half of a sine function. This pattern most closely mimics the normal inspiratory pattern but is not an option on most ventilators.
- *Descending ramp wave:* The flow increases rapidly and then decreases linearly until inspiration is cycled off (aka “decelerating” wave).

In addition, the inspiratory flow pattern can be modified by adjusting the inspiratory flow rate, inspiratory time, and by providing an inspiratory pause (i.e., changing the I:E ratio).

Ventilator Trigger Variables

With all modes of mechanical ventilation a predetermined threshold must be created by the patient or the ventilator before the ventilator will deliver prescribed control parameters. In spontaneously breathing patients, pressure and flow triggering are the most commonly used trigger variables. With pressure triggering, a set negative pressure (relative to PEEP) must be attained for the ventilator to deliver fresh gas into the inspiratory circuit. This is commonly set at −2 cm H_2O. The higher (more negative) the trigger sensitivity, the harder the patient has to work to trigger a breath. With flow triggering, the patient must inspire a predetermined inspiratory flow rate (usually between 1 and 4 L/min) to start inspiration. During the initial phase of inspiration, the patient is able to inspire fresh gas which is supplied from a base flow which circulates continuously throughout the inhalation and exhalation circuit. The base flow for adults can range between 4 and 20 L/min, however, with most ventilators it is automatically increased in proportion to the set flow trigger sensitivity. The initial demand for flow is satisfied by the base flow, while at the same time generating the inspiratory flow signal according to the set flow sensitivity. In both the healthy subject and in the intubated patient the inspiratory muscle work has been demonstrated to be significantly higher with pressure-triggered CPAP (without PSV) than with flow-triggered CPAP. However, pressure support of 5 cm H_2O, has been demonstrated to reduce the inspiratory muscle work of pressure-triggered CPAP to a level comparable with that of flow triggered CPAP. The goal of the bedside clinician is to reduce the trigger sensitivity as much as possible in attempt to minimize the patient work to trigger without creating inadvertent ventilator auto-triggering.

Inspiratory to Expiratory Ratio (I:E)

Some ventilators allow the operator to set the I:E ratio directly. Other ventilators allow adjustment of the I:E ratio by altering the flow rate, respiratory rate, and inspiratory time or percentage (including an inspiratory pause). For most adults, a normal I:E ratio of 1:2 or 1:3 is used. In patients with chronic obstructive lung disease and asthma, longer I:E ratios (>1:4) are necessary to allow the lungs time to exhale to resting functional residual capacity (FRC) and to avoid hyperinflation. Patients who are hypoxemic secondary to ARDS require increased mean airway pressure (mPaw) to increase the FRC and allow more surface area for gas transfer to occur. This is achieved using both PEEP and inverse ratio ventilation. In addition, studies have demonstrated that prolonging inspiration can result in a more homogeneous distribution of ventilation within abnormal lungs. When the I:E ratio is increased to

1:1 or more, the inspiratory pressure is maintained for a longer period of time, however, the peak inspiratory pressure does not increase.

Common Modes of Mechanical Ventilation

Volume Control Continuous Mandatory Ventilation (VC-CMV)

In the VC-CMV mode, the ventilator delivers a preset Vt, inspiratory flow pattern, flow rate, and inspiratory time, within a machine or patient triggered breath. In this mode the control parameter is Vt, which also implies flow control. The inspiratory pressure will fluctuate from breath to breath. In the passively ventilated patient, a set frequency determines the rate of mandatory breath delivery. In the spontaneously breathing patient, if the patient effort is detected before the next time triggered mandatory breath is scheduled to be delivered, the ventilator will deliver the breath to the patient. The set rate also serves as a back up rate in the event of apnea. Unless the patient is ventilated using a mode which allows them to dictate their own frequency in which the mandatory breath delivery is not based on a time cycle, this mode will always deliver ventilation at the set frequency. In a recent study of ARDS patients, patient work of breathing (WOB) was lower with the use of VC-CMV with an inspiratory pause compared to PC-CMV and Dual Controlled Continuous Mandatory Ventilation (DC-CMV) [16].

Pressure Controlled Continuous Mandatory Ventilation (PC-CMV)

This mode of ventilation delivers a preset pressure and inspiratory time within a machine or patient triggered breath. The control parameters are pressure and time. Tidal volume and inspiratory flow will vary for each breath as determined by respiratory system mechanics and patient inspiratory effort. As the lungs are filled, the inspiratory flow decreases (decelerating wave) in order to maintain a constant pressure. The point at which inspiratory flow decays to zero represents completed filling of the lung at the preset pressure. This inspiratory waveform has been shown to result in a more homogeneous distribution of gas flow in patients with the acute respiratory distress syndrome (ARDS). Improved patient comfort and lower WOB have been observed in spontaneously breathing patients with the use of PC-CMV in comparison to VC-CMV [17, 18].

Volume Controlled and Pressure Controlled Intermittent Mandatory Ventilation (VC-IMV and PC-IMV) (Also Termed IMV, SIMV)

When using a mode that provides an IMV breath sequence, the patient is subjected to inspiring two different breath types: (1) a mandatory volume controlled or pressure controlled mandatory breath and (2) a spontaneous breath that may be assisted

(e.g. with Pressure Support) or unassisted (pressure does not rise above PEEP during inspiration). The original clinical intent was to partition ventilatory support between assisted and unassisted breaths. Historically, this was an evolutionary milestone in mechanical ventilation, as it was the first breath sequence of its kind to allow patients to breathe spontaneously through the ventilator circuit at a Vt and RR that he/she determined according to need. Although it is perceived to "synchronize" with the patients respiratory efforts (i.e., SIMV), this was later realized to be untrue as synchrony is based on frequency of breath detection, satisfying inspiratory flow demand, and ability to cycle into exhalation, which are present in most modes of ventilation (see Fig. 19.4).

Continuous Mandatory Ventilation (CMV)

The acronym "CMV" has been used by ventilator manufacturers to define a variety of modes of ventilation and has blurred the historical distinction between CMV and IMV [14]. With continuous mandatory ventilation (commonly known as "Assist/Control"), all breaths are mandatory unless there is provision for spontaneous breaths during mandatory breaths (i.e., using a so-called active exhalation valve). The defining characteristic of CMV is that spontaneous breaths are not permitted between mandatory breaths because an inspiratory effort after a mandatory breath triggers another mandatory breath. Typically, CMV provides a preset mandatory breath frequency in the case of apnea, but the actual breathing frequency at any time is a function of the patient's inspiratory efforts (i.e., the actual frequency is usually higher than the set frequency).

Continuous Spontaneous Ventilation (CSV) with Pressure Support Ventilation (PSV) (PC-CSV)

Pressure Support Ventilation (classified as a type of PC-CSV) was developed to reduce the work of spontaneous breathing in the IMV and CPAP modes. With Pressure Support, each breath is patient triggered, pressure-targeted, and flow-cycled. This is different from a PC-CMV breath, for which breaths are patient or machine triggered, pressure-targeted and time cycled. Therefore this breath type allows the patient to have a more flexible inspiratory time in proportion to their neural inspiratory time. PSV also compensates for the inherent impedance of the ventilator circuit and endotracheal tube, enabling the patient to establish a more natural breathing pattern. A PSV of between 5 and 10 cm H_2O will overcome the resistance of the ventilator circuit and endotracheal tube. With PSV the patient controls the rate, volume, and duration of each breath.

Airway Pressure Release Ventilation (APRV)

APRV is a time triggered, pressure targeted, time cycled mode of ventilation that allows unrestricted spontaneous breathing throughout the entire ventilatory cycle (see Fig. 19.5). It is an alternative approach to the "open-lung" ventilation strategy [19]. Although recruitment maneuvers may be effective in improving gas exchange and compliance, these effects are not sustained; APRV may be viewed as a nearly continuous recruitment maneuver [20]. The ventilator maintains a high-pressure setting for the bulk of the respiratory cycle (PHigh), which is followed by a periodic release to a low pressure (PLow) [21]. The periodic releases aid in carbon dioxide elimination (CO_2). The release periods (TLow) are kept short (0.2–1.0 s) in order to induce a level of intrinsic AutoPEEP which prevents alveolar derecruitment and enhances spontaneous breathing during THigh [19, 22]. The advantages of APRV over VC-CMV include an increase in mean alveolar pressure with alveolar recruitment, improved patient/ventilator synchrony, the hemodynamic and ventilatory benefits associated with spontaneous breathing and the reduced requirement for sedation.

Indications for APRV

- ALI/ARDS with
  - $FiO_2 \geq 60$ %
  - $Peep \geq 10$
- Cardiogenic pulmonary edema
- Morbid obesity with basal atelectasis [23]
- Segmental/lobar atelectasis [24]
- Pregnancy [25]

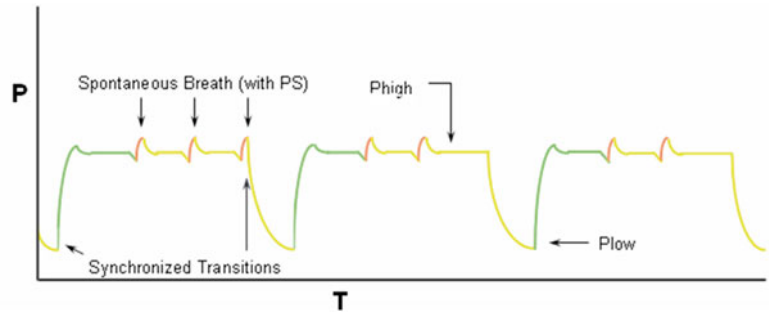

Fig. 19.5 Airway pressure release ventilation (APRV)

Exclusion

- COPD/Asthma
- Contra-indication to permissive hypercapnia

Potential Advantages of APRV

- Lung protective—minimizes VILI
  - Alveolar recruitment
  - Decreases over-inflation
  - Enhanced gas exchange
- Improves hemodynamic profile
  - Reduced need for pressors
  - Enhanced venous return
  - Increased cardiac output
  - Reduced myocardial work
- Provides benefit from spontaneous breathing
  - Improves V/Q mismatching
  - Preferentially aerates dependent lung
  - Limited adverse effects on cardio-pulmonary function
- Decreased work of breathing
- Decreased need for sedation

Initial Settings

- Release rate (frequency) 12–14/min
- PHigh 20–25 cm H_2O (75 % of Pplat)
- PLow 5–10 cm H_2O (75 % of orig PEEP)
- TimeL 0.7—1 s
- PS 5 cm H_2O

An alternative method of setting up and adjusting APRV is by measuring transalveolar pressures using an esophageal balloon. PLow is set such that transalveolar end-expiratory pressure (release pressure) is 0–5 cm H_2O and the transalveolar inspiratory pressures <30 cm H_2O.

Transalveolar pressure = the airway pressure − esophageal pressure

Monitoring on APRV

- Minute Ventilation
- Tidal volume
  - APRV (release volume)
  - Spontaneous
- SaO_2
- Patient Rate
- $PaCO_2$

In order to prevent alveolar over-distension the release volume should be monitored and should be kept below 8 mL/kg-PBW. If the release volumes are excessive this can be corrected by either reducing PHigh or increasing PLow.

Weaning from APRV

- Decrease FiO_2
- Decrease PHigh
- Increase TimeL
- Goal is to arrive at a straight CPAP usually at 12 cm H_2O

Positive End-Expiratory Pressure (PEEP)

PEEP provides positive end-expiratory pressure above atmospheric pressure (see Fig. 19.3). The mean airway pressure increases in proportion to the level of PEEP. In patients with pulmonary edema, PEEP shifts the pressure-volume inflation curve toward normal, increasing compliance, recruiting alveoli, and increasing FRC. It is thought that PEEP redistributes lung water. In patients with a large shunt increasing FiO_2 has little effect on arterial PaO_2; increased PEEP is required to increase PaO_2 in patients with a large shunt. It should be noted that PEEP is "good" for left ventricular function but may cause cardiovascular collapse in patients with severe right ventricular dysfunction. Some clinicians use "physiological" or prophylactic PEEP (5 cm H_2O) to prevent atelectasis/pneumonia. Manzano et al. randomized 131 mechanically ventilated patients with normal chest radiograph and PaO_2/FiO_2 above 250 to receive mechanical ventilation with 5–8 cm H_2O PEEP or no-PEEP [26]. Ventilator-associated pneumonia was detected in 16 (25.4 %) patients in the control group and 6 (9.4 %) in the PEEP group. The number of patients who developed hypoxemia was significantly higher in the control group (34 of 63 patients, 54 %) than in the PEEP group (12 of 64, 19 %).

Increased PEEP (>5 cm H_2O) is primarily used in patients' with pulmonary edema (non-cardiogenic and cardiogenic) with a large intra-pulmonary shunt who become refractory to increasing FiO_2. The optimal method of setting PEEP in patients with ARDS is controversial. Excessive PEEP will overinflate compliant lungs and increase ventilation/perfusion (V/Q) mismatching as well as reduce cardiac output. However, inadequate PEEP may result in airway collapse at the end of expiration, leading to the cyclic opening and closing of alveolar units than may further perpetuate lung injury. The goal is to set PEEP at a level that does not overdistend healthy alveoli but at the same time does not let diseased airways collapse. The term "Open Lung Approach" has been used to describe this method of ventilation [27]. It has been reported that in patients with ARDS a mean PEEP level of 15 cm H_2O is required to sustain alveolar opening at end-expiration [27]. While the beneficial effects of a low tidal volume strategy is largely accepted, the role of PEEP as part of the "Lung Protective Strategy" is more controversial [28–30]. A meta-analysis demonstrated a trend towards improved mortality with high PEEP,

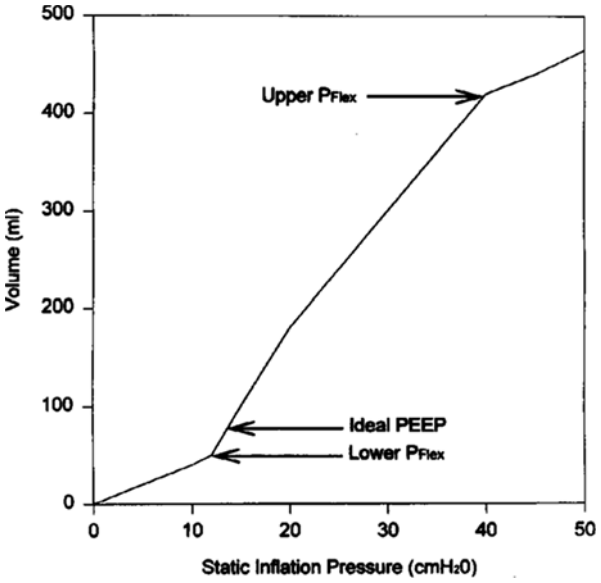

Fig. 19.6 Static pressure-volume curve and "Ideal" PEEP

even though the difference did not reach statistical significance; with the pooled cumulative risk of 0.90 (95 % CI 0.72–1.02, P = 0.077) [31]. "Best PEEP" can be estimated by plotting a static pressure/volume curve measuring airway pressure at each incrementally higher tidal volume (see Fig. 19.6). This curve classically demonstrates an upper and lower inflection point representing respiratory system opening and overdistention. PEEP should be set above the lower inflection point such that the sum of the PEEP and the inspiratory pressure should be below 30 cm H_2O (a plateau pressure up to 35 cm H_2O may be acceptable) or the upper inflection point. Should an inflection point not be present on the pressure/volume curve or it not be possible to perform this maneuver, the initial PEEP should be set between 10 and 15 cm H_2O.

Ideally, both Vt and PEEP should be adjusted according to transpulmonary pressures (airway pressure minus pleural pressure) to maintain oxygenation while minimizing repeated alveolar collapse (negative end-expiratory transpulmonary pressure) and minimizing alveolar overdistension (high end-inspiratory transpulmonary pressure). While pleural pressure is very difficult to measure clinically it can be estimated using esophageal manometry [32]. According to this approach, in patients with high estimated pleural pressure increasing PEEP to maintain a positive transpulmonary pressure might improve aeration and oxygenation without causing overdistention. Conversely, in patients with low pleural pressure maintaining low PEEP would keep transpulmonary pressure low, preventing overdistention and minimizing the adverse hemodynamic effects of high PEEP. Talmor and colleagues performed a randomized controlled study in which PEEP and Vt were set according to measurement of esophageal pressures or according to the ARDSNet protocol

[33]. In this pilot study, oxygenation and respiratory compliance were significantly better in the esophageal pressure group with a trend towards improved survival.

Indications for PEEP

- Cardiogenic pulmonary edema
- Acute lung injury and ARDS
- Postoperative patients (decreased FRC)
- Prevent basal atelectasis in morbidly obese patients

Contraindications

- Bullous lung disease and emphysema
- Unilateral lung disease (relative contra-indication)

PEEP valve: When using >5 cm H_2O PEEP, a PEEP valve should be used when suctioning the patient. Disconnecting the endotracheal tube will result in a loss of PEEP, a rapid reduction in the FRC, and alveolar flooding.

Detrimental Effects of PEEP Include

- Reduced venous return and cardiac output
- Reduction in hepatic and renal blood flow
- Barotrauma
- Increased intra-abdominal pressure
- Fluid retention
- Increased inspiratory workload
- Increased extravascular lung water
- Alveolar overdistension
- Ileus

Auto-PEEP

As with spontaneous ventilation, exhalation during mechanical ventilation is a passive event and continues until the FRC is achieved. In patients with airflow limitation (asthma and chronic obstructive pulmonary disease) and in patients ventilated with reversed inspiratory/expiratory (I:E) ratios a positive pressure breath may be initiated before exhalation is complete. This process leads to air trapping and intrinsic PEEP or auto-PEEP (see Fig. 19.7). Auto-PEEP is common in mechanically ventilated patients. Auto-PEEP increases intrathoracic pressure, thereby exacerbating the effects of positive pressure ventilation. In patients with severe airflow limitation, severe auto-PEEP may develop. Patients may present with hemodynamic collapse similar to that of a tension pneumothorax. Auto-PEEP is treated by disconnecting the patient from the ventilator to "vent" the trapped air, and then changing the I:E ratio, allowing more time for exhalation. The presence of auto-PEEP cannot be detected unless the exhalation port venting to the atmosphere is occluded at end

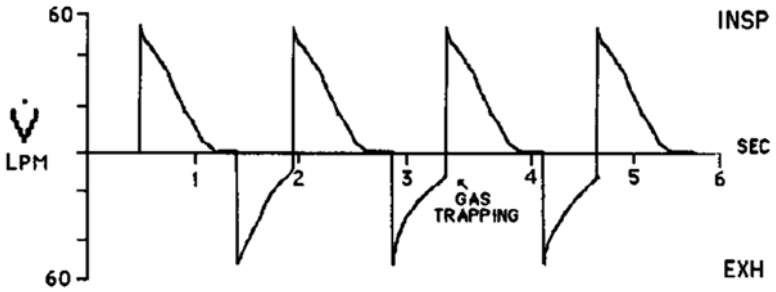

Fig. 19.7 Gas trapping and Auto-PEEP

expiration (using a one-way valve). Some ventilators have an expiratory hold valve, enabling the auto-PEEP to be measured directly.

Monitoring Patients Undergoing Mechanical Ventilation

All patients receiving mechanical ventilation should be monitored by pulse oximetry. Arterial blood gas (ABG) analysis should be performed during the initial ventilator adjustments and then when clinically indicated. The arterial saturation as measured by pulse oximetry provides adequate information for managing most ventilated patients. Patients with CO_2 retention and patients with complex metabolic derangements generally require regular ABG. It is not necessary to perform an ABG analysis after every ventilator change. In fact, studies have demonstrated that obtaining a routine ABG following completion of a spontaneous breathing trial (SBT) did not affect extubation decision making with similar outcomes to those who did not receive routine ABG [34, 35]. Therefore, routine ABG following SBT is not recommended unless clinically indicated. All the ventilator parameters, including plateau pressure, mean airway pressure, Vt, minute volume should be monitored and recorded periodically. A chest radiograph should be performed after intubation and repeated as clinically indicated. Routine daily chest radiographs are not cost effective [36].

The following formulas are useful in evaluating patients in respiratory failure:

- Age-predicted PaO_2 = Expected PaO_2 − 0.3(age-25) [expected PaO_2 at sea level is 100 mg/Hg]
- As a rough rule of thumb: Expected $PaO_2 \approx FiO_2$ (%) × 5
- $AaDO_2 = (FiO_2 \times [BP^*\text{-}47]) - (PaO_2 + PaCO_2)$ where BP = barometric pressure

- the PaO_2/FiO_2 ratio, is a better indicator of the degree of intra-pulmonary shunting than the $AaDO_2$
- $Vd/Vt = (PaCO_2 – PECO_2)/PaCO_2$ (N = 0.2–0.4)

Sudden Increase in Airway Pressure and/or Fall in Arterial Saturation

Causes

- Blocked endotracheal tube
- Herniated endotracheal tube cuff
- Tension pneumothorax
- Kinked endotracheal tube
- Tube migration (right main stem bronchus)
- Mucous plug with lobar atelectasis
- Patient biting down on tube
- Patient ventilator synchrony

Management

- Bag patient with 100 % oxygen
- Check position of endotracheal tube
- Suction through endotracheal tube: If unable to pass catheter, then reintubate
- Listen for tension pneumothorax: place chest drain if silent and deviated trachea.
- Urgent chest X-ray.

When to Perform a Tracheostomy

The decision to perform a tracheostomy in critically patients should be adapted to each patient and his/her pathology—balancing the patient's wishes, expected recovery course, risk of continued translaryngeal intubation and surgical risks of the procedure. Medical indications for tracheostomy include:

- failure of extubation
- upper airway obstruction
- airway protection
- airway access for secretion removal
- avoidance of serious oropharyngeal and laryngeal injury from prolonged translaryngeal intubation.

Beneficial effects of tracheostomy include

- Improved patient comfort through allowance of speech, oral nutrition, and easier nursing care
- The need for less sedation and analgesia requirements
- Reduced airway resistance is thought to facilitate the weaning process
- Ventilator-associated pneumonia may also be reduced by substituting a tracheostomy for translaryngeal intubation.

Timing of Tracheostomy in the Critically Ill

Optimal timing for tracheostomy (early versus late) has until recently been controversial with some clinicians recommending tracheostomy with 48 of intubation [37]. A recent RCT has resolved this issue, demonstrating no advantage to early tracheostomy. The TracMan study randomized 990 mechanically ventilated patients to early tracheostomy (within 4 days) or late tracheostomy (after 10 days if still indicated) [38]. The primary outcome measure was 30-day mortality. In this study tracheostomy within 4 days of ICU admission was not associated with an improvement in 30-day mortality or other secondary outcomes.

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Chapter 20
Non-invasive Ventilation

Non-invasive ventilation (NIV) has become a common treatment for acute and chronic respiratory failure. The main theoretical advantage of NIV is avoiding the side effects and complications related to endotracheal intubation, improving patient comfort and preserving airway defense mechanisms. NIV has been demonstrated to reduce ICU and hospital length of stay and improve outcome in select patient groups.

NIV can be delivered nasally or by face-mask, using either a conventional mechanical ventilator or a machine designed specifically for this purpose. NIV has two major modes of supplying ventilatory support, namely, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). CPAP provides continuous positive pressure throughout the respiratory cycle. CPAP recruits underventilated alveoli by increasing lung volume at the end of expiration, resulting in improved gas exchange. CPAP is also effective in decreasing work of breathing compared with unsupported ventilation [1].

NIV is usually delivered either by portable positive pressure BiPAP ventilators or critical care ventilators designed to deliver invasive mechanical ventilation. No study has shown better NIV success rates for one type of ventilator than the other, but the ventilator mode used and specific settings are important for patient comfort and decreased work of breathing. Generally, pressure support ventilation is rated as more tolerable by patients than assist-control modes when using a conventional ventilator [2].

BiPAP ventilators provide high-flow positive airway pressure that cycles between high-positive pressure and low-positive pressure. In the spontaneous mode, BiPAP responds to the patient's own flow rate and cycles between high-pressure inspiration and low-pressure exhalation. BiPAP reliably senses the patient's breathing efforts and even air leaks that occur within the unit. When inspiration is detected the inspiratory pressure is known as inspiratory positive airway pressure (IPAP). During this cycle, higher pressures are delivered for a fixed time or until the gas flow rate falls below a threshold level, usually 25 % of the expiratory volume. At this point in time, the expiratory positive airway pressure (EPAP) cycle begins delivering a lower

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positive pressure that splint and maintains a fixed alveolar pressure. BiPAP is similar to pressure support ventilation. The terminology differs, however; for BiPAP, the expiratory pressure is equivalent to the sum of the positive end-expiratory pressure and the inspiratory pressure. Thus, a BiPAP setting of 12 cm of inspiratory pressure and 5 cm of for expiratory pressures is equivalent to a standard ventilator setting of 7 cm for pressure support and 5 cm for positive end-expiratory pressure (PEEP).

The advantages of NIV include improved patient comfort, reduced need for sedation, and avoidance of the complications of endotracheal intubation, including upper airway trauma, sinusitis, and nosocomial pneumonia. Furthermore, airway defense mechanisms and speech and swallowing are left intact, and the patient remains alert and communicative. NIV has been used successfully to treat acute respiratory failure in postoperative patients and in those with pulmonary edema, chronic obstructive pulmonary disease, and obstructive sleep apnea. NIV has also been used to facilitate weaning. However, NIV appears to be particularly effective in patients with an exacerbation of COPD who are alert and cooperative.

The most common complication with the use of NIV is facial trauma related to the use of tight fitting masks. The problem of skin necrosis, particularly over the bridge of the nose, makes it difficult for patients to be ventilated continuously for more than 1–2 days. Retention of secretions and gastric distension may be problematic in some patients.

Set Up

NIV works best in patients relaxed and prepared. The first few seconds should be used to fit the mask and familiarize the patient with equipment. Patients may feel claustrophobic, especially when increasing respiratory drive and when difficult breathing is present. NIV is tolerated best when pressures are increased gradually, as the work of breathing and respiratory drive eases

Initial Settings

- Spontaneous trigger mode with backup rate
- Start with low pressures
  - IPAP 8–12 cm H_2O
  - PEEP 3–5 cm H_2O
- Adjust inspired O_2 to keep O2 sat >90 %
- Increase IPAP gradually up to 20 cm H_2O (as tolerated) to:
  - alleviate dyspnea
  - decrease respiratory rate
  - increase tidal volume
  - establish patient-ventilator synchrony

Indications of NIV

Many applications of NIPPV have been tried in the critical care setting, but as of yet, only five are supported by multiple randomized controlled trials and meta-analyses (see below) [3]. In addition to these indications, NIV can be useful in selected patients with asthma and in extubation failure.

COPD Exacerbations

The strongest level of evidence supports the use of NIV to treat exacerbations of COPD. NIV results in more rapid improvements in vital signs and gas exchange, reduction in the need for intubation, decreased mortality and decreased hospital length of stay [4]. In a systematic Cochrane Database review, Picot and colleagues analyzed 14 randomized controlled trials, and found that NIV in COPD exacerbations is associated with a 60 % reduction in risk of intubation (number needed to treat of 4) and a 50 % reduction in mortality risk (number needed to treat of 5) [5]. Based on these findings NIV should now be considered the ventilatory modality of first choice to treat acute respiratory failure caused by exacerbations of COPD.

Acute Cardiogenic Pulmonary Edema

Similarly strong evidence supports the use of NIV to treat acute cardiogenic pulmonary edema. Both CPAP and BiPAP lower intubation and mortality rates compared to conventional therapy with oxygen. Gray et al., published a large multi-center randomized controlled trial that included over 1,000 patients [6]. All were patients admitted with acute cardiogenic pulmonary edema and randomized to usual care, CPAP or NIV. When comparing both NIV groups to the usual care group, they reported that NIV is associated with a quicker resolution of respiratory distress and metabolic derangements, but that there is no difference in 7- or 30-day mortality. A 2008 Cochrane systematic review assessed a total of 21 randomized controlled trials comparing NIPPV, CPAP, and standard care for patients with acute cardiogenic pulmonary edema [7]. This review reported that NIPPV and CPAP are both associated with a mortality benefit and a decreased risk of intubation when compared to the control group. CPAP should be considered as the first line intervention as it is as efficacious as BiPAP and CPAP is cheaper and easier to implement in clinical practice [8, 9].

Facilitating Extubation in COPD Patients

NIV has been successfully used to facilitate extubation in patients with hypercapnic respiratory failure and to avoid the complications of prolonged intubation.

Immunocompromised Patients

NIV has traditionally not been considered in the management strategy of patients with malignancy, however, this mode of ventilatory support may be appropriate in three specific situations, namely [10],

- avoiding endotracheal intubation in patients with hematologic malignancy or following bone marrow transplant
- in patients with malignancy who have refused invasive mechanical ventilation (DNI) but who still desire aggressive treatment
- for the relief of disabling dyspnea.

In neutropenic patients mechanical ventilation is associated with significant mortality and morbidity, with in-hospital mortality rates as high as 90–97 % [11, 12]. Ewig and colleagues demonstrated that endotracheal intubation and mechanical ventilation increases the risk of death by 43 fold in patients with hematologic malignancy [11]. Consequently, any less invasive method of ventilatory support which is able to avoid the use of endotracheal ventilation would appear to be particularly useful in these high risk patients. Hilbert and colleagues randomized 52 immunosuppressed patients with early hypoxic acute respiratory failure to NIV or standard treatment with supplemental oxygen and no ventilatory support [13]. In this study, fewer patients in the NIV group required endotracheal intubation (46 vs 77 %), had serious complications (50 vs 81 %) or died in hospital (50 vs 81 %). NIV should be considered in the management strategy in immunocompromised patients who develop respiratory failure [10]. However careful patient selection is crucial and early identification of patients likely improves outcome.

Post-operative Patients

Due to pain, poor cough, delayed ambulation and underlying co-morbidities postoperative pulmonary complications have been reported in up to 50 % of patients undergoing abdominal surgery. A meta-analysis by Ferreyra and colleagues demonstrated that CPAP used prophylactically reduced the risk of post-operative respiratory complications in patients undergoing abdominal surgery [14]. Similarly, Squadrone and colleagues demonstrated that CPAP reduced the incidence of endotracheal intubation and other severe complications in patients who developed hypoxemia after elective major abdominal surgery [15].

When to Use NIV

Hypercapnic Respiratory Failure

- Severe dyspnea at rest
- Respiratory rate >25 breaths/min
- Use of accessory muscle of respiration
- Acute respiratory acidosis (pH <7.30)
- An alert and cooperative patient

Hypoxemic Respiratory Failure

- Respiratory rate >30 breaths/min
- PaO_2/FiO_2 <200
- Increased use of accessory muscle or $PaCO_2$ retention
- Alert and cooperative patient

Contraindications to NIPPV

- Hemodynamic or electrocardiographic instability
- Patient at risk for aspiration
- Inability to clear copious secretions
- Cardiac or respiratory arrest
- Nonrespiratory organ failure
- Severe encephalopathy (e.g., GCS <10)
- Severe upper gastrointestinal bleeding
- Facial surgery, trauma, or deformity
- Upper airway obstruction
- Inability to cooperate/protect the airway
- Inability to clear respiratory secretions
- Obtunded or uncooperative patient

Patient selection and monitoring are crucial to reduce NIV failure. NIV should not be used in patients suffering from claustrophobia or who are unable to tolerate the NIV device because of agitation or uncooperativeness. NIV is contraindicated in patients who are unable to protect their airway due to a swallowing impairment or excessive secretions not sufficiently managed by clearance techniques, and after recent upper airway surgery.

Success and Failure Criteria for NIPPV

- Improvements in pH and PCO_2 occurring within 2 h predict the eventual success of NIV.
- If stabilization or improvement has not been achieved during this time period, the patient should be considered an NPPV failure and intubation must be strongly considered.
- Other criteria for a failed NPPV trial include:
  - worsened encephalopathy or agitation
  - inability to clear secretions
  - inability to tolerate any available mask
  - hemodynamic instability
  - worsened oxygenation

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Chapter 21
Liberation (Weaning from Mechanical Ventilation)

General Concepts

Liberation is the process by which a patient is removed from the ventilator. This process has also been referred to as separation-, liberation-, and withdrawal- from the ventilator, as well as discontinuation of mechanical ventilation. The currently popular term is liberation from mechanical ventilation [1]. Early liberation studies demonstrated that "weaning" contributed at least 40 % of the total duration of mechanical ventilation [2, 3]. Optimizing the process of liberation may therefore be the major means of shortening the duration of mechanical ventilation and ICU length of stay thereby limiting complications.

Early weaning studies suggested that physicians did not initiate liberation early enough and this increased time spent on the ventilator as well as ICU length of stay. Furthermore, the weaning process was extended over many days by gradually reducing the rate (on IMV) or degree of ventilator support (PS) [4]. This concept of weaning was replaced by the concept of "liberation" whereby the patient was either ready (and hence *readiness testing* was done) or not ready for extubation and that the classic weaning method slowed the process and may have further compromised respiratory muscle fatigue [1]. A number of respiratory therapy/nurse driven "liberation protocols" which screen patients daily for "readiness to wean" and who then undergo a spontaneous breathing trial (SBT) followed by a decision to extubate have been demonstrated to significantly reduce the liberation time [5–8]. Daily readiness screening is now coupled with "sedation vacations" to expedite the process [9]. This is now the preferred method of liberation. A Cochrane metaanalysis reviewed the impact of weaning protocols compared to "standard care" [10]. This analysis included 11 trials and 1,971 patients. Compared with usual care, duration of mechanical ventilation in the weaning protocol group was reduced by 25 % (CI 9–39 %, $p=0.006$), the duration of weaning was reduced by 78 % (31–93 %, $p=0.009$) and length of ICU stay by 10 % (2–19 %, $p=0.02$).

The factors that need to be evaluated when considering liberating a patient from mechanical ventilation include the patient's underlying disease process, the reasons

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for intubation and mechanical ventilation in the first instance, the patient's level of consciousness, ability to protect his/her airway, pulmonary mechanics, and oxygenation defect. In many patients, ventilatory assistance need not be decreased gradually; mechanical ventilation and artificial airways can simply be removed (liberated). According to this thesis patients can simply be removed from the ventilator once the disease process that led to intubation and mechanical ventilation has improved or resolved; a prolonged liberation process is therefore not required. Treatment of reversible factors and "medical optimization" should be performed in those patients who fail a SBT (see below). A daily SBT should be performed until the patient is ready for extubation. The practice of respiratory muscle training with a gradual reduction of ventilatory support has fallen out of favor. A randomized trial showed no benefit to inspiratory muscle training [11].

Effect of Liberation on Oxygen Consumption and Cardiac Function

It has been demonstrated that oxygen consumption increases by about 15 % when critically ill patients are switched from assist-control mechanical ventilation to spontaneous breathing (continuous positive airway pressure). The increased oxygen consumption is likely due to the increased mechanical load and the inefficiency of the respiratory muscles. This increased oxygen consumption must be met by an increased oxygen delivery. In patients who are unable to increase oxygen delivery, this may result in tissue hypoxia in vital organs due to a redistribution of blood flow.

Positive-pressure ventilation (PPV) decreases left ventricular preload as well as left ventricular afterload. Therefore, PPV may improve left ventricular performance. Removing PPV results in both an increased cardiac demand and an increased workload on the heart. In patients with coronary artery disease (CAD), this may result in myocardial ischemia and pulmonary edema (which further increases pulmonary workload). Chatila et al. detected electrocardiographic evidence of cardiac ischemia in 10 % of patients with a history of CAD who were being weaned [12]. Evidence of myocardial ischemia was associated with a failure to wean in 22 % of these patients. Antianginal medication and diuretics may be useful in preventing both myocardial ischemia and cardiac failure in patients with CAD. Similarly, in patients with systolic heart failure liberating the patient from mechanical ventilation may worsen the cardiac failure. In these patients heart failure management should be optimized prior to weaning and a "prophylactic" infusion of nitroglycerin is recommended.

Fluid Overload and Liberation Failure

As discussed extensively in Chap. 9 volume overload has become a common problem in ICU patients. Fluid overload will increase extra-vascular lung water (EVLW) and increase chest wall edema. Increased EVLW impedes gas exchange and decreases

pulmonary compliance. Chest wall edema decreases chest wall compliance. These factors combined will increase the work of breathing post extubation. Furthermore, the loss of positive pressure will result in decreased FRC further compromising gas exchange. These factors may result in extubation failure. Clinical studies have demonstrated that a positive fluid balance is associated with prolonged mechanical ventilation and extubation failure [13–15]. These data suggest that the patient's cumulative fluid balance and intra-vascular volume status be closely evaluated prior to attempts at extubation. Diuresis may be appropriate at this time.

Increased levels of BNP (and NT-proBNP) indicate volume overload and/or cardiac failure and may be useful during liberation. Zapata et al. demonstrated that a high BNP (threshold above 263 pg/mL) could accurately predict weaning failure [16]. Similarly, Mekontso-Dessap and colleagues demonstrated that the baseline plasma BNP level before the first weaning attempt was higher in patients with subsequent weaning failure and correlated with the weaning duration [17]. Dessap and colleagues performed a RCT evaluating a natriuretic peptide driven fluid management strategy during ventilator weaning [18]. In the BNP-guided group, on days with a BNP level ≥200 pg/mL, fluid intake was restricted and furosemide was administered (as intravenous bolus doses of 10–30 mg every 3 h, to achieve a target urine output of 4.5–9 mL/kg/3 h). In the BNP-driven group, furosemide was given more often and in higher doses than in the control group, resulting in a more negative median fluid balance during weaning (−2,320 vs. −180 mL, $p<0.0001$). Time to successful extubation was significantly shorter with the BNP-driven strategy (58.6 vs. 42.4 h; $p=0.034$).

Vasopressors and Inotropic Agents and Weaning

Standard clinical practice recommends discontinuation of vasoactive drug treatment before attempts of liberation. The requirement that all pressors be weaned off prior to liberation likely prolongs with liberation process. In a case controlled study Teixiera et al. evaluated the use of norepinephrine during weaning in patients treated for septic shock [19]. In the noradrenaline group, the mean dose of noradrenaline during initial shock treatment was 0.52 ± 0.29 μg/kg/min and 0.12 ± 0.10 μg/kg/min during weaning. The reintubation rate was 12/63 (19 %) in the noradrenaline group and 15/82 (18.3 %) in the control group ($P=1.00$). In a survey of Canadian intensivists, most respondents considered that the use of low dose and non-escalating doses of vasopressors/inotropic agents did not preclude liberation [20]. In the Dessap et al. study, low doses of vasoactive agents were permitted during liberation (dopamine <10 mg/kg/min and dobutamine <10 mg/kg/min) [18]. These data suggest that once hemodynamic stability is achieved liberation from mechanical ventilation can be attempted as long as the dose of vasopressors are not excessively high and that dose escalation has not occurred in the previous 24 h. Liberation should be delayed in patients receiving multiple vasoactive agents.

Mechanical Ventilation Liberation Process

Recognizing that respiratory failure and respiratory muscle function have improved and the patient is capable of spontaneous breathing is termed *readiness testing*. Most patients satisfying readiness criteria tolerate *spontaneous breathing* (with no or minimal ventilator support) indicating that mechanical ventilation is no longer necessary.

The liberation process is best classified as follows: [21]

- Simple liberation. Patient tolerates first spontaneous breathing trial (SBT) and is successfully extubated (70 % of all patients)
- Difficult liberation: Patient fails to tolerate initial SBT, successful liberation requires up to 3 SBT's or up to 7 days from first SBT
- Prolonged liberation: Patient fails at least 3 SBT's or takes more than 7 days after first SBT.

"Readiness" Testing

General weaning prerequisites

- Reversal of the condition requiring ventilator support
- Manageable secretions
- Adequate cough
- FiO_2 <0.5 and/orPaO_2:FiO_2 >200
- minute ventilation <10 L/min
- Alert and able to follow commands
- No significant acid-base abnormalities
- No severe hypokalemia, hypophosphatemia, or hypomagnesemia
- No need for ongoing volume expansion
- No planned general anesthesia the same day

Over 50 physiologic tests (liberation parameters) have been studied to assess the patients' readiness for spontaneous breathing. Of these tests only five have been demonstrated to be able to predict liberation success or failure, however, the predictive value of these tests is only modest; they include

- Negative inspiratory force
- Minute ventilation
- Respiratory frequency
- Tidal volume
- Frequency-tidal volume ratio (Tobin index). Of these the Tobin index has proven to be the most accurate.

Tanios and colleagues randomized 304 ventilated patients to a daily readiness screen (PaO_2/FiO_2, PEEP, hemodynamic stability, mental status, cough) that

included or excluded the Tobin index [22]. The group randomized to use the Tobin index took longer to wean. The results of this study are supported by the ABC trial in which greater than 50 % passed a SBT when readiness was assessed using the "liberal criteria" [9]. Recent consensus guidelines do not recommend the routine application of liberation predictors for liberation decision making [21, 23]. Rather patients are considered for a SBT when there is evidence of clinical improvement, oxygenation is adequate, hemodynamics are stable and spontaneous breathing efforts are present (i.e. liberal criteria).

Liberal readiness criteria:

- Underlying disease has improved
- Patient off sedative agents
- Hemodynamically stable
- Awake and responsive
- SaO_2 >88 % on FiO_2 ≤50 %
- PEEP <8 cm H_2O,

Spontaneous Breathing Trials

Direct extubation after satisfying readiness criteria alone is unwise, as 40 % of such patients require reintubation [24]. Therefore a trial of spontaneous breathing, carried out on low level pressure support (PSV 5–10 cm H_2O), CPAP or unassisted through a T-piece is indicated. RCT's indicate these techniques are equivalent [25, 26].

Theoretically, PSV more effectively counterbalances endotracheal tube related resistive workload, but a given level may either over-compensate or under compensate for imposed work [27, 28]. This limitation might be overcome by using automatic tube compensation (ATC), a technique that continuously adjusts PSV on the basis of tube characteristics [29]. In a nonrandomized study of patient failing a 30-min T-tube trial, immediate conversion to PSV 7 cm H_2O for additional 30 min led to liberation success in 21 of 31 patients, suggesting the endotracheal tube can contribute to iatrogenic liberation failure [30]. For this reason as well as its simplicity we prefer PSV over a T-tube trial. Optimal SBT duration has been examined in two studies suggesting that 30 min is equivalent to 120 min [31, 32]. The SBT is usually terminated if the patient meets any of the following criteria:

- Respiratory rate >35/min
- Arterial saturation <90 %
- Heart rate >140 or heart rate change (either direction) >20 % or arrhythmias
- Systolic blood pressure >180 or <90 mmHg
- Increased anxiety and diaphoresis

Should the patient "pass" the SBT he/she should be placed on increased ventilator support (PSV of 10–12 cm H_2O) to prevent excessive fatigue. If the patient is at risk for post-extubation stridor a cuff leak test should be performed (see below).

Tube feeds should be stopped and a D5 1/2 NS infusion started (to prevent hypoglycemia). The stomach should be emptied and the OG/NG tube removed to reduce the risk of aspiration. Once these preparations have been performed the patient can be extubated to a face mask or nasal cannulae. Extubation to high flow nasal cannulae is however preferred, as it is associated with better oxygenation, improved patient comfort, fewer desaturations and interface displacements, and a lower reintubation rate than a venturi mask [33].

Causes of Liberation Failure

- Critical illness polyneuropathy. This is one of the most common causes of failure to wean.
- Adrenal insufficiency [34]
- Electrolyte disturbances
  - Hypophosphatemia
  - Hypokalemia
  - Hypomagnesemia
  - Hypocalcemia (ionized)
- Malnutrition
- Myocardial ischemia
- Cardiac failure
- Volume overload-positive fluid balance

Early Extubation Followed by NIV in COPD

Nava and colleagues reported a novel method of liberating COPD patients who required mechanical ventilation for respiratory failure [35]. These authors provided intensive medical management for 48 h, followed by extubation at 48 h, regardless of the patient's respiratory parameters. These early extubated patients were then treated with noninvasive positive-pressure ventilation (NIV) until their respiratory function returned to baseline. The authors reported a high success rate with a shortened length of ICU stay, lower mortality, and decreased complication rate using this approach.

NIV for Persistent Liberation Failure

A number of RCT's have explored the use of NIV in patients having difficulty with liberation from mechanical ventilation. Ferrer and colleagues randomized 43 patients who had failed three SBT's, 77 % of whom had chronic lung disease [36].

This study was stopped at an interim analysis finding that NIV was associated with shorter duration of mechanical ventilation, shorter ICU and hospital stay, fewer tracheotomies, higher ICU survival, and a lower incidence of nosocomial pneumonia and septic shock. A Cochrane meta-analysis compared traditional weaning with NIV weaning; this study included 12 trials, enrolling 530 patients most with COPD [37]. In this study NIV weaning was significantly associated with reduced mortality (RR 0.55, 95 % confidence interval 0.38–0.79), ventilator associated pneumonia (0.29, 95 % 0.19–0.45), length of stay in intensive care unit (weighted mean difference −6.27 days, −8.77 to −3.78) and hospital (−7.19 days, −10.80 to −3.58), total duration of ventilation, and duration of invasive ventilation. These studies indicate that NIV can facilitate liberation in a highly select group of patients with acute on chronic lung disease. Important caveats include the following: SBT readiness criteria must be satisfied, the patient must be a good candidate for NIV and not be a difficult reintubation.

Extubation Failure

Despite advances is predicting extubation failure, between 25 and 40 % of patients develop signs of respiratory distress after extubation. Extubation failure, when defined as reintubation within the subsequent 24–72 h, occurs in 5–20 % of patients, depending on the patient population. Extubation failure often results from the inability to protect the airway and manage secretions as well as from post-extubation stridor. Salam et al. demonstrated that cough strength, volume of respiratory secretions and mental status were major determinants of reintubation [38].

Randomized trials in heterogeneous populations (few with COPD) with overt or those with early signs of extubation failure found that NIV does not reduce the need for reintubation or improve survival [39, 40]. The preemptive use of NIV in the early period after discontinuation of mechanical ventilation in patients deemed to be at increased risk for extubation failure appears to be effective in reducing the need for reintubation. However, patients who have respiratory distress in the postextubation period may not benefit from NIV if it is started after respiratory distress begins; in fact, it may be harmful for some patients.

Patients at High Risk of Extubation Failure

- Chronic heart failure
- Age >65 years
- More than one failed liberation trial
- More than one comorbidity
- $PaCO_2$ >45 after extubation
- Weak cough
- Voluminous secretions

The Cuff Leak Test

The cuff leak test is performed in patients suspected of having laryngeal edema. The cuff of the endotracheal tube is deflated; if there is no laryngeal edema, the patient should be able to breathe around the tube. A patient with a positive cuff leak test (i.e., no leak) has approximately a 30 % chance of developing postextubation stridor; however the risk is negligible in patients with a negative cuff leak test [41]. The degree of leak can be quantified by comparing the returned tidal volume before and after the cuff is deflated. A cuff leak of less than 110 mL or <24 % has been shown to be associated with an increased risk of post-extubation stridor [42, 43].

The cuff leak test should be performed before extubation in the following circumstances:

- Traumatic intubation
- Prolonged intubation; i.e. longer than 7 days
- Patients with head and neck trauma
- Head and neck surgery
- Patients with previous failed extubation accompanied by stridor
- Patients with airway edema (e.g., angioedema)

Corticosteroids for the Prevention of Post-extubation Stridor

RCT's have demonstrated that systemic corticosteroids reduce the risk of post-extubation stridor [44]. Cheng et al. randomized 128 high risk patients with a cuff leak volume <24 % to placebo or methylprednisolone injection (multi-dose or single dose) during the 24 h prior to extubation. Treatment with methylprednisolone significantly reduced the risk of post-extubation stridor and the need for reintubation [43]. Lee et al. demonstrated similar findings using a cuff-leak volume of <110 mL [45].

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Chapter 22
Arterial Blood Gas Analysis

Arterial blood gas (ABG) analysis plays a pivotal role in the management of critically ill patients. Although no randomized controlled study has ever been performed evaluating the benefit of ABG analysis in the ICU, it is likely that this technology stands alone as that diagnostic test which has had the greatest impact on the management of critically ill patients; this has likely been translated into improved outcomes. Prior to the 1960s clinicians were unable to detect hypoxemia until clinical cyanosis developed. ABG analysis became available in the late 1950s when techniques developed by Clark, Stow and coworkers, and Severinghaus and Bradley permitted the measurement of the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) [1–3]. The ABG remains the definitive method to diagnose, categorize and quantitate respiratory failure. In addition, ABG analysis is the only clinically applicable method of assessing a patient's acid-base status. ABGs are the most frequently ordered test in the ICU and have become essential to the management of critically ill patients [4]. Indeed, a defining requirement of an ICU is that a clinical laboratory should be available on a 24-h basis to provide blood gas analysis [5].

Indications for ABG Sampling

ABGs are reported to be the most frequently performed test in the ICU [4]. There are however no published guidelines and few clinical studies which provide guidance as to the indications for ABG sampling [6]. It is likely that many ABGs are performed unnecessarily. Muakkassa and coworkers studied the relationship between the presence of an arterial line and ABG sampling [7]. These authors demonstrated that patients' with an arterial line had more ABGs drawn than those who did not regardless of the value of the PaO_2, $PaCO_2$, APACHE II score or the use of a ventilator. In this study, multivariate analysis demonstrated that the presence of an arterial line was the most powerful predictor of the number of ABGs drawn per patient independent of all other measures of the patient's clinical

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status. Roberts and Ostryznuik demonstrated that with use of a protocol they were able to reduce the number of ABGs by 44 % with no negative effects on patient outcomes [4]. The ubiquitous use of pulse oximetry in the ICU has made the need for frequent ABG sampling to monitor arterial oxygenation unnecessary. Furthermore (as discussed below), venous blood gas analysis can be used to estimate arterial pH and bicarbonate (HCO_3^-) but not arterial carbon dioxide tension ($PaCO_2$). Previously, ABGs were drawn after every ventilator change and with each step of the weaning process; such an approach is no longer recommended. The indications for ABG analysis should be guided by clinical circumstances. However, as a "general rule" all patients should have an ABG performed on admission to the ICU and/or following (10–15 min) endotracheal intubation. Patients' with respiratory failure should have an ABG performed at least every 24–48 h. Patients with type II respiratory failure will require more frequent ABG sampling than those with type I respiratory failure. Furthermore, patients with complex acid-base disorders and patients undergoing permissive hypoventilation will require more frequent ABG sampling.

ABG Sampling

ABG specimens may be obtained from an indwelling arterial catheter or by direct arterial puncture using a heparinized 1–5 mL syringe. Indwelling arterial catheters should generally not be placed for the sole purpose of arterial blood gas sampling as they are associated with rare but serious complications. Arterial puncture is usually performed at the radial site. When a radial pulse is not palpable the brachial or femoral arteries are suitable alternatives. Serious complications from arterial puncture are uncommon; the most common include pain and hematoma formation at the puncture site. Laceration of the artery (with bleeding), thrombosis and aneurismal formation are rare but serious complications [8, 9].

ABG analysis is typically performed on whole blood. The partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and pH are directly measured with standard electrodes and digital analyzers; oxygen saturation is calculated from standard O_2 dissociation curves or may be directly measured with a co-oximeter. The bicarbonate (HCO^-_3) concentration is calculated using the Henderson-Hasselbalch equation:

$$\mathrm{pH} = \mathrm{pK_A} + \log\left\{\left[\mathrm{HCO_3^-}\right] / \left[\mathrm{CO_2}\right]\right\}$$

where pK_A is the negative logarithm of the dissociation constant of carbonic acid. The base excess is defined as the quantity of strong acid required to titrate blood to pH 7.40 with a $PaCO_2$ of 40 mmHg at 37 °C. In practice, acid is not titrated as suggested but calculated using a variety of established formulae or nomograms. The base excess thus 'removes' the respiratory element of acid-base disturbance

and identifies the metabolic contribution to interpret with pH and [H^+]. The standard bicarbonate is broadly similar and is the calculated [HCO_3^-] at a $PaCO_2$ of 40 mmHg. Although the base excess and standard bicarbonate allow for a metabolic acidosis to be diagnosed, it provides few clues as to the pathophysiology or underlying diagnosis.

As with any diagnostic test it is important that the specimen be collected and processed correctly and that quality assurance methods exist to ensure the accuracy of the measurements. Aside from inter-laboratory variation, errors in calibration and electrode contamination with protein or other fluids may alter results. Heparin is usually added to the blood to prevent coagulation and dilution with older liquid solutions previously caused spuriously low $PaCO_2$. Sample preparation is important because air bubbles falsely elevate PaO_2.

The following points must be considered before obtaining sample to avoid errors in blood gas interpretation:

- *Steady State*: Blood sampling must be done during steady state following the initiation or change in oxygen therapy or changes in ventilatory parameters in patients on mechanical ventilation. In most ICU patients a steady state is reached between 3 and 10 min and in about 20–30 min in patients with chronic airways obstruction [10].
- *Anticoagulants*: Excess of heparin may affect the pH. Only 0.05 mL is required to anticoagulate 1 mL of blood.
- *Delay in processing of the sample*: Because blood is a living tissue, O_2 is being consumed and CO_2 is produced in the blood sample. Red blood cell glycolysis may generate lactic acid and change pH. Significant increases in $PaCO_2$ and decreases in pH occur when samples are stored at room temperature for more than 20 min. In circumstances when a delay in excess of 20 min is anticipated, the sample should be placed in ice; iced samples can be processed up to 2 h without affecting the blood gas values.
- *Hypothermia.* Blood gas values are temperature dependent, and if blood samples are warmed to 37 °C before analysis (as is common in most laboratories), PO_2 and PCO_2 will be overestimated and pH underestimated in hypothermic patients. The following correction formulas can be used:
  - Subtract 5 mmHg PO_2 per 1 °C that the patient's temperature is <37 °C
  - Subtract 2 mmHg PCO_2 per 1 °C that the patient's temperature is <37 °C
  - Add 0.012 pH units per 1 °C that the patient's temperature is <37 °C.

ABG Analysis

An ABG provides a rapid and accurate assessment of oxygenation, ventilation, and acid-base status. These three processes are closely interrelated with each other and an alteration in one process will affect the other two. However, for the sake of simplicity and ease of understanding each will be discussed separately.

Alveolar Ventilation

The arterial CO_2 content as reflected by arterial CO_2 tension ($PaCO_2$) at any given moment depends on the quantity of CO_2 produced and its excretion through alveolar ventilation (VA) and can be expressed by the equation, $PaCO_2 \sim CO_2/VA$. The alveolar ventilation is that portion of total ventilation that participates in gas exchange with pulmonary blood. If it is assumed that CO_2 production is constant, then CO_2 homeostasis can be simplified to $1/VA \sim PaCO_2$. Thus $PaCO_2$ becomes very useful for the assessment of alveolar ventilation. High $PaCO_2$ (>45 mmHg) indicates alveolar hypoventilation and low $PaCO_2$ (<35 mmHg) implies alveolar hyperventilation.

Oxygenation

The ultimate aim of the cardio-respiratory system is to provide adequate delivery of oxygen to the tissues. This is largely dependent upon cardiac output, hemoglobin concentration and hemoglobin saturation. The PaO_2 is a measure of the oxygen tension in plasma; while the dissolved fraction makes a negligible contribution to oxygen delivery (<2 %) it is a major factor affecting hemoglobin saturation. In turn the PaO_2 is dependent on the concentration of oxygen in the inspired air (FiO_2), oxygen exchange in the lung (V/Q mismatching) and the venous oxygen saturation ($SmvO_2$). The PaO_2 must always be interpreted in conjunction with the FiO_2 and age.

The PaO_2 is primarily used for assessment of oxygenation status since PaO_2 accurately assesses arterial oxygenation from 30 to 200 mmHg, whereas SaO_2 is normally a reliable predictor of PaO_2 only in the range of 30–60 mmHg. However, oxygen saturation as measured by pulse oximetry (SpO_2) or by ABG analysis (SaO_2) is a better indicator of arterial oxygen content than PaO_2, since approximately 98 % of oxygen is carried in blood combined with hemoglobin. Hypoxemia is defined as a PaO_2 of less than 80 mmHg at sea level in an adult patient breathing room air; the concomitant decrease in cell/tissue oxygen tension is known as hypoxia (or tissue hypoxia). The degree of hypoxia in patients with hypoxemia depends on the severity of the hypoxemia and the ability of the cardiovascular system to compensate. Hypoxia is unlikely in mild hypoxemia ($PaO_2 = 60–79$ mmHg). Moderate hypoxemia ($PaO_2 = 45–59$ mmHg) may be associated with hypoxia in patients with anemia or cardiovascular dysfunction. Hypoxia is almost always (but with a few exceptions) associated with severe hypoxemia ($PaO_2 < 45$ mmHg). However, it must be recognized that the human body has an extraordinary capacity to adapt to hypoxemia. Indeed, patients with cyanotic heart disease do not have evidence of tissue hypoxia at rest. Most remarkably, at the balcony of Mount Everest (27,559 ft; 272 Torr) and without supplemental oxygen, experienced mountain climbers have been reported to have a mean PaO_2 of 24.6 mmHg in the absence of tissue hypoxia (lactate 2.2 mmol/L) [11]. It would appear that a PaO_2 <20 mmHg is unable to sustain life. There is a very steep oxygen diffusion gradient from arterial blood

($PaO_2 \sim 100$) to mixed venous blood ($PmvO_2 \sim 40$ mmHg) to tissue partial pressure PtO_2 (10–17 mmHg) to 3–7 mmHg for the cytosolic compartment. Such low values suggest that the oxygen tension at the mitochondria, being at the lowest end of the diffusion pathway which oxygen must travel, is below 5 mmHg. Mitochondria can perform oxidative metabolism at PtO_2 as low as 2 mmHg [12, 13].

Relation Between PaO_2 and FiO_2

The PaO_2 alone provides little information regarding the efficiency of oxygen loading into the pulmonary capillary blood. The PaO_2 is determined largely by the FiO_2 and the degree of intra-pulmonary shunting. The PaO_2 must therefore always be interpreted in conjunction with the FiO_2. The PaO_2 alone does not quantitate the degree of intra-pulmonary shunt, which is required for assessing the severity of the underlying lung disease and in guiding the approach to oxygen therapy and respiratory support. There are various formulas for calculating the intra-pulmonary shunt, including the classic "shunt equation", which is the gold standard but requires mixed venous sampling through a pulmonary artery catheter, and the alveolar-arterial oxygen gradient equation (*see* Table 22.1). Clinically the PaO_2 to FiO_2 ratio (PaO_2/FiO_2) is commonly used to quantitate the degree of ventilation/perfusion mismatching (V/Q). Since the normal PaO_2 in an adult breathing room air with a FiO_2 of 0.21 is 80–100 mmHg, the normal value for PaO_2/FiO_2 is between 400 and 500 mmHg. A PaO_2/FiO_2 ratio of less than 200 most often indicates a shunt of greater than 20 %. A notable limitation of the PaO_2/FiO_2 is this it does not take into account changes in $PaCO_2$ at a low FiO_2, which tends to have a considerable effect on the ratio.

PaO_2 and Age

The normal arterial oxygen tension decreases with age. The normal PaO_2 at sea level and breathing room air is approximately 85–90 mmHg at the age of 60 and 80–85 mmHg at the age of 80 years.

Table 22.1 Formulas for evaluating patients in respiratory failure

Age-predicted PaO_2 = Expected $PaO_2 - 0.3(age - 25)$ [expected PaO_2 at sea level is 100 mg/Hg]
As a rough rule of thumb: Expected $PaO_2 \approx FiO_2$ (%) × 5
$AaDO_2 = (FiO_2 \times [BP^* - 47]) - (PaO_2 + PaCO_2)$ where BP = barometric pressure
PaO_2/FiO_2 ratio
Oxygenation index = [(Mean airway pressure × FiO_2)/PaO_2] × 100
$Vd/Vt = (PaCO_2 - PECO_2)/PaCO_2$ (N = 0.2–0.4)

Respiratory Failure

Acute respiratory failure occurs when pulmonary system is no longer able to meet the metabolic demands of the body. Respiratory failure is classically divided into type I and type II respiratory failure:

- Hypoxemic respiratory failure (type 1)
  - $PaO_2 \leq 60$ mmHg when breathing room air (sea level)
- Hypercapnic respiratory failure (type 2)
  - $PaCO_2 >= 45$ mmHg

Acid-Base Balance

The normal diet generates volatile acid (CO_2), primarily from carbohydrate metabolism, and nonvolatile acid (hydrogen ion, H^+) from protein metabolism. The aim of the body's homeostatic system is to maintain pH within a narrow range. pH homeostasis is accomplished through the interaction of the lungs, kidneys and blood buffers. Alveolar ventilation allows for excretion of CO_2. The kidneys must reclaim filtered bicarbonate (HCO_3^-), because any urinary loss leads to gain of H^+. In addition, the kidney must excrete the daily acid load generated from dietary protein intake. Less than half of this acid load is excreted as titratable acids (i.e., phosphoric and sulfuric acids); the remaining acid load is excreted as ammonium. The blood pH is determined by the occurrence of these physiologic processes and by the buffer systems present in the body.

The history of assessing the acid–base equilibrium and associated disorders is intertwined with the evolution of the definition of an acid. In the 1950s clinical chemists combined the Henderson–Hasselbalch equation and the Bronsted–Lowry definition of an acid to produce the current *bicarbonate ion* centered approach to metabolic acid–base disorders [14]. Stewart repackaged pre-1950 ideas of acid–base in the late 1970s, including the Van Slyke definition of an acid [15]. Stewart also used laws of physical chemistry to produce a "new acid–base" approach [14]. This approach, using the strong ion difference (SID)[1] and the concentration of weak acids (particularly albumin), pushes bicarbonate into a minor role as an acid–base indicator rather than as an important mechanism.

The strong ion difference (SID) is not identical to anion gap (AG) and it contains [lactate], although it does share a number of parameters and the trends will often be close. The normal SID has not been well established, although the quoted range is 40–42 mEq/L. As the SID approaches zero, anions 'accumulate' and acidity increases. This approach provides a physicochemical model for 'hyperchloremic acidosis' following 0.9 % saline administration [21], and the systemic alkalosis of hypoalbuminemia (regarded as a weak acid).

[1] $\mathrm{SID} = \left(\left[\mathrm{Na}^+\right] + \left[\mathrm{K}^+\right] + \left[\mathrm{Ca}^{2+}\right] + \left[\mathrm{Mg}^{2+}\right]\right) - \left(\left[\mathrm{Cl}^-\right] + \left[\mathrm{Lactate}\right]\right)$.

Most clinicians use the *bicarbonate ion* centered approach for the diagnosis and management of acid-base disorders; this approach is easier to understand and more practical. Furthermore, there is no clinical data to suggest that the Steward approach has any advantages over the classic (bicarbonate) approach [16]. The Steward approach serves to make acid-base interpretation more complex (than it already is) to the point that it confuses rather than simplifies. However, many consider it old fashioned and not "cool" to use the HCO_3^- Henderson-Hasselbalch approach. The Henderson-Hasselbalch equation describes the fixed inter-relationship between $PaCO_2$, pH and HCO_3^- being described as $pH = pK_c log\ HCO_3^-/dissCO_2$. If all the constants are removed, the equation can be simplified to $pH = HCO_3^-/PaCO_2$ (~Kidney/Lung). The HCO_3^- is controlled mainly by the kidney and blood buffers. The lungs control the level of $PaCO_2$ by regulating the level of volatile acid, carbonic acid, in the blood. Buffer systems can act within a fraction of a second to prevent excessive change in pH. Respiratory system takes about 1–15 min and kidneys many minutes to days to readjust H^+ ions concentration.

The Anion Gap

Following the principle of electrochemical neutrality, total [cations] must equal total [anions], and so in considering the commonly measured cations and anions and subtracting them, a fixed number should be derived. The measured cations are in excess; mathematically this 'gap' is filled with unmeasured anions ensuring electrochemical neutrality. There is never a 'real' anion gap, in line with the law of electrochemical neutrality; it is rather an index of non-routinely measured anions. The anion gap is calculated using the following formula [17]:

$$\text{Anion Gap} = \left[\text{Na}\right] - \left(\left[\text{Cl}\right] + \left[\text{HCO}_3^-\right]\right) : \text{Normal} 10 \pm 2\,\text{meq / L}$$

Critical illness is typically associated with a rapid fall in the plasma albumin concentration. Albumin is an important contributor of the "normal" anion gap. Therefore, as the albumin concentration falls it tends to reduce the size of the anion gap, or have an alkalinizing effect. Various corrections are available, however, Figge's AG correction (AGcorr) is most commonly used [17]:

Albumin gap = 40 − Apparent albumin (normal albumin = 40 g l).
AGcorr = AG + (Albumin gap/4).

A Step Wise Approach to Acid-Base Disorders

Step 1. Do a comprehensive history and physical exam

A comprehensive history and physical examination can often give clues as to the underlying acid-base disorder (*see* Table 22.2). For example, patients who present with gastroenteritis manifested as diarrhea typically have a non-anion gap meta-

Table 22.2 Common clinical states and associated acid-base disorders

Clinical state	Acid-base disorder
Pulmonary embolus	Respiratory alkalosis
Hypotension/shock	Metabolic acidosis
Severe sepsis	Metabolic acidosis, respiratory alkalosis
Vomiting	Metabolic alkalosis
Severe diarrhea	Metabolic acidosis
Renal failure	Metabolic acidosis
Cirrhosis	Respiratory alkalosis
Pregnancy	Respiratory alkalosis
Diuretic use	Metabolic alkalosis
COPD	Respiratory acidosis
Diabetic keto-acidosis	Metabolic acidosis
Ethylene glycol poisoning	Metabolic acidosis
Post Normal Saline resuscitation	Metabolic acidosis (non-anion gap)

Table 22.3 Normal Acid-Base values

	Mean	1 SD	2 SD
$PaCO_2$ (mmHg)	40	38–42	35–45
pH	7.4	7.38–7.42	7.35–7.45
HCO_3 (meq/L)	24	23–25	22–26

bolic acidosis from loss of fluid containing HCO_3^-. Patients who present with chronic obstructive lung disease usually have underlying chronic respiratory acidosis from retention of CO_2.

Step 2. Order simultaneous arterial blood gas measurement and chemistry profile

Step 3. Check the consistency and validly of the results. Normal ABG results are provided in Table 22.3.

Step 4. Identify the primary disturbance

The next step is to determine whether the patient is acidemic (pH < 7.35) or alkalemic (pH > 7.45) and whether the primary process is metabolic (initiated by change in HCO_3^-) or respiratory (initiated by a change in $PaCO_2$) See Table 22.4.

Step 5. Calculate the expected compensation

Any alteration in acid-base equilibrium sets into motion a compensatory response by either the lungs or the kidneys. The compensatory response attempts to return the ratio between $PaCO_2$ and HCO_3^- to normal and thereby normalize the pH. Compensation is predictable; the adaptive responses for the simple acid-base disorders have been quantified experimentally [18] (see Table 22.5). Determine whether the compensatory response is of the magnitude expected i.e. is there a secondary (uncompensated) acid-base disturbance.

Step 6. Calculate the "gaps"

(6a) Calculate the Anion Gap

Table 22.4 Acid Base disorders

Acid-base disorder	Criteria
Respiratory acidosis	>45 mmHg
Respiratory alkalosis	$PaCO_2$ <35 mmHg
Acute respiratory failure	$PaCO_2$ >45 mmHg; pH <7.35
Chronic respiratory failure	$PaCO_2$ >45 mmHg; pH 7.36–7.44
Acute respiratory alkalosis	$PaCO_2$ <35 mmHg; pH >7.45
Chronic respiratory alkalosis	$PaCO_2$ < 35 mmHg; pH 7.36–7.44
Acidemia	pH < 7.35
Alkalemia	pH > 7.45
Acidosis	HCO_3 < 22 meq/L
Alkalosis	HCO_3 > 26 meq/L

Table 22.5 Compensation formulas for simple acid-base disorders

Acid-base disorder	Compensation formula
Metabolic acidosis	Change in $PaCO_2 = 1.2 \times$ change in HCO_3^-
Metabolic alkalosis	Change in $PaCO_2 = 0.6 \times$ change in HCO_3^-
Acute respiratory acidosis	Change in $HCO_3^- = 0.1 \times$ change in $PaCO_2$
Chronic respiratory acidosis	Change in $HCO_3^- = 0.35 \times$ change in $PaCO_2$
Acute respiratory alkalosis	Change in $HCO_3^- = 0.2 \times$ change in $PaCO_2$
Chronic respiratory alkalosis	Change in $HCO_3^- = 0.5 \times$ change in $PaCO_2$

In high anion gap metabolic acidosis, acid dissociates into H^+ and an unmeasured anion. H^+ is buffered by HCO_3^- and the unmeasured anion accumulates in the serum, resulting in an increase in the anion gap. In non-anion gap metabolic acidosis, H^+ is accompanied by Cl^- (a measured anion); therefore, there is no change in the anion gap. Acid-Base disorders may present as two or three coexisting disorders. It is possible for a patient to have an acid-base disorder with a normal pH, PCO_2 and HCO_3^-, the only clue to an acid-base disorder being an increased anion gap. If the anion gap is increased by >5 meq/L (i.e. an anion gap >15 meq/L), the patient most likely has a metabolic acidosis. Compare the fall in plasma HCO_3^- ($25 - HCO_3^-$) with the increase in the plasma anion gap (delta anion gap); these should be of similar magnitude. If there is a gross discrepancy (>5 meq/L), then a mixed disturbance is present:

- if increase AG >fall HCO_3^-; suggests that a component of the metabolic acidosis is due to HCO_3^- loss
- if increase AG <fall HCO_3^-; suggests coexistent metabolic alkalosis

(6b) Osmolar Gap

Calculate the Osmolar Gap in patients with an unexplained AG metabolic acidosis to exclude ethylene glycol or methanol toxicity (see Table 22.6).

Estimated serum osmolality = $2 \times [Na] + [Glucose]/18 + [BUN]/2.8$.

Normal ≈ 290 mOsm/kg H_2O

Osmolal gap = Osm(measured) − Osm(calculated).

Normal <10

Table 22.6 Causes of an increased Osmolar gap

• Causes an anion gap and acidosis
– Ethylene glycol
– Methanol
– Acetone
• Does not cause an anion gap nor acidosis
– Alcohol (ethanol)
– Isopropyl alcohol
– Mannitol
– Sorbitol
– Paraldehyde

Common Acid Base Disturbances in the ICU

Metabolic Acidosis

The clinical manifestations of a metabolic acidosis are largely dependent on the underlying cause and the rapidity with which the condition develops. An acute severe metabolic acidosis results in myocardial depression with a reduction in cardiac output, decreased blood pressure and decreased hepatic and renal blood flow. Reentrant arrhythmias and a reduction in the ventricular fibrillation threshold can occur. Brain metabolism becomes impaired with progressive obtundation and coma.

A metabolic acidosis in the critically ill patient is an ominous sign and warrants an aggressive approach to the diagnosis and management of the cause(s) of the disorder (see Table 22.7). In the vast majority of patients the cause(s) of the metabolic acidosis are usually clinically obvious, with hypoperfusion, ketoacidosis and renal failure being the commonest causes. In patients with an unexplained anion gap metabolic acidosis methanol or ethylene-glycol toxicity should always be considered [19]. Accumulation of 5-oxoproline related to the use of acetaminophen is a rare cause of an anion gap metabolic acidosis [20]. Prolonged high dose administration of lorazepam can result in the accumulation of the vehicle, propylene glycol, resulting in worsening renal function, metabolic acidosis and altered mental status [21, 22].

The prognosis of patients with a metabolic acidosis is related to the underlying disorder causing the acidosis. In almost all circumstances the treatment of a metabolic acidosis involves the treatment of the underlying disorder. Except in specific circumstances (outlined below), there is no scientific evidence to support treating a metabolic or respiratory acidosis with sodium-bicarbonate [23]. Furthermore, it is the intracellular pH which is of importance in determining cellular function. The intracellular buffering system is much more effective in restoring pH to normal than the extracellular buffers. Consequently, patients have tolerated a pH as low as 7.0 during sustained hypercapnia without obvious adverse effects. Paradoxically, sodium-bicarbonate can decrease intra-cellular pH (in circumstances where CO_2 elimination is fixed). The infusion of bicarbonate can lead to a variety of problems in patients with acidosis, including fluid overload, a post-recovery metabolic alka-

Table 22.7 Causes of metabolic acidosis

Elevated anion gap
Renal failure
Rhabdomyolysis
Ketoacidosis
• Diabetes mellitus
• Starvation
• Alcohol associated
• Defects in gluconeogenesis
Acidosis associated with an increased lactate concentration
• Hypotension/shock
• Sepsis
• Drugs
• Liver failure
Toxins/drugs
• Ethylene glycol
• Methanol
• Salicylates
• Paraldehyde
• Lorazepam
• Propofol
• Metformin
5-Oxoproline
Beriberi
Normal anion gap
Hypokalemic acidosis
• Renal tubular acidosis
• Diarrhea
• Post-hypocapnic acidosis
• Carbonic anhydrase inhibitors
• Uteral diversions
Normal to hyperkalemic acidosis
• Early renal failure
• Excessive 0.9 % NaCl
• Hydronephrosis
• Addition of HCL
• Sulphur toxicity

losis and hypernatremia. Furthermore, studies in both animals and humans suggest that alkali therapy may only transiently raise the plasma bicarbonate concentration. This finding appears to be related in part to the carbon dioxide generated as the administered bicarbonate buffers excess hydrogen ions. Unless the minute ventilation is increased (in ventilated patients) CO_2 elimination will not be increased and this will paradoxically worsen the intracellular acidosis. Currently, there is no data to support the use of bicarbonate in patients with an acidosis associated with an

increased lactate concentration [23, 24]. Bicarbonate is frequently administered to "correct the acidosis" in patients with diabetic ketoacidosis. However, paradoxically bicarbonate has been demonstrated to increase ketone and lactate production. Studies have demonstrated an increase in acetoacetate levels during alkali administration, followed by an increase in 3-hydroxybutyrate levels after its completion [25, 26]. In pediatric patients treatment with bicarbonate has been demonstrated to prolonged hospitalization [27]. In addition, bicarbonate may decrease CSF pH, as increased CO_2 produced by buffering acid crosses the blood brain barrier combines H_2O and regenerates H^+. It is generally believed that adjunctive bicarbonate is unnecessary and potentially disadvantageous in severe diabetic ketoacidosis [28].

Bicarbonate is however considered "life-saving" in patients with severe ethylene glycol and methanol toxicity. In hyperchloremic acidosis endogenous regeneration of bicarbonate cannot occur (as bicarbonate has been lost, rather than buffered). Therefore, even if the cause of the acidosis can be reversed, exogenous alkali is often required for prompt attenuation of severe acidemia. Bicarbonate therapy is therefore indicated in patients with severe hyperchloremic acidosis when the pH is less than 7.2; this includes patients with severe diarrhea, high-output fistulas and renal tubular acidosis. In order to prevent sodium overload we suggest that 2×50 mL ampoules of Na HCO_3^- (each containing 50 mmol of Na HCO_3^-) be added to 1 L of 5 % D/W, and infused at a rate of 100–200 mL/h.

Does Lactic Acidosis Exist?

Lactate is produced by glycolysis and metabolized by the liver and to a lesser degree by the kidney. Lactate is produced in the cytoplasm according to the following reaction:

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \leftrightarrow \text{Lactate} + \text{NAD}^+$$

Classic teaching suggests that increased production of lactate results in an acidosis, known widely as a lactic acidosis [29]. Close examination of glycolysis reveals that complete metabolism of glucose to lactate results in no net release of protons and, thus, does not contribute to acidosis. In fact, during the production of lactate from pyruvate, protons are consumed and acidosis is inhibited [30]. This implies that "lactic acidosis" is a condition that does not exist (see also Chap. 13). This concept, however, is very controversial with many clinicians still believing in the concept of "lactic acidosis" and this concept is widely promoted in almost all medical textbooks.

The classic theory in critical care is that hyperlactatemia is a marker of tissue hypoperfusion or tissue hypoxia, and is indicative of the onset of anaerobic glycolysis. However, findings of studies in human beings have repeatedly failed to show an association between hyperlactatemia and any indicators of perfusion or oxygenation (oxygen consumption or oxygen delivery) or of intracellular hypoxia [31]. As discussed in Chap. 13, hyperlactemia is a marker of metabolic stress and hypermetabo-

lism rather than an indicator of anaerobic glycolysis. However, in many but not all circumstances of hyperlactemia, patients' have an anion gap metabolic acidosis. These two phenomenon may not be causally related, but rather both may be a manifestation of a hypermetabolic state with hydrogen ions being generated from the hydrolysis of ATP. Additional hydrogen ion accumulation could arise from an accumulation of $NADH + H^+$ produced by the glyceraldehyde 3-phosphate dehydrogenase reaction [30]. These products would increase during any cellular condition that caused a greater rate of substrate flux through glycolysis than the rate of electron and proton uptake by the mitochondria, or lactate production.

To quote Robergs et al.:

> "*The lactic acidosis explanation of metabolic acidosis is not supported by fundamental biochemistry, has no research base of support, and remains a negative trait of all clinical, basic, and applied science fields and professions that still accept this construct. Nevertheless, statements that imply that "lactic acid" or a "lactic acidosis" causes metabolic acidosis can still be found in the current literature and remains an explanation for metabolic acidosis in current textbooks of biochemistry, exercise physiology, and acid-base physiology. Clearly, academics, researchers, and students of the basic and applied sciences, including the medical specialties, need to reassess their understanding of the biochemistry of metabolic acidosis*" [30].

D-Lactic Acidosis

Certain bacteria in the GI tract may convert carbohydrate into organic acids. The two factors that make this possible are slow GI transit (blind loops, obstruction) and change of the normal flora (usually with antibiotic therapy). The most prevalent organic acid is D-lactic acid. Since humans metabolize this isomer more slowly than L-lactate and production rates can be very rapid, life threatening acidosis can be produced [32]. The usual laboratory test for lactate is specific for the L-lactate isomer. Therefore, to confirm the diagnosis the plasma D-lactate must be measured.

Metabolic Alkalosis

Metabolic alkalosis is a common acid-base disturbance in ICU patients, characterized by an elevated serum pH (>7.45) secondary to plasma bicarbonate (HCO_3^-) retention. The metabolic alkalosis is usually the result of several therapeutic interventions in the critically ill patient (*see* Table 22.8). Nasogastric drainage, diuretic induced intravascular volume depletion, hypokalemia and the use of corticosteroids are common causes of a metabolic alkalosis in these patients. In addition, the citrate in transfused blood is metabolized to bicarbonate which may compound the metabolic alkalosis. Over-ventilation in patients with type 2 respiratory failure may result in a posthypercapnic metabolic alkalosis. In many patients the events that generated the metabolic alkalosis may not be present at the time of diagnosis.

Table 22.8 Causes of metabolic alkalosis

• *Low urine chloride (volume or saline responsive)*
– Gastric volume loss
– Diuretics
– Posthypercapnia
– Villous adenoma (uncommon)
– Cystic fibrosis (if there has been excessive sweating)
• *High Urine Chloride with hypertension*
– Primary and secondary hyperaldosteronism
– Apparent mineralocorticoid excess
– Liddle's syndrome
– Conn's syndrome
– Cushing disease
• *High Urine Chloride without hypertension*
– Bartter syndrome
– Gitelman syndrome
– Excess bicarbonate administration

Metabolic alkalosis may have adverse effects on cardiovascular, pulmonary, and metabolic function. It can decrease cardiac output, depress central ventilation, shift the oxyhemoglobin saturation curve to the left, worsen hypokalemia and hypophosphatemia, and negatively affect the ability to wean patients from mechanical ventilation. Increasing serum pH has been shown to correlate with ICU mortality. Correction of metabolic alkalosis has been shown to increase minute ventilation, increase arterial oxygen tension and mixed venous oxygen tension and decrease oxygen consumption. It is therefore important to correct a metabolic alkalosis in all critically ill patients.

The first therapeutic maneuver in patients with a metabolic alkalosis is to replace any fluid (with normal saline) and electrolyte deficits. Aggressive potassium supplementation is warranted to achieve a K+ >5 meq/L. If these interventions fail, ammonium chloride, hydrochloric acid, or arginine hydrochloride may be given. The disadvantage of these solutions is that they are difficult to use are require the administration of a large volume of hypotonic fluid. Extravasation of hydrochloric acid may result in severe tissue necrosis, mandating administration through a well-functioning central line. Acetazolamide is a carbonic anhydrase inhibitor that promotes the renal excretion of bicarbonate and has been demonstrated to be very effective in treating a metabolic alkalosis in ICU patients. A single dose of 500 mg is recommended. The onset of action is within 1.5 h with a duration of approximately 24 h [33–36]. Repeat doses may be required as necessary.

Venous Blood Gas Analysis (VBGs)

Studies performed in the emergency department have demonstrated a strong correlation between arterial and venous blood pH and HCO_3^- levels in patients with diabetic ketoacidosis and uremia [35, 36]. In these studies the difference between

arterial and venous pH varied from 0.04 to 0.05, and the difference in bicarbonate levels varied from −1.72 to 1.88. However, as one would anticipate the correlation between arterial and venous PCO_2 was poor. These observations have been confirmed in a cohort of unselected emergency department patients [37] and patients with tricyclic antidepressant poisoning [38]. Similarly, an excellent correlation has been demonstrated between mixed venous pH and HCO_3^- with arterial pH and HCO_3^- in ICU patients [39, 40]. The association between arterial and venous pH, HCO_3^- and PCO_2 is, however, not valid in shocked patients. In a now "classic study", Weil and coauthors reported that during cardiopulmonary resuscitation, the arterial blood pH averaged 7.41, whereas the average mixed venous blood pH was 7.15 [41]. Similarly, the $PaCO_2$ was 32 mmHg, whereas the mixed venous PCO_2 was 74 mmHg. Androgue and colleagues have reported similar findings in patients with circulating failure [42]. This data suggests that in hemodynamically stable (and resuscitated patients) without known hypercarbia arterial blood gas analysis may not be required; pulse oximetry and venous blood gas analysis should suffice in most circumstances. Furthermore, a venous blood gas can be useful to screen for arterial hypercarbia, with a venous PCO_2 level >45 mmHg being highly predictive of arterial hypercarbia (sensitivity and negative predictive value of 100 %) [43]. In hemodynamically unstable patients and those with complex acid-base disorders a venous blood gas cannot be substituted for an arterial blood gas analysis. In these situations both arterial and mixed venous/central venous blood gas analysis provides useful information (see below).

Mixed Venous/Central Venous Oxygen Saturation

Monitoring of the mixed venous oxygen saturation ($SmvO_2$) has used as a surrogate for the balance between systemic oxygen delivery and consumption during the treatment of critically ill patients. Generally a SvO_2 of less than 65 % is indicative of inadequate oxygen delivery. Measurement of SvO_2 involves placement of a pulmonary artery catheter (PAC); as this is an invasive device that has not been shown to improve patient outcome the use of the PAC has fallen out of favor. However, as most critically ill patients' have a central venous catheter in-situ, the central venous oxygen saturation ($ScvO_2$) has been used as an alternative to the $SmvO_2$.

Regional variations in the balance between DO_2 and VO_2 result in differences in the hemoglobin saturation of blood in the superior and inferior vena cavae. Streaming of caval blood continues within the right atrium and ventricle and complete mixing only occurs during ventricular contraction. The drainage of myocardial venous blood directly into the right atrium via the coronary sinus and cardiac chambers via the Thebesian veins results in further discrepancies [44, 45]. Consequently, $SmvO_2$ reflects the balance between oxygen supply and demand averaged across the entire body but $ScvO_2$ is affected disproportionately by changes in the upper body. In healthy individuals, $ScvO_2$ is usually 2–5 % less than $SmvO_2$, largely because of the high oxygen content of effluent venous blood from the kidneys [46]. This relationship changes during periods of hemodynamic instability because blood is redistributed

to the upper body at the expense of the splanchnic and renal circulations. In shock states, therefore, the observed relationship between $ScvO_2$ and SvO_2 may reverse, and the absolute value of $ScvO_2$ may exceed that of $SmvO_2$ by up to 20 % [47]. This lack of numerical equivalence has been demonstrated in various groups of critically ill patients, including those with cardiogenic, septic and hemorrhagic shock. Based on this data The Surviving Sepsis Campaign has recommended obtaining a $SmvO_2$ level of 65 % or a $ScvO_2$ level of 70 % in patients with severe sepsis and septic shock [48]. Although trends in $ScvO_2$ may reflect those of $SmvO_2$, the absolute values differ and the variables cannot be used interchangeably [47, 49–51]. In addition to guiding resuscitation, $ScvO_2$ may have prognostic significance with low values during the first 24 h of hospitalization or in the postoperative period being predictive of a worse outcome [52–54].

In patients with sepsis and liver failure a low $ScvO_2/SmvO_2$ is usually indicative of decreased cardiac output (oxygen delivery) [55], however normal values does not exclude adequate resuscitation [56, 57]. The presence of functional and/or anatomical shunting results in "arterialization" of venous blood. Patients dying of both sepsis and liver failure usually have a high $ScvO_2/SmvO_2$. Pope and colleagues demonstrated that in patients with sepsis a high $ScvO_2$ (90–100 %) at any time during hospitalization was an independent predictor of mortality, whereas a low $ScvO_2$ (<70 %) was only predictive of mortality if this value remained low following resuscitation [58]. The ProCESS trial has clearly demonstrated that titrating treatment according to the $ScvO_2$ does not improve outcome and has no utility in the management of patients with sepsis [59]. However, as discussed in Chap. 11 monitoring $ScvO_2$ play a central role in "goal directed therapy" in the peri-operative setting.

Experimental models have demonstrated that a high mixed venous to arterial PCO_2 gradient is a reliable marker of a decreased cardiac output and global tissue ischemia [60, 61]. This observation has been confirmed by Weil and coauthors and Androgue and colleagues who demonstrated that a high mixed venous to arterial PCO_2 gradient is a sensitive marker of global tissue ischemia during cardiopulmonary resuscitation and in patients with circulatory failure [42, 62, 63]. In patients with septic shock Bakker and colleagues demonstrated that the venous to arterial PCO_2 gradient was directly related to cardiac output [64]. In resuscitated patients ($ScvO_2$ >70 %) with septic shock, Vallee and coworkers demonstrated that a widened central venous to arterial PCO_2 gradient (> 6 mmHg) identified patients with a low cardiac index who were inadequately resuscitated [57] The central venous to arterial PCO_2 gradient may prove to be a better end-point for resuscitation of septic patients than the $ScvO_2$.

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Chapter 23
ARDS

If we are to survive, we must have ideas, vision, and courage. These things are rarely produced by committees. Everything that matters in our intellectual and moral life begins with an individual confronting his own mind and conscience in a room by himself.

Arthur M. Schlesinger, Jr, American Historian (1917–2007).

Definition, Causes and Assessment of Severity

The adult respiratory distress syndrome (ARDS) was initially described by Ashbaugh and Petty as a syndrome characterized by diffuse pulmonary infiltrates, with decreased pulmonary compliance and hypoxemia [1]. It has however been recognized that "ARDS" is a spectrum varying from mild acute lung injury (ALI) at one end to ARDS at the other. The diagnosis of ARDS should be reserved for patients with ALI who have severe disease (see criteria below). The outcome of ALI is largely dependent on both the severity of ALI and the causative factors. It should be emphasized that in most cases ALI is a multi-system disease; the microcirculatory changes which occur in the lung occur in all organs; the pathophysiological derangements however, are most evident in the lung.

Definition of ALI According the American European Consensus [2]

A condition involving:

- an oxygenation defect with bilateral alveolar infiltrates,
- a patient who has suffered an acute catastrophic event,
- who has a pulmonary capillary wedge pressure ≤18 mmHg or no clinical evidence of an elevated left atrial pressure.

Acute Lung Injury (ALI)

A patient is defined as having ALI when the PO_2/FiO_2 ≤300 (regardless of the amount of PEEP).

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Table 23.1 The Berlin Definition of Acute Respiratory Distress Syndrome [3]

Criteria	Definition
Timing	Within 1 week of known clinical insult or new or worse respiratory symptoms
Chest Imaging	Bilateral opacities- not fully explained by effusions, lobar/lung collapse or nodules
Origin of edema	Resp. failure not explained by cardiac failure or fluid overload. Need objective assessment (ECHO) to exclude hydrostatic edema
Oxygenation	
Mild	PaO_2/FiO_2 between 200 and 300 with PEEP ≥5 cm H_2O
Moderate	PaO_2/FiO_2 between 100 and 200 with PEEP ≥5 cm H_2O
Severe	PaO_2/FiO_2 < 100 with PEEP ≥5 cm H_2O

Acute Respiratory Distress Syndrome (ARDS)

A patient is said to have ARDS when the PO_2/FiO_2 ≤200 (regardless of the amount of PEEP).

In 2012 the ARDS Task Force published the "Berlin Definition of Acute Respiratory Distress Syndrome." (See Table 23.1) [3] This definition seems to add little to American European Consensus Definition published in 1994. However it seems that if you have nothing better to do, you assemble a tasks force of your own "co-conspirators", develop a new definition/or guideline which you must then publish.

Pathophysiological Definition of ARDS

The typical pathological feature of ARDS is diffuse alveolar damage (DAD), which result in interstitial and alveolar edema and accumulation of extravascular lung water (EVLW). Since it is possible to accurately measure EVLW (see transpulmonary thermo-dilution, Chap. 10) this would appear to be the most precise method to diagnose and quantitate the severity of ARDS. The normal EVLW value has been shown to be approximately 7 ± 3 mL/kg [4]. Furthermore, transpulmonary thermodilution can accurately distinguish between cardiogenic and non-cardiogenic pulmonary edema.

Tagami et al. compared the postmortem weights of normal lungs with those from patients with diffuse alveolar damage [5]. These lung weights were converted to extravascular lung water (EVLW) values using a validated equation. The extravascular lung water value that indicated diffuse alveolar damage was estimated using receiver operating characteristic analysis. The EVLW of the lungs showing diffuse

alveolar damage were approximately twofold higher than those of normal lungs (normal group, 7.3 ± 2.8 mL/kg vs diffuse alveolar damage group 13.7 ± 4.5 mL/kg; $p < 0.001$). An EVLW of >9.8 mL/kg had an area under the ROC curve of 0.90 (CI, 0.88–0.91) for the diagnosis of ALI. Furthermore, EVLW has been demonstrated to be highly predictive of outcome with an EVLW >16 mL/kg being associated with a very high mortality [6, 7].

Causes of ALI [8, 9]

ALI may result from either direct or indirect lung injury. It is likely that the severity of ALI and the outcome is related to the causation of ALI. The common causes include:

- Direct lung injury
  - pneumonia
  - aspiration pneumonitis
  - smoke inhalation
  - chemical inhalation
  - drowning
- Indirect lung injury
  - sepsis and sepsis syndrome
  - poly-trauma
  - Transfusion of blood and blood products (TRALI)
  - pancreatitis
  - drug induced (heroin, tricyclic antidepressants, etc.)
  - fat embolism
  - burns

Management of the Acute Phase of ARDS

The management of ARDS is essentially supportive; cardio-respiratory and nutritional support, the prevention of further lung injury and the prevention of complications while waiting for the acute inflammatory response to resolve and lung function to improve [9–11]. Tonelli et al. performed an umbrella review of 159 published randomized trials and 29 meta-analyses which evaluated the outcome of specific interventions in ARDS [12]. The authors concluded that there was only consistent evidence for low tidal volume ventilation and prone positioning in severe ARDS.

Ventilatory Strategy

The most important "recent" advance in the management of patients with ARDS (indeed in critical care medicine) is the realization that overdistension of alveoli causes acute lung injury. Hence a "lung protective strategy" is the standard of care and the cornerstone of the management of patients with ARDS [13]. Tidal volumes (Vt) should not exceed 6 mL/kg PBW (see Chap. 19).

The chest radiographs of patients with ARDS classically show widespread involvement of all lung fields. It was therefore assumed that ARDS was a homogenous process. However, high resolution computed tomographic scans performed in patients with ARDS have demonstrated areas of normal, consolidated and overinflated lung. The large area of consolidated and collapsed lung is predominantly distributed in the dependent areas, and participates minimally in gas exchange. The normal lung is usually anterior and often markedly overdistended. In addition, in the early stages of ARDS, consolidated lung units can be "recruited" with the application of modest distending pressures. Consequently, patients with ARDS typically have three functionally distinct lung zones; namely;

- that portion of the lung that is diseased and not recruitable,
- that portion of the lung that is diseased but recruitable and
- that portion of the lung that is normal.

Because a significant portion of the lung is consolidated and not recruitable, only a small amount of aerated lung receives the total tidal volume—ARDS leads to "baby lungs" [14]. The use of "traditional" tidal volumes (12 mL/kg) in these patients will result in high inspiratory pressures with overdistension of the normally aerated lung units. A growing body of experimental evidence has demonstrated that mechanical ventilation that results in high trans-pulmonary pressure gradients and overdistension of lung units will cause acute lung injury, characterized by hyaline membranes, granulocytic infiltration, pulmonary hypertension, and increased pulmonary and systemic vascular permeability. Animal studies have demonstrated that a trans-pulmonary pressure in excess of 35 cm H_2O will lead to alveolar damage [15]. These studies have demonstrated that ventilation with low tidal volumes preserves pulmonary ultrastructure. Furthermore, it has been postulated that the cyclic opening and closing of lung units (recruitment and derecruitment) in patients with ARDS who are ventilated with insufficient PEEP may further potentiate this iatrogenic lung injury [8, 9, 16]. It has therefore been suggested that ventilatory strategies that avoid regional or global overdistension of lung units and also avoids end-expiratory alveolar collapse may limit the degree of lung injury in ARDS…the open lung approach [17].

The Acute Respiratory Distress Syndrome Network randomized patients with ARDS to receive traditional volume controlled ventilation (an initial tidal volume of 12 mL/kg and an plateau pressure of ≤50 cm of water) or low tidal volume ventilation (an initial tidal volume of 6 mL/kg and a plateau pressure of ≤30 cm of water) [13]. In the low Vt group, Vt was reduced further to 5 or 4 mL/kg PBW if necessary to

maintain plateau pressure (Pplat) at less than 30 cm H_2O. The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes (31.0 % vs. 39.8 %, $p = 0.007$). This study has provided convincing evidence that a strategy that avoids alveolar overdistension in ARDS improves outcome.

The response to low-tidal-volume ventilation should be assessed initially on the basis of plateau airway pressure. The goal should be to maintain a plateau airway pressure (i.e., the pressure during an end-inspiratory pause) of 30 cm of water or less; if this target is exceeded, the tidal volume should be further reduced to a minimum of 4 mL per kilogram of predicted body weight. An important caveat relates to patients who have stiff chest walls (for example, those with massive ascites or morbid obesity). In such patients, it is reasonable to allow the plateau pressure to increase to values greater than 30 cm of water, since the pleural pressures are elevated and hence the transpulmonary pressures are not elevated (i.e., there is not necessarily alveolar overdistention). Ideally in these patients ventilatory management is guided by placing an esophageal balloon and adjusting the Tv and PEEP such that one avoids a high transpulmonary pressure at end-expiration (<25 cm H_2O) and thereby avoiding alveolar overdistension while adjusting PEEP such that the transpulmonary pressure is greater than 0 cm H_2O at end-expiration (0–5 cm H_2O) to avoid alveolar derecruitment thereby preventing repetitive alveolar collapse and reopening (aletectrauma). Talmor and colleagues performed a randomized controlled study in which PEEP and Vt were set according to measurement of esophageal pressures or according to the ARDSNet protocol [18]. In this pilot study, oxygenation and respiratory compliance were significantly better in the esophageal pressure group with a trend towards improved survival.

The available data does not support the commonly held view that inspiratory plateau pressures of 30–35 cm H_2O are safe [19]. There is no safe upper limit for plateau pressures in patients with ALI/ARDS. The lower the plateau pressure the lower the mortality (see Fig. 23.1); i.e. a Vt of 6 mL/kg/PBW should be used even if the plateau pressures are less than 28 cm H_2O.

A number of authors have suggested that a low-tidal volume ventilatory strategy is cardio protective rather than lung protective. Jardin and Vieillard-Baron have demonstrated a progressive increase in the incidence of acute cor pulmonale as the plateau pressure increases [20]. In their study the mortality rate and incidence of acute cor pulmonale increased markedly in ARDS patients above a plateau of 26 cm H_2O (see Fig. 23.2).

While sepsis and multi-system organ failure (MSOF) remain the most common cause of death in patients with ARDS up to 20 % of deaths are attributable to progressive respiratory failure [21]. A number of interventions have been attempted in this group of patients including inhaled nitric oxide, nebulized prostacyclin and surfactant, recruitment maneuvers, liquid ventilation, high frequency oscillation and prone positioning. With the exception of prone positioning in patients with severe ARDS (see below) there is little evidence that these interventions improve outcome [9–11, 22].

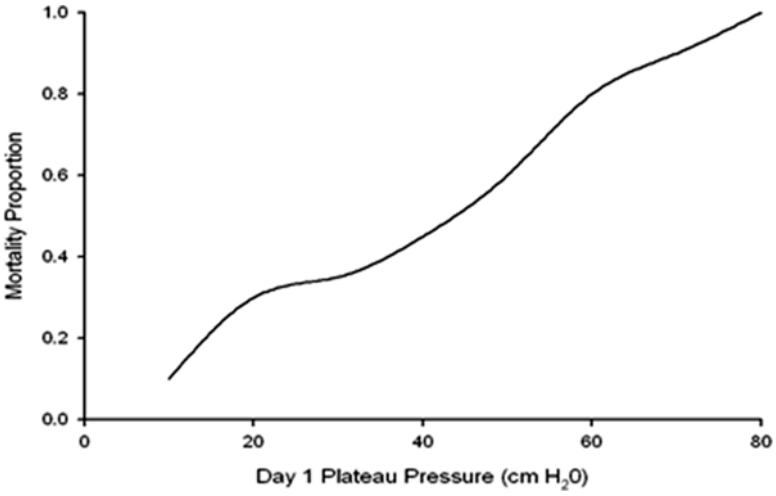

Fig. 23.1 Relationship between mortality and plateau pressure

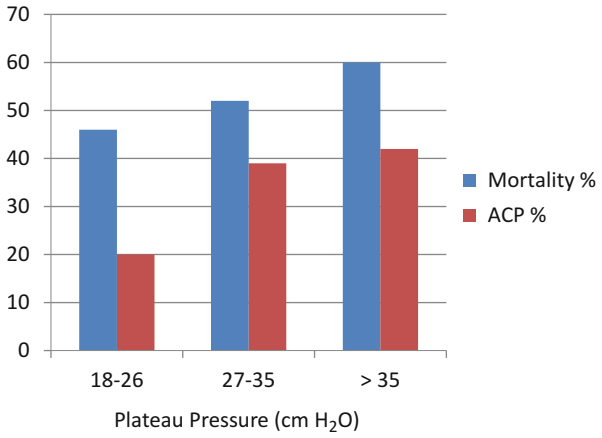

Fig. 23.2 Mortality and incidence of acute cor pulmonale (ACP) plotted against plateau pressure. Adapted from Jardin and Vieillard-Baron [20]

Pressure controlled ventilation (PCV) and Airway Pressure Release Ventilation (APRV) have been used in patients with refractory hypoxemia ventilated with a low-tidal volume ventilatory strategy. APRV has emerged as an alternative ventilatory strategy in patients with severe ARDS (see Chap. 19) [23–25]. PCV and APRV have however, yet to be carefully compared with volume-cycled ventilation in patients with ARDS in terms of morbidity, length of mechanical ventilation and ultimate patient outcome in a RCT. It is unlikely that such a trial will be performed; however, from the forgoing it is likely that ventilation strategies that achieve the same end-points (i.e. prevent alveolar overdistension and limit airway pressures) will have similar outcomes.

High frequency oscillation has been used as a rescue ventilatory strategy in patients with ARDS and refractory hypoxemia. High-frequency oscillatory ventilation

(HFOV) delivers very small tidal volumes (approximately 1 to 2 mL/kg) at very high rates (3–15 breaths per second) and is considered a true lung protective ventilatory strategy. HFOV combines small pressure oscillations to minimize overdistension with high mean airway pressure to prevent atelectrauma. Two randomized controlled studies were reported in 2013 that failed to show a benefit of this strategy. The OSCILLATE trial randomized 548 patients with moderate-to-severe ARDS at 39 ICUs to HFOV or a control strategy with the use of low tidal volumes (mean Tv 6.1 mL/kg IBW) and high PEEP (mean 18 cm H_2O) [26]. The trial was terminated prematurely due to an increase in mortality in the HFOV arm (47 % vs. 35 %, RR 1.33; CI 1.09–1.64, p = 0.005). HFOV was associated with higher mean airway pressures and with greater use of sedatives, neuromuscular blockers, and vasoactive drugs. The OSCAR trial randomized 795 patients with ARDS and a PaO_2/FiO_2 of less than 200 to HFOV or "usual care" in 29 hospitals in England, Wales, and Scotland [27]. Unlike the OSCILLATE trial a lung protective strategy was recommended but not mandated in the control arm (average Tv ? 8.3 mL/kg IBW). In this study there was no significant difference in mortality (41.7 vs 41.1 %) or other secondary end-points. The hemodynamic compromise associated with HFOV was minimal in the OSCAR trial as compared to the oscillate trial, perhaps owing to the lower applied ventilatory pressures in the OSCAR trial. In both trials the patients in the HFOV group received more muscle relaxants and sedatives than did patients in the control group.

Pressure Controlled Ventilation

To prevent alveolar overdistension and reduce the transpulmonary pressure gradients the inspiratory pressure is set such that the peak inspiratory pressure is less than 30 cm H_2O (i.e. applied PEEP + Inspiratory Pressure <30 cm H_2O) when possible, and always less than 35 cm H_2O. An inspiratory pressure of 20 cm H_2O (plus PEEP of 10 cm H_2O) with a respiratory rate of 16 breaths/min are convenient starting points.

The inspiratory and expiratory times (or I:E ratio) and respiratory rate are best determined by analyzing the Flow vs. Time Waveform (See Fig. 23.3). Flow will initially enter the lung rapidly because the ventilator attempts to reach the set airway pressure as quickly as it can (point A, Fig. 23.3). Airways that are open and have the least resistance will receive the greatest amount of gas flow and reach equilibrium with the pre-set pressure more quickly than airways with greater resistance. As the open airways fill and the lung pressure reaches equilibrium with the pre-set pressure, flow will decelerate as the airways with higher resistance continue to fill with gas (point B, Fig. 23.3). Flow into the lung will continue until one of two events occur,

- the preset pressure reaches equilibrium throughout all lung units (indicated by the flow pattern decelerating to zero), or
- the pre-set inspiratory time ends inspiration before pressure has equilibrated throughout all lung units (indicating by the flow pattern not reaching zero).

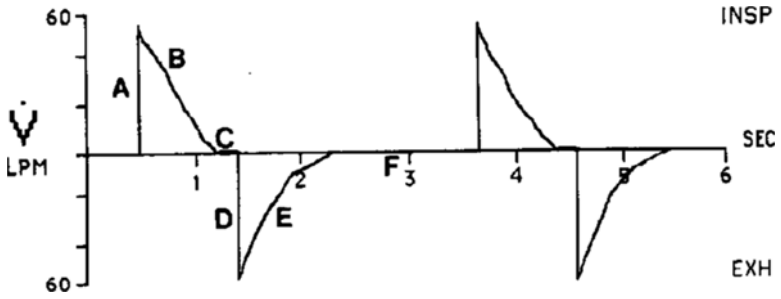

Fig. 23.3 Flow vs Time during pressure control ventilation

When inspiratory flow reaches zero it means the pressure in the lung is equal to the pressure set on the ventilator (point C, Fig. 23.3). It is essential that adequate inspiratory time be given so that all the airways, both healthy and diseased, have time to reach the preset pressure level. In ARDS much of the airway bed may take a relatively long time to open. For this reason it may be necessary to lengthen the inspiratory time, sometimes to the point that the inspiratory time is longer than the expiratory time. If air trapping is not present this approach will increase mean airway pressure without increasing maximal end expiratory pressure. In patients with ARDS oxygenation is primarily a function of mean airway pressure. This strategy will therefore increase alveolar ventilation and improve oxygenation.

The inspiratory time can be lengthened in 2 ways;

- if the ventilator will allow for the adjustment of inspiratory time, then simply increase the inspiratory time until the inspiratory flow reaches zero (recommended method),
- if the ventilator will allow adjustment of the I/E ratio, then reducing the "E" part of the ratio will increase "I".

If flow reaches zero and there is a long inspiratory pause, this is an indication that inspiratory time is too long. There is little benefit of having a prolonged inspiratory pause. Setting inspiratory time longer than that which is required to open recruitable airways increases the likelihood of significant auto-peep with its attendant hemodynamic complications.

To evaluate the adequacy of the expiratory time, the Flow vs. Time Waveform (Fig. 23.3) needs to be studied again. This waveform shows whether the patient has enough time to exhale to the pre-set PEEP level before the ventilator gives the next breath. In Fig. 23.3, point D represents the beginning of exhalation. When exhalation begins gas will exit the lungs quickly at first because a large pressure gradient exists between the lungs and the atmosphere. As gas continues to exit the lungs the pressure gradient will become smaller and flow will decelerate (point E, Fig. 23.3). Exhalation will continue until one of two events occur;

- the pressure in the lung reaches atmospheric pressure plus the set PEEP pressure (point F, Fig. 23.3) or
- the set inspiratory time mandates that inhalation begin before exhalation of the previous breath is complete thus causing auto-peep.

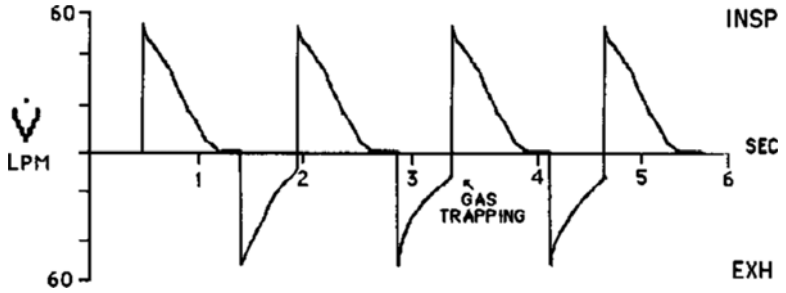

Fig. 23.4 Flow vs Time during pressure control ventilation demonstrating air trapping

Figure 23.4 demonstrates gas trapping as inhalation begins before expiratory flow is allowed to reach zero. Should gas trapping be evident on the Flow vs. Time Waveform, either the respiratory rate or inspiratory time should be reduced, allowing time for complete exhalation and thereby minimizing auto-PEEP. The respiratory rate and inspiratory time should both be independently and sequentially reduced, in order to determine which maneuver affects ventilation the least.

It is essential that the level of auto-PEEP be measured in all patients receiving PCV. There is no data that intrinsic PEEP has any advantage over extrinsic (i.e. applied) PEEP. However, the unrecognized development of auto-PEEP may result in hemodynamic compromise leading to the inappropriate use of fluid and vasopressor therapy. The Flow vs Time waveform should be monitored regularly. As the patients pulmonary mechanics change the inspiratory time and respiratory rate may need to be altered. Once the patients' condition has stabilized attempts should be made to reduce the level of PEEP (and FiO_2).

Airway Pressure Release Ventilation

APRV was first described by Stock and colleagues in 1987, and has been commercially available since the mid 1990s [28]. APRV can be classified as a pressure-limited, time-cycled mode of mechanical ventilation that allows the patient unrestricted spontaneous breathing during the application of continuous positive airway pressure [29–31]. It is an alternative approach to the "open-lung" ventilation strategy [31]. Although recruitment maneuvers may be effective in improving gas exchange and compliance, these effects are not sustained; APRV may be viewed as a nearly continuous recruitment maneuver [29]. The ventilator maintains a high-pressure setting for the bulk of the respiratory cycle (PHigh), which is followed by a periodic release to a low pressure (PLow) [32](see Fig. 23.5). The periodic releases aid in carbon dioxide elimination (CO_2). The release periods (TLow) are kept short (0.7–1 s); this prevents derecruitment and enhances spontaneous breathing during THigh [31, 33]. The release volumes must be monitored during APRV and should be kept below 8 mL/kg/ IBW to prevent alveolar overdistension. The advantages of

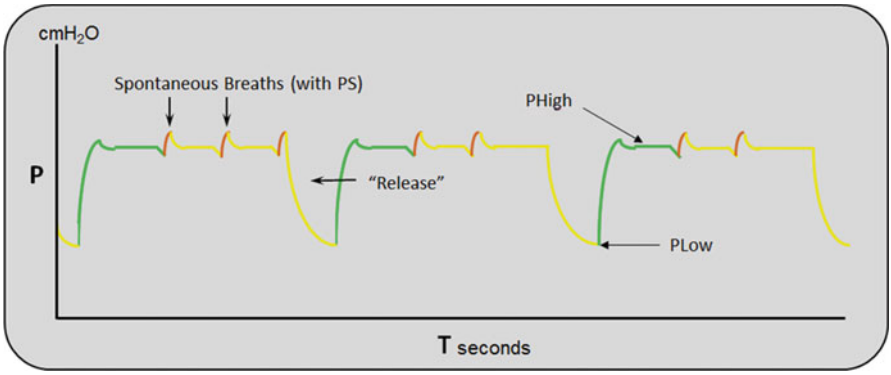

Fig. 23.5 Pressure time waveform during APRV

APRV over volume controlled ventilation include an increase in mean alveolar pressure with alveolar recruitment, the hemodynamic and ventilatory benefits associated with spontaneous breathing and the reduced requirement for sedation.

APRV uses an active exhalation valve that allows spontaneous breathing throughout the respiratory cycle. Due to the short release time (TLow) the spontaneous breaths occur almost exclusively during the PHigh [31, 33]. Both experimental and clinical studies have demonstrated that the addition of spontaneous breaths to APRV recruits dependent lung regions, increases end-expiratory lung volume, decreases V/Q mismatching, and improves oxygenation, cardiac function (cardiac index) and organ blood flow [34–40].

Lung protective strategies using both volume and pressure controlled ventilation are usually poorly tolerated requiring deep sedation. APRV however, is extremely well tolerated by patients allowing sedation to be reduced and even discontinued in many patients. This is a very important issue as the increased use of sedation has been associated with a longer duration of mechanical ventilation as well as an increased incidence of ventilator associated pneumonia, delirium and an increased mortality.

We have previously demonstrated a significant improvement in oxygenation with decreased V/Q mismatching (increased PaO_2/FiO_2 and decreased Vd/Vt) in a cohort of patients with severe ARDS who were switched from volume-controlled ventilation to APRV [41]. Similarly, improved oxygenation and hemodynamic parameters with APRV have been demonstrated in other observational studies [25, 39, 40, 42–44]. Andrews et al. compared the outcomes reported in the literature of patients with acute traumatic injuries that were ventilated using conventional ventilation with their experience in which APRV is used as the default mode of ventilation [45]. In this uncontrolled comparative observational study the early use of APRV was associated with a lower incidence of ARDS (14.0 % vs. 1.3 %) and in-hospital mortality (14.1 % vs. 3.9 %). These authors postulated that the early use of APRV may prevent progression of acute lung injury in high-risk trauma. A limitation of this

study is that it is likely that a preventative lung protective strategy was not adopted in the control trauma centers, as it has been now well established that "high" tidal volumes will cause ALI in perviously normal lungs.

It is important to emphasize that a ventilatory strategy that results in an improvement in oxygenation may not translate into an improvement in patient outcome (may even be worse). Since APRV has not been compared to conventional low tidal volume ventilation in a RCT, this strategy should only be considered in patients who have "failed" the conventional low tidal volume lung protective strategy. Currently a number of (small) RCTs are being conducted comparing conventional low tidal volume ventilation with APRV; these studies should provide additional information on the value of this ventilatory mode (NCT01339533, NCT01901354, and NCT00793013).

Permissive Hypercapnia

The strategy to reduce volume induced lung injury by using small tidal volumes may lead to CO_2 retention. The term "permissive hypercapnia" has been used to describe this ventilatory strategy. Hypercapnic acidosis is generally well tolerated by the patients, especially when it develops gradually over 1 to 2 days. The intracellular acidosis is corrected rapidly during sustained hypercapnia, whereas the extracellular acidosis may persist for much longer. The lowest pH that can be safely tolerated in unknown, however, a pH greater than 7.2 is generally recommended. Some patients, however, have tolerated a pH as low as 7.05 without obvious adverse effects. It has been suggested that bicarbonate should be used to correct the pH. However, the administration of bicarbonate may paradoxically increase intracellular acidosis. Permissive hypercapnia should not be used in patients with acute intracranial pathology as this may cause a precipitous increase in intracranial pressure. Furthermore in patients with ischemic heart disease, arrhythmias and patients requiring high doses of inotropic drugs, hypercapnia should be allowed to develop gradually. Surprisingly, permissive hypercapnia itself has anti-inflammatory effects and has been shown to attenuate lung injury in animal models [46, 47]. Furthermore, permissive hypercapnia has beneficial hemodynamic effects [47].

Best PEEP

Positive end-expiratory pressure (PEEP) appears to be protective against ventilator-induced lung injury in animal studies, perhaps by recruiting more aerated lung and preventing shear forces produced during repetitive opening of closed airways or alveoli. Low tidal volume ventilation has been demonstrated to cause a decline in compliance in healthy subject as well as patients in respiratory failure. It has been suggested that the smaller the tidal volume the higher the PEEP level need to optimize lung mechanics. It is generally believed that PEEP set below 10 cm H_2O will

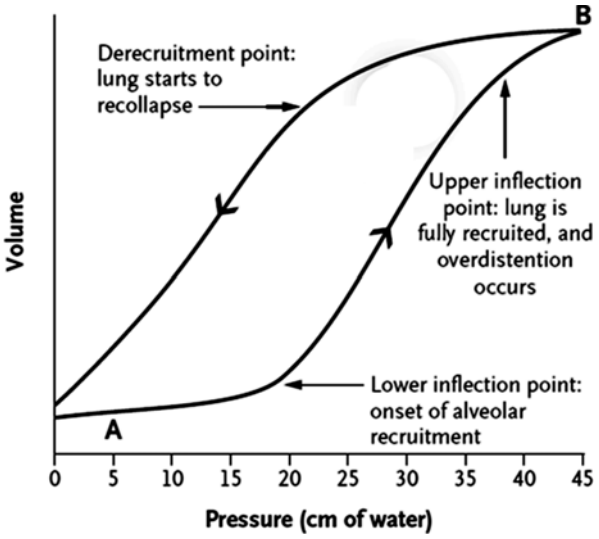

Fig. 23.6 Dynamic pressure volume curve

probably keep healthy alveoli open at end exhalation, but will not be enough to distend diseased airways. These airways will then continually open and collapse throughout the ventilator cycle. The goal is to set PEEP at a level that does not overdistend healthy alveoli but at the same time does not let diseased airways collapse. The term the "Open Lung Approach" has been used to describe this method of ventilation [17]. It has been reported that in patients with ARDS a mean PEEP level of 15 cm H_2O is required to keep the airways "open" at end-expiration [17].

While the beneficial effects of a low tidal volume strategy is largely accepted, the role of PEEP as part of the "Lung Protective Strategy" is more controversial [48–50]. A meta-analysis demonstrated a trend towards improved mortality with high PEEP, even though the difference did not reach statistical significance; with the pooled cumulative risk of 0.90 (95 % CI 0.72–1.02, P = 0.077) [51]. The reduction in absolute risk of death was approximately 4 %. There was no evidence of a significant increase in baro-trauma in patients receiving high PEEP, with a pooled risk of 0.95 (95 % CI 0.62–1.45, P = 0.81).

"Best PEEP" can be estimated from a static/dynamic pressure/volume curve (see Fig. 23.6). This curve classically demonstrates an upper and lower inflection point. PEEP should be set above the lower inflection point such that the sum of the PEEP and the inspiratory pressure should be below 30 cm H_2O (a plateau pressure up to 35 may be acceptable) or the upper inflection point. Should an inflection point not be present on the pressure/volume curve or it not be possible to perform this maneuver, the initial PEEP should be set between 10 and 15 cm H_2O. Alternate methods of setting PEEP include setting PEEP above the point of derecruitment on the expiratory limb of the dynamic pressure volume curve (see Fig. 23.6) or by measuring transpleural pressures with an esophageal balloon (as discussed previously).

Recruitment Maneuvers

Recruitment refers to the dynamic process of reopening unstable airless alveoli through an intentional transient increase in transpulmonary pressure. The rationale for the use of recruitment maneuvers (RMs) in ALI is to promote alveolar recruitment, leading to increased end-expiratory lung volume. An increase in end-expiratory lung volume may improve gas exchange and attenuate ventilator-induced lung injury by preventing repetitive opening and closing of unstable lung units. However, RMs may directly overdistend aerated lung units and could, paradoxically, lead to increased lung injury. Clinical studies of RMs in ALI have yielded variable results. A systematic review on the topic concluded that "given the uncertain benefit of transient oxygenation improvements in patients with ALI and the lack of information on their influence on clinical outcomes, the routine use of RMs cannot be recommended or discouraged at this time" [52].

Non-Ventilatory Adjuncts to Gas Exchange

Prone Positioning

Prone positioning has been used for many years to improve oxygenation in patients who require mechanical ventilatory support for ARDS. Prone positioning improves V/Q mismatching and oxygenation. The use of prone positioning has been somewhat controversial, with this technique being used earlier and more frequently in Europe as compared to North America. Randomized, controlled trials have confirmed that oxygenation is significantly better when patients are in the prone position than when they are in the supine position. Furthermore, several lines of evidence have shown that prone positioning could prevent ventilator-induced lung injury. However, in several trials these physiological benefits did not translate into improved patient outcomes. More recently Guerin et al. randomized 466 patients with severe ARDS to undergo prone-positioning for at least 16 h/day or to be left in the supine position [53]. Severe ARDS was defined as a PaO_2/FiO_2 ratio of less than 150 mmHg, with a FiO_2 of at least 0.6, a PEEP of at least 5 cm H_2O and a tidal volume close to 6 mL/kg PBW. The 28-day mortality was 16.0 % in the prone group and 32.8 % in the supine group ($p < 0.001$). A meta-analysis of 11 RCT which included 2,246 adult patients demonstrated that prone positioning significantly reduced overall mortality (OR 0.77; CI, 0.59–0.99; $p = 0.039$, and the effects were marked in the subgroup in which the duration of prone positioning was more than 10 h/session, compared with the subgroup with a short-term duration of prone positioning [54]. These data suggest that prone positioning should be considered in patients with severe ARDS ($PaO_2/FiO_2 < 150$) and that the patients should be proned for at least 10 h per day.

Neuromuscular Blocking Agents

In patients with refractory hypoxemia neuromuscular blocking agents (NMBA) have been used to facilitate mechanical ventilation. NMBA improve oxygenation presumably by improving patient-ventilator synchrony. NMBA may also reduce lung injury. The use of NMBA is however associated with significant complications, most notably muscle weakness. Indeed, the combination of corticosteroids and a NMBA is associated with a severe and irreversible quadriparesis due to a necrotizing myopathy [55, 56]. This neuromuscular complication dampened the enthusiasm for the use of NMBA in patients with severe ARDS. However, in a multicenter, double-blind trial, Papazian et al. randomized 340 patients with an onset of severe ARDS within the previous 48 to receive, for 48 h, either cisatracurium besylate or placebo. Severe ARDS was defined as a PaO_2/FiO_2 ratio <150 [57]. Mortality at 28 days was 23.7 % with cisatracurium and 33.3 % with placebo ($p=0.05$). The Cox regression model yielded a hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, of 0.68 (CI, 0.48 to 0.98; $p=0.04$). The rate of ICU-acquired paresis did not differ significantly between the two groups. Using a large database, Steingrub et al. examined the association between receipt of a NMBA and in-hospital mortality among mechanically ventilated patients with severe sepsis [58]. In this study the use of a NMBA within 2 days of ICU admission was associated with a lower in-hospital mortality rate (31.9 % vs 38.3 %). The mechanisms underlying the beneficial effect of neuromuscular blocking agents in patients with ARDS remain speculative. A brief period of paralysis early in the course of ARDS may facilitate lung-protective mechanical ventilation by improving patient–ventilator synchrony and allowing for the accurate adjustment of tidal volume and pressure levels, thereby limiting the risk of both asynchrony related alveolar collapse and regional alveolar pressure increases with overdistention. Another possible mechanism of the benefit involves a decrease in lung or systemic inflammation. These data suggest that a NMBA may improve the outcome of patients with severe ARDS when used early in the course of the disease and when the duration of neuro-muscular blockade is less than 48 h. CPK's should be monitored in these patients in order to limit the development of a myopathy.

ECMO

Extracorporeal CO_2 removal with apneic oxygenation (ECMO) has been used to avoid additional ventilator induced lung injury in patients with severe ARDS. In venovenous ECHMO blood is withdrawn from a central vein into an extracorporeal circuit by a mechanical pump before entering an oxygenator. Within the oxygenator, blood passes along one side of a membrane, which provides a blood–gas interface for diffusion of gases. The oxygenated extracorporeal blood is returned to a central vein.

The use of ECMO is patients with ARDS is controversial. The "*Conventional Ventilatory Support* vs. *Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure* (CESAR)" study, conducted in the UK randomized 180 adults with ARDS to receive conventional management or referral to an ECMO center for consideration for treatment by ECMO [59]. 63 % of patients allocated to consideration for treatment by ECMO survived to 6 months without disability compared with 47 % of those allocated to conventional management (RR 0.69, CI 0.05–0.97, $p=0.03$). It is important to note that CESAR was a "pragmatic trial" in which "standard practice" was compared with a protocol that included ECMO. A standardized ventilatory and management strategy was not used in the "standard practice" group. A lung protective ventilation strategy was not mandated in the conventional-management group, and only 70 % of patients in that group were treated with such a strategy at any time during the study. Patients transferred to the ECMO centers were managed by standardized protocols. This study was not a randomized trial of ECMO as compared with standard-of-care mechanical ventilation. Substantial differences in overall care between the study groups may account for the beneficial effect that was associated with referral for consideration for ECMO. While the lack of standardized treatment in the control group is a confounding factor, this trial established that ECMO is feasible in patients with severe ARDS and that this intervention may improve outcome.

Many patients with ARDS caused by influenza A(H1N1) infection received extracorporeal membrane oxygenation (ECMO) as a rescue therapy [60]. The benefit of ECMO in these patients is unclear. Noah performed a propensity score–matched analysis of patients with H1N1 undergoing ECMO compared to standard care. The mortality was 24.0 % with ECMO vs 46.7 % with standard care (RR 0.5, CI 0.31–0.81; $p=0.008$). However, Pham et al. performed a similar propensity score–matched analysis and demonstrated no difference in mortality between the two groups [61].

ECHO is very labor intensive, complex to set up and manage and associated with numerous complications. ECMO should therefore be performed only at centers with high case volumes, established protocols, and clinicians who are experienced in its use [62].

Corticosteroids

The use of corticosteroids in patients with ARDS is controversial with widely dissenting opinions on this topic [63]. At least six meta-analyses have been performed with conflicting conclusions [64–69]. However, a summation of this data would suggest that glucocorticoids improve oxygenation, increase the number of ventilator free days, decrease ICU and hospital length of stay with a possible mortality benefit with no clear evidence of an increase in complications. Despite the potential benefit of glucocorticoids in patients with ARDS, survey data suggest that most clinicians do not prescribe these agents to their patients with ARDS [70].

Myths About Complications of Glucocorticoid Treatment

The most commonly cited complications that might temper enthusiasm for glucocorticoid treatment include increased risks of infection and neuromuscular weakness.

i. Glucocorticoid treatment does not increase infection risk. Contrary to older studies investigating a time-limited (24–48 h) massive daily dose of glucocorticoids (methylprednisolone, up to 120 mg/kg/day), recent trials have *not* reported an increased rate of nosocomial infections. In fact, new cumulative evidence indicates that down-regulation of life-threatening systemic inflammation with prolonged low-to-moderate dose glucocorticoid treatment improves innate immunity and provides an environment less favorable to the intra- and extracellular growth of bacteria. Glucocorticoids, however, do blunt the signs and symptoms of infection. .

ii. Glucocorticoid treatment does not increase the risk of neuromuscular weakness. The incidence of neuromuscular weakness is similar between groups treated with or without glucocorticoids (17 % vs. 18 %) [66]. Two recent studies found no association between prolonged glucocorticoid treatment and electrophysiologically or clinically proven neuromuscular dysfunction [71, 72]. Given that neuromuscular dysfunction is an independent predictor of prolonged weaning [73] and ARDS randomized trials have consistently reported a significant reduction in duration of mechanical ventilation [74–78], clinically relevant neuromuscular dysfunction caused by glucocorticoid or glucocorticoid-induced hyperglycemia seems highly unlikely.

It is likely that both the dose and dosing schedule are major determinants of the outcome of patients with ARDS treated with corticosteroids. The recommended dosing schedule is methylprednisolone in a dose not to exceed 1 mg/kg/day for 14 days followed by a slow taper [76, 79]. We recommend the use of corticosteroids within 48 h of admission to the ICU in patients with severe and progressive ALI.

Glucocorticoids to Prevent ALI/ARDS

As glucocorticoids have demonstrated a benefit in patients with established ARDS is has been postulated that these agents may be useful in preventing ARDS. Four studies have tested this hypothesis, however this strategy was associated with a trend to an increase in both the odds of developing ARDS and the risk of mortality in those who developed ARDS [64]. The reason for the seemingly differential effect of preventative and therapeutic steroid therapy in ARDS is unclear. In a propensity based analysis of a large hospital database, the concurrent use of corticosteroids at the time of hospitalization did not reduce the risk of developing ARDS nor did it affect the requirement for mechanical ventilation or influence mortality [80].

Inhaled Nitric Oxide

Nitric oxide is an endogenous vasodilator. When administered by inhalation at concentrations up to 20 ppm, it reduces pulmonary vascular resistance. Although about 60 % of patients with acute lung injury have an initial noticeable improvement in oxygenation, the effect is transient (48 h) and does not confer mortality benefit or reduction in the duration of mechanical ventilation [22, 81]. Nitric oxide should not be used routinely in the treatment of ARDS but may have a role as salvage therapy for patients in whom adequate oxygenation cannot be achieved with lung protective mechanical ventilation, neuromuscular paralysis and prone positioning.

Nebulized Prostacyclin

Prostacyclin is an endogenous vasodilator with similar physiological effects to nitric oxide. When nebulized, it has an equivalent effect on pulmonary vasodilation and oxygenation but is easier to administer, has harmless metabolites, and requires no special monitoring. However, no large randomized controlled trials in acute respiratory distress syndrome have been conducted.

β_2-Adrenergic Receptor Agonists

Alveolar epithelial fluid clearance is impaired during ALI/ARDS, and decreased resolution of alveolar edema is associated with increased mortality. In experimental and clinical studies β2-agonists have been demonstrated to accelerate resolution of pulmonary edema. It was therefore postulated that β2-agonists may have a role in the treatment of patients with ARDS.

The ARDSnet group conducted a multicenter, randomized, placebo controlled clinical trial in which 282 patients with ARDS receiving mechanical ventilation were randomized to receive aerosolized albuterol (5 mg) or saline placebo every 4 h for up to 10 days [82]. In this study there was no improvement in any outcome variable in the patients receiving the inhaled β2-agonist. Smith and colleagues randomized 326 patients with ARDS to receive intravenous salbutamol or placebo for up to 7 days [83]. This study was prematurely stopped due to increased mortality in the salbutamol (34 % vs. 23 %; RR 1·47, CI 1·03–2·08).

Surfactant

Although patients with acute respiratory distress syndrome have decreased and dysfunctional surfactant, no benefit has been found after the administration of both natural and synthetic formulations—in terms either of mortality or of the need for mechanical ventilation.

Omega-3 Enteral Nutrition

Omega-3 fatty acids have important anti-inflammatory and immunomodulating properties. However, the use of O-3 fatty acid supplemented enteral formulas in patients with ARDS is controversial. Three RCT's demonstrated that an enteral formula high in O-3 fatty acids, improved oxygenation, the number of ventilator free days, ICU LOS and mortality [84, 85].

The OMEGA study was a RCT that randomized 272 adults within 48 h of developing ALI to receive twice-daily enteral supplementation with O-3 fatty acids or an isocaloric control [86]. Enteral nutrition was delivered separately from the study supplement. The study was stopped early for futility. The adjusted 60-day mortality was 25.1 % and 17.6 % in the O-3 and control groups respectively. Despite millions of patients being treated with O-3 fatty acids, this is the first study to demonstrate an "apparent harm" from this nutritional supplement. A number of peculiarities of this study make the results difficult to interpret [87]; nevertheless, this study has tempered the enthusiasm for the use of high concentrations of O-3 fatty acids in ARDS. A meta-analysis of O-3 fatty acids in ARDS did not demonstrate a survival advantage nor a reduction in ventilator-free days or other secondary outcomes [88]. Nevertheless the use of O-3 fatty acids in ARDS is supported by a sound physiological basis and extensive experimental studies. Furthermore, O-3 fatty acids together with essential amino acids promote muscle synthesis [89]. However O-3 fatty acids have diverse biological effects and additional studies are required to resolve this issue [87, 90, 91]. Nevertheless, I still recommend a high quality semi-elemental nutritional supplement with a structured lipid containing O-3 fatty acids and high biological value protein (see Chap. 32). Such a formula has anti-inflammatory properties and may limit protein breakdown, two very important properties in patients with ARDS.

"Our" Approach to Refractory Hypoxemia

All patients with ALI/ARDS should initially be ventilated using volume controlled ventilation with a Vt of 6 mL/kg-PBW and a PEEP of 10–15 cm H_2O. They should be kept "dry" and receive an enteral formula with omega-3 fatty acids. Corticosteroids should be added within 48 h in patients with progressive ALI. The following sequential interventions should be attempted (and withdrawn if no response) in patients with refractory hypoxemia:

- Neuromuscular blockade (early and for no longer than 48 h)
- APRV/PCV
- Nebulized prostacyclin
- Prone positioning
- ECMO

ECMO should only be considered in suitable candidates with single organ failure (lung failure) and no associated co-morbidities.

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Chapter 24
COPD Exacerbation

A COPD exacerbation is defined as an increase in the symptoms of COPD (dyspnea, cough, sputum production, sputum purulence) of a magnitude greater than the normal day-to-day variability [1, 2]. An increase in airway inflammation is considered central to the pathogenesis of a COPD exacerbation. A stimulus that acutely increases airway inflammation results in increased bronchial tone, increased bronchial wall edema and increased mucus production. These processes worsen ventilation–perfusion mismatch and expiratory flow limitation. Corresponding clinical manifestations would include worsening gas exchange, dyspnea, cough, sputum production and sputum purulence, which are the cardinal manifestations of an exacerbation. The in-hospital mortality rate for acute COPD exacerbations is approximately 10 %, and approximately 25 % of patients require admission to an ICU [3].

Patients with chronic obstructive pulmonary disease (COPD) who acutely decompensate may benefit from admission to the ICU. Patients with COPD admitted to an ICU for an acute exacerbation of COPD have a hospital mortality between 10 and 25 % with a 1-year mortality of about 40 % [4, 5]. Long-term survival of patients with COPD who required mechanical ventilation for an acute exacerbation of their disease cannot be predicted simply from data available at the time of intubation. Furthermore, the need for mechanical ventilation appears not to influence either short- or long-term outcome; therefore, the need for mechanical ventilation should not be used as a reason for not offering respiratory support [4, 5]. Noninvasive positive-pressure ventilation (NPPV) should be considered prior to endotracheal intubation in suitable candidates (see Chap. 20).

Patients with COPD often have risk factors for cardiac disease and it is often difficult to distinguish cardiogenic pulmonary edema from a COPD exacerbation. A BNP (or pro-BNP) may help distinguish between these two conditions however the BNP may be mildly increased in patients with a COPD exacerbation [6, 7]. Furthermore patients with the Malignant Obesity Hypoventilation Syndrome (MOHS) are frequently misdiagnosed as having a COPD exacerbation; these patients do not benefit from COPD therapy [8].

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Common Precipitating Events

Precipitating factors must be determined in patients with COPD who present with an acute deterioration in respiratory status [4]. While chest infection is the most common precipitating factor, other readily treatable factors (e.g, atrial fibrillation, cardiac failure) should actively be investigated, including the following:

- Upper respiratory tract infection
- Chest infection: acute bronchitis or pneumonia
- Pneumothorax
- Pleural effusion
- Pulmonary embolus
- Heart failure
- Arrhythmias
- Atelectasis/mucous plugging
- Use of sedative agents

Lower airway colonization by bacteria is common in patients with stable COPD. *Haemophilus Influenzae*, *Streptococcus pneumonia* and *Moraxella Catarrhalis* are the most common colonizing organisms. Exacerbations of COPD are frequently associated with viral infections; influenzae, parainfluenzae, and respiratory syncytial virus are the most common etiological agents. Studies using invasive diagnostic testing suggest that between 50 and 70 % of exacerbations of COPD are related to bacterial infection [2]. Approximately 25 % of patients admitted to hospital with an exacerbation of COPD have co-infection with bacteria and viruses [9]. It is not possible to differentiate clinically those patients whose exacerbation of COPD is caused by a bacterial infection. *H. Influenzae*, *S. pneumoniae*, *M. Catarrhalis*, and *Chlamydia pneumoniae* are the most common pathogens; however, multi-drug resistant (MDR) gram negative rods (including *Pseudomonas aeruginosa*) are not uncommon [10–12]. Risk factors for MDR gram –ve's include previous antimicrobial treatment and previous intubation [10]. Gram-stain and culture should therefore be performed in all patients admitted to the ICU with an exacerbation of COPD (not to diagnose infection but to identify the potential pathogens).

Pulmonary embolism has been implicated in up to 25 % of patients with a COPD exacerbation who require hospitalization [13]. Based on this data all patients with a COPD exacerbation requiring admission to the ICU should undergo lower extremity Doppler studies. D-dimer levels have a high negative but a low positive predictive value for PE in COPD exacerbations because a multitude of different inflammatory and infectious etiologies can cause blood D-dimers to rise [14]. A CTPA should be considered in those patients with –ve Doppler's, a +ve D-Dimer and an intermediate to high pretest probability of PE.

Classic teaching suggests that treatment with β-blockers should be avoided in patients with COPD. However many patients with COPD have cardiovascular diseases that may benefit from the use of such agents. Paradoxically, treatment with β-blockers may reduce the risk of exacerbations and improve survival in patients with COPD [15]. The benefit β-blockers may be related to the fact that many patients

with COPD have unrecognized heart failure. Furthermore, β-blockers may upregulate β2-receptors in the lung and thus improve the bronchodilator responsiveness and effectiveness of inhaled β2-agonists. These data suggest that patients with COPD may be treated with β-blockers (β1 selective preferred) [15].

Indications for Hospitalization

- Co-morbid conditions
  - Pneumonia
  - Heart failure
  - Renal or liver failure
- Inadequate response of symptoms to outpatient management
- Marked increase in dyspnea
- Worsening hypoxemia
- Worsening hypercapnia
- Changes in mental status
- In ability for patient to care for her/himself

Indications for ICU Admission

- Impending or actual respiratory failure
- Hemodynamic instability
- Increasing confusion or obtundation

Treatment

- Correct hypoxia; this usually requires only small increases in FiO_2 A high PaO_2 may cause an increase in CO_2; the mechanisms of this phenomenon are complex and include an increase in V/Q mismatching, the Haldane effect and possibly a suppression of the "hypoxic drive." Patients with severe COPD develop chronic compensatory mechanisms for a low PaO_2 and therefore do not require a "normal" PaO_2; a PaO_2 between 50 and 60 mmHg is usually well tolerated. An elevated $PaCO_2$ is acceptable as long as the patient is alert and cooperative and the arterial pH >7.2.
- The results of RCT's demonstrate that NPPV reduces the need for intubation, reduces in-hospital mortality, and shortens hospital stay during acute COPD exacerbations. NPPV should be considered in all patients who are alert and cooperative and able to tolerate NPPV (see Chap. 20) [3, 16].

- Empiric antibiotics are usually given even in the absence of clinical features of infection. A meta-analysis demonstrated that antibiotics significantly reduced treatment failures in hospitalized patients (RR, 0.34; 95 % CI, 0.20–0.56) and mortality (RR, 0.22; 95 % CI, 0.08–0.62) [3]. More recent data suggests that that the addition of antibiotics to systemic corticosteroids has a limited and short-lived effect on clinical outcome and symptoms and no effect on lung function and systemic inflammation [17]. In this RCT the authors found no significant difference in clinical outcome on Day 30 among patients with a COPD exacerbation who were randomly assigned to doxycycline as compared to placebo. The antibiotic of choice in a patient with a COPD exacerbation should be guided by knowledge of the local pathogens and their sensitivity patterns. Ampicillin/clavulanate, doxycycline or respiratory fluoroquinolones (levofloxacin, moxifloxacin) are suitable choices. The antibiotics may need to be changed, guided by sputum/lower respiratory tract sampling culture results. Antipseudomonal/ extended spectrum B-lactams will be required in patients "colonized" with *Pseudomonas aeruginosa* or other MDR gram –ve's and vancomycin/ linezolid in those with MRSA [12]. Procalcitonin has been used to guide the use of antibiotics in patients with a COPD exacerbation. This approach is however controversial. Stolz et al performed a RCT in which patients were randomized to standard care (which included antibiotics) or a group in which the use of antibiotics was guided by the admission PCT level [18]. A procalcitonin level of >0.25 ng/mL was used as an indication for antibiotics. Clinical outcome and improvement in FEV1 at 14 days and 6 months did not differ between groups. Within 6 months, the exacerbation rate, the rehospitalization rate, and meantime to the next exacerbation were similar in both groups. We suggest that the decision to treat with antibiotics be based on the patients' clinical features, severity of illness, chest radiograph as well as the PCT level.
- Inhaled bronchodilators are usually given to all patients even if the patient does not have measurable reversible airway disease. Beta-2 agonists and ipratropium bromide should be used.
- A short course of intravenous corticosteroid has been shown to be beneficial even in patients with no demonstrable airway obstruction. A meta-analysis demonstrated that corticosteroid treatment was associated with a more rapid improvement in FEV1, significantly fewer treatment failures and a shorter duration of hospitalization as compared to placebo [3, 19]. The dose and duration of treatment have however been controversial. Leuppi and colleagues randomized patients with a COPD exacerbation to treatment with 40 mg of prednisone daily for either 5 or 14 days [20]. In this study there was no difference in the risk of exacerbations within 180 days or any of secondary outcome measures. Long term corticosteroids have significant effects on bone and muscle metabolism, cause hyperglycemia and are immunosuppressive; effects that are particularly hazardous in the frail patient with COPD. Furthermore, long-term use of systemic glucocorticoids is an independent risk factor for increased mortality in COPD [21]. These data suggest that patients with

COPD should receive a short course (5 days) of low dose corticosteroids (40 mg prednisone/day).
- DVT prophylaxis; LMWH or subcutaneous heparin
- Do not use sedative drugs unless the patient is on a ventilator
  - Dexmedetomidine may be a suitable choice in patients with a COPD exacerbation (See Chap. 15)

Indications for NPPV

- Respiratory rate >30 breaths/min
- PaO_2 <45–50 mmHg (on room air)
- $PaCO_2$ >45–50 mmHg
- pH <7.32

Indications for Endotracheal Intubation

- Somnolence/decreased level of arousal
- Unable to protect airway
- Unable to deal with pulmonary secretions
- Failed trial of NPPV

Mechanical Ventilation in COPD

Despite the use of NPPV as many as 50 % of patients with a COPD exacerbation will require intubation and mechanical ventilation. Most of these patients have underlying chronic ventilatory failure with a baseline state of chronic compensated respiratory acidosis (i.e high baseline PCO_2, high HCO_3 with a low-normal pH). The serum bicarbonate level on admission, or even better, obtained during a recent period of stability, may provide an indirect indication of the patient's baseline $PaCO_2$. Ventilator settings that produce a "normal" $PaCO_2$ will likely lead to renal dumping of bicarbonate, leading to difficulty weaning from the ventilator since this level will be needed to maintain the status quo off the mechanical ventilator. "Controlled hypoventilation" should guide management, aiming for a $PaCO_2$ at or above the patient's usual baseline with a pH target of 7.32–7.36 [16]. Do not aim to normalize blood gasses in patients with COPD; these patients are usually members of the "50-50 club" so aim to keep PCO_2 and PO_2 near baseline levels.

Worsened airway inflammation, edema, bronchospasm, and increased secretions cause patients with COPD exacerbation to experience increased airways obstruction and greater than usual degrees of airway closure and inhomogeneous ventilation.

If adequate time is not given for expiration, end-expiratory lung volume increases beyond the normal functional residual capacity (FRC). The result is dynamic hyperinflation of the lung, with positive end-expiratory pressure in the lung due to this trapped gas, referred to as intrinsic PEEP (PEEPi), air-trapping, or auto-PEEP. Gas trapping and PEEPi have multiple adverse consequences. Other than treating the underlying condition with bronchodilators and antiinflammatory agents, the primary method by which dynamic hyperinflation is reduced is through increasing expiratory time [16]. This is accomplished by reducing the respiratory rate but can also be treated by altering the inspiratory to expiratory (I:E) ratio. A decelerating waveform results in the lowest peak inspiratory pressure, physiologic dead-space ratio, and $PaCO_2$ compared to square and sine wave patterns. Somewhat more controversial is the application of PEEPe to decrease airtrapping in patients with COPD. In most instances, PEEPe is best avoided as it may worsen lung hyperinflation and airtrapping. Patients with COPD should not be oversedated as they are likely to lose their respiratory drive. A combination of dexmedetomidine and fentanyl are suggested.

Suggested Initial Settings

- Mode: AC
- Rate: 12–14 /min
- Tidal volume: 6–8 mL/kg IBW
- PEEP: 0
- FiO_2: 40–60 %

These setting should be dynamically adjusted to achieve an arterial saturation of 88–92 % (by pulse oximetry) and a low-normal pH (a venous blood gas is just fine). The Time-Flow waveform should be monitored to ensure adequate expiratory time and the PEEPi should be measured.

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Chapter 25
Acute Severe Asthma

Status asthmaticus (SA) and near-fatal asthma are common medical emergencies faced by critical care physicians. Status asthmaticus is defined as an acute, severe asthma exacerbation that does not respond readily to initial intensive therapy, while near-fatal asthma (NFA) refers loosely to a status asthmaticus attack that progresses to respiratory failure. In an analysis of nearly 30,000 hospital admissions for acute asthma, 10.1 % required admission to the ICU and 2.1 % required intubation and mechanical ventilation [1]. Two distinctive phenotypes of near-fatal asthma have been identified: one with eosinophilic inflammation associated with a gradual onset and a slow response to therapy and a second phenotype with neutrophilic inflammation that has a rapid onset and rapid response to therapy (see Table 25.1). Patients who develop sudden-onset near-fatal asthma seem to have massive allergen exposure and emotional distress.

The vital signs of a patient in SA will consistently include a respiratory rate >30 per minute and a heart rate >120 per minute. Patients with SA will often be sitting upright, tachypneic, wheezing, and have sternocleidomastoid contraction with respiration. However, the classic signs of wheezing correlate poorly with the degree of airflow limitation. Severely obstructed patients may have a silent chest if there is insufficient alveolar ventilation and airflow for wheezes to occur. In these patients, the development of wheezes generally indicates improved airflow. Localized wheezing or crackles on chest auscultation may represent mucous plugging or atelectasis, but they should prompt consideration of pneumonia, pneumothorax, endobronchial lesions, or a foreign body.

Early response to treatment (PEFR or FEV1 at 30 min) in the ED is the most important predictor of outcome and a useful guide for admission to the ICU. PEFR increase over baseline >50 L/min and PEFR >40 % of normal, both measured at 30 min after beginning of treatment are predictors of good outcome.

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Table 25.1 Asthma phenotypes

	Gradual onset	Sudden onset
Course	Days	Hours, asphyxic
Incidence	80–85 %	15–20 %
Airway pathology	Gelatinous mucous plugging	No mucous plugging
Pred. inflammatory cell	Eosinophil	Neutrophil
Response to treatment	Slow	Faster
Hospitalization course	Long	Short
Prevention	Possible	Unclear

Indications for Admission to the ICU

- Difficulty talking due to breathlessness
- Altered level of consciousness
- Inability to lie supine
- FEV1 and/or peak flow <40 % predicted
- Pulsus paradoxus >18 mmHg
- Pneumothorax or pneumomediastinum
- PaO_2 <65 mmHg on 40 % O_2
- $PaCO_2$ >40 mmHg
- Patient tiring
- Poor (or no) response to initial bronchodilator therapy (<10 % increase in peak expiratory flow rate)
- Heart rate >120/min

Initial Treatment

- Supplemental oxygen by mask or nasal canula to achieve an arterial saturation >90 %.
- Short acing β-2 agonist by nebulization every 15–20 min initially then 1–4 hourly. Administration via pressurized metered-dose inhaler with spacer provides equivalent efficacy to nebulized treatments. Seventy percent of patients respond to between four and eight puffs every 10 min or between 5.0 and 7.5 mg of nebulized albuterol [2]. Delivery by continuous nebulization may offer distinct advantages to intermittent dosing in patients with SA [3].
- Ipratropium bromide nebulization, q2 to 4 h, has synergistic bronchodilatory activity with β-2 agonists and should be considered in SA. Children with an asthma exacerbation experience a lower risk of admission to hospital if they are treated with the combination of inhaled β-2 agonist plus anticholinergic versus β-2 agonist alone [4].

- Corticosteroids: Methylprednisolone 60 mg IV q6h [5]. There is typically a 6–24-h delay in clinical response to corticosteroids in SA. If the patient improves within 24 h, the dose of methylprednisolone is decreased to 60 mg every 12 h for the next day or two after which prednisone 1 mg/kg is substituted or no greater than 60 mg daily for 2 days, followed by a drop to 40 mg for the next 3 days. If improvement continues, the patient may be discharged from the hospital with a prednisone taper.
- Do not use sedative drugs unless the patient is on a ventilator. If the patient has a large psychosomatic component to his/her asthma and sedative drugs are deemed necessary, use small doses and observe closely in an ICU.
- Keep the patient well hydrated.

Subcutaneously administered epinephrine or terbutaline sulphate has no advantage over inhaled beta-agonists. Subcutaneous therapy should be considered, however, in patients not responding to inhaled beta-agonists. Similarly, the available data do not support the routine use of intravenous beta-agonists in the treatment of patients with severe asthma [6, 7]. Several studies have demonstrated inhaled therapy to be equal to or better than intravenous therapy in treating airflow obstruction, and less likely to cause cardiac toxicity. However, intravenous beta-agonists may be considered in patients who have not responded to inhaled therapy and have life-threatening disease.

Other Therapeutic Options

- Leukotriene antagonists. Despite limited data leukotriene antagonists should be considered in patients who have responded poorly to initial therapy. In a randomized trial patients with asthma and a FEV1 $\leq$50 % predicted were randomized to intravenous montelukast 7 mg (n = 291) or placebo (n = 292) in addition to standard care [8]. Montelukast significantly increased FEV1 at 60 min postdose. Similar improvements in FEV1 were seen at all-time points. Patients treated with montelukast tended to receive less ß2-agonists and have fewer treatment failures than patients receiving placebo. Intravenous montelukast is not available in the US, however oral montelukast is rapidly absorbed and should therefore be considered in patients with SA. Zafirlukast has been shown to reduce the need for hospitalization among patients with acute exacerbation [9].
- Theophylline is not recommended and has not been shown to be beneficial in the emergency department setting [10]. A Cochrane review demonstrated that the use of intravenous aminophylline did not result in significant additional bronchodilation compared to standard care with inhaled β-2 agonist in patients experiencing an asthma exacerbation in the ED setting, or in a significant reduction in the risk of hospital admission. For every 100 people treated with aminophylline an additional 20 people had vomiting and 15 people arrhythmias or palpitations. No subgroup in which aminophylline might be effective was identified [11].

- Subcutaneous epinephrine 0.3–0.5 mL (1:1,000) can be administered every 20 min to a maximum of three doses. Terbutaline can be administered subcutaneously (0.25–0.5 mg) and is the preferred treatment in pregnant females. Epinephrine should be avoided in patients with a history of ischemic heart disease and/or hypertension.
- Heliox is a blend of helium and oxygen (80:20, 70:30, or 60:40) with a gas density approximately one third that of air. In normal subjects Heliox reduces airway resistance (Raw) by about 40 % and increases maximum expiratory flows by about 50 %. Heliox may be useful in buying time and avoiding intubation in acute attacks of asthma. In mechanically ventilated patients with severe asthma, Heliox (60:40) has been demonstrated to reduce peak inspiratory pressure and $PaCO_2$ by up to 50 %.
- Mechanically ventilated patients with severe bronchospasm in whom mechanical ventilation has become extremely difficult (cannot get air in or out) may benefit from enflurane anesthesia. This procedure should only be performed in the operating room by an experienced anesthesiologist.
- Intravenous and inhaled magnesium has no proven benefit in acute severe asthma [12, 13].

Complications of Acute Asthma

- Pneumothorax
- Pneumomediastinum, pneumopericardium
- Myocardial infarction
- Mucous plugging
- Atelectasis
- Theophylline toxicity
- Lactic acidosis
- Myopathy

Noninvasive Positive-Pressure Ventilation in Status Asthmaticus

Patients with severe asthma have a significant increase in both inspiratory and expiratory indexes of airway obstruction and considerable dynamic compliance. Inspiratory muscle failure and increased physiologic dead space lead to ventilatory failure. Endotracheal intubation is associated with a high rate of complications and results in increased airway resistance. In patients with COPD with acute respiratory failure noninvasive positive pressure ventilation (NPPV) has been demonstrated to

be very effective in reducing the work of breathing, improving oxygenation and reducing the need for intubation. Several studies have demonstrated that in severe asthma mask continuous positive airway pressure (CPAP) causes:

- bronchodilation and decreases airway resistance
- reexpands atelectasis and promotes removal of secretions
- rests the diaphragm and inspiratory muscles and may offset intrinsic positive end-expiratory pressure (iPEEP), and
- decreases the adverse hemodynamic effects of large negative peak and mean inspiratory pleural pressures.

Meduri et al. have demonstrated that NPPV can safely be applied to patients with severe asthma and hypercarbia whose condition has failed to improve with aggressive medical management [14]. In their series only 2 of 17 patients required intubation. Similarly, Fernandez described the successful use of NPPV in 19 of 22 patients with status asthmatics; the remaining three patients required mechanical ventilation. Soroksky et al, in a prospective, randomized, placebo-controlled study, compared 15 patients with status asthmatics who received NIPPV plus conventional therapy vs conventional therapy alone. The use of NIPPV significantly improved lung function and decreased hospitalization rate. Beers et al reported that BiPAP was safe and well tolerated in pediatric patients with SA [15]. It may be reasonable to try NPPV before intubation in alert cooperative patients. NPPV should not be attempted in patients who are rapidly deteriorating or are somnolent or confused.

Indications for Intubation

Endotracheal intubation is not curative, is associated with significant morbidity, and can increase the degree of airway narrowing and inflammation. The timing of intubation is essentially one of clinical judgment. A high $PaCO_2$ in itself is not an indication for intubation if the patient is alert and cooperative and the arterial pH >7.2. The following are indications for intubation and mechanical ventilation:

- Altered consciousness
- PaO_2 <50 mmHg on a rebreathing mask
- Rising $PaCO_2$ with a falling pH
- Anaphylactic asthma with rapidly deteriorating clinical course
- Patient fatigue

Intubating an asthmatic patient can be extremely difficult and should be performed by an operator with extensive experience in upper airway management. It should be remembered that it may be impossible to ventilate a severe asthmatic with an Ambubag (air will follow the path of least resistance and go into the stomach). Orotracheal intubation will invariably require rapid-sequence anesthesia.

Sedation Post-intubation

Sedation is invariably required post-intubation as the settings required to achieve hypoventilation are not tolerated by awake and alert patients. In the past paralytics were often administered to facilitate synchronization of the asthmatic with the mechanical ventilator, to avoid excessive hyperinflation, to facilitate permissive hypercapnea, and to decrease respiratory muscle activity. However, numerous studies have indicated an unacceptable incidence of pot-paralytic myopathy in patients with asthma who have respiratory failure [16]. In most cases, the myopathy is reversible but may take weeks to resolve. This complication is associated with a significant increase in complications as well as length of ICU and hospital stay. Neuromuscular blockers should therefore be avoided in patients with asthma at all costs. The combination of propofol and fentanyl is suggested to avoid the use of paralytic agents. Propofol has the additional advantage of having bronchodilator properties [17].

Mechanical Ventilation

Mechanical ventilation may precipitate cardiorespiratory collapse in patients with severe asthma. Causative factors are pulmonary hyperinflation, hypovolemia, and sedation [14]. In the post-intubation period, dangerous levels of pulmonary hyperinflation can develop if patients are "bagged" excessively in a misguided attempt to stabilize or resuscitate the patient. With severe airflow obstruction, even delivery of a normal minute ventilation may cause substantial gas trapping that reduces venous return and hence cardiac output. Concomitantly, hypovolemia related to previous dehydration, sedation, and muscle relaxation all act to decrease mean systemic vascular pressure, further decreasing venous return to the heart.

Mechanical ventilation of patients with severe asthma is fraught with difficulties. Severe airflow obstruction results in a prolonged expiratory time with incomplete exhalation even at low ventilator rates. This results in progressive dynamic hyperinflation and the development of auto-PEEP (iPEEP), until a new equilibrium is reached at some volume above functional residual capacity (FRC). This equilibrium occurs because increasing lung volume increases both the lung elastic recoil pressure driving expiratory flow and reduced airway resistance by expansion of the small airways in parallel with lung volume. If large tidal volumes and rates are used, significant iPEEP will develop. iPEEP acts as an inspiratory threshold load and contributes to the increased work of breathing. Furthermore, iPEEP may be associated with severe hemodynamic compromise. These effects are compounded by the fact that the minute ventilation required for normocapnia is increased to approximately 16 ± 3 L/min in patients with severe asthma. These changes will result in increased morbidity and mortality if patients are ventilated to achieve normocapnia.

The use of PEEP (extrinsic PEEP) in patients with asthma is controversial. PEEP has been demonstrated to reduce the work of breathing and dyspnea in patients with severe COPD and acute respiratory failure. Because flow is limited in the small airways, low levels of pressure applied downstream from the compression site may alter its anatomic location without causing a proportional rise in alveolar pressure. PEEP that is set at a level below iPEEP might then dilate collapsed or severely narrowed airways, enabling decompression of the alveolar units they serve. In addition, this will narrow the gradient between end-expiratory alveolar pressure (total PEEP) and the pressure in the central airways. This would then reduce the effort required to trigger the ventilator. However, PEEP has been demonstrated to increase lung volumes and alveolar pressures with a concomitant fall in venous return and hypotension. A practical method of identifying those patients who may benefit from PEEP may be to observe the response of the ventilator cycling pressures to small increments of PEEP. If little change in peak dynamic and static cycling pressures occurs after PEEP, then extensive dynamic collapse is unlikely and PEEP may be helpful. The level of PEEP should not be set higher than the level of the original iPEEP. On the other hand, if the cycling pressures increase in direct relationship to the level of applied PEEP, additional hyperinflation will develop.

It is rarely a problem to oxygenate the patient with severe asthma; the problem is one of achieving adequate alveolar ventilation. The goals of ventilatory therapy include the following

- Keep end-inspiratory pressure (plateau) <35 cm H_2O
- Maintain arterial pH >7.2
- Limit iPEEP to <5–10 cm H_2O

Synchronized intermittent mandatory ventilation (SIMV) with no or very low pressure support is recommended. The assist-control ventilation should not be used, because it can lead the patient to generate excessive minute ventilation, resulting in excessive iPEEP. The setting of the inspiratory flow rate remains controversial, with both high and low flow rates being recommended. The weight of evidence appears to favor a high inspiratory flow. However, in patients with severe airways obstruction, a prolonged inspiratory time may be required; a high flow rate will result in excessive pressures in these patients.

Initial Ventilator Settings [18]

- FiO_2 60–80 %
- Respiratory rate of 8–12/min, depending on the degree of airway obstruction
- Peak flow of 80–100 L/min
- Tidal volume of 5–7 mL/kg IBW

The iPEEP and the exhaled tidal volumes must be measured in all patients to avoid significant air trapping… and the flow-time waveforms followed closely. A low I:E ratio (long expiration) should always be used. Permissive hypoventilation

should be used in patients with severe airway obstruction aiming to maintain the arterial pH above 7.20 (if possible). Sodium bicarbonate should be avoided as it is likely to make matters worse (increased intracellular CO_2 and acidosis) due to reduced CO_2 elimination.

- Atelectasis should be treated by chest physiotherapy and airway humidification
- Bronchoscopy is potentially dangerous in intubated asthmatic patients
- Maintain adequate hydration

Paradoxical vocal cord motion disorder (PVCM), also called vocal cord dysfunction, is an important differential diagnosis for asthma [19]. The disorder is often misdiagnosed as asthma leading to unnecessary drug use, very high medical utilization and occasionally tracheal intubation or tracheostomy. Although laryngoscopy is the gold standard for diagnosis of PVCM (during an episode); the diagnosis is usually made based on the clinical features alone. However, it is important to recognize that patients may have both asthma and PVCM, which complicates the management of these very "difficult" patients. Benzodiazepines used to sedate patients and relieve their anxiety, have been shown to be effective in terminating acute symptoms of PVCM. However, it is prudent to confirm normal oxygen saturation and exclude hypercapnia before administering these drugs.

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Chapter 26
Pleural Effusions and Atelectasis

Both pleural effusions and atelectasis are exceeding common in mechanically ventilated patients [1]. While is some patients the diagnosis is clearly obvious, in many it may be difficult to distinguish these two entities apart. Furthermore, both entities may coexist in the same patient (atelectasis over and above "compression atelectasis" caused by the effusion) [1]. Attempting to drain a "pleural effusion" by sticking a needle into an atelectatic lung is a recipe for disaster (potentially fatal bleed). A bedside ultrasound (or chest CT) is recommended in *all circumstances* of suspected atelectasis/pleural effusion excepting for those patients with obvious lobar lung collapse. Drainage of a pleural effusion must always be performed under ultrasound guidance.

Pleural Effusions

Pleural effusions are common and related to:

- Volume overload in the setting of sepsis/SIRS/ALI
- Left sided heart failure
- Chronic critical illness and hypo-proteinemia
- Cirrhosis
- Pneumonia
- Pancreatitis

Pathophysiology

Experimental studies demonstrate that hydrostatic and permeability pulmonary edema are followed by pleural fluid accumulation that comes from the lung interstitium [2–4]. Furthermore there is a good correlation between extravascular lung

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water content and pleural effusion volume. The notion that the major source of hydrostatic effusion is the lung is further supported by clinical studies showing that in patients with chronically elevated hydrostatic pressures, the presence of pleural effusion correlates better with left than right heart filling pressures. These data suggest that the excess fluid exits the lung via the visceral pleura into the pleural space.

Lung collapse associated with pleural effusions may lead to hypoxemia due to ventilation-perfusion mismatch or true shunt. The extent of these abnormalities depends upon the extent of perfusion of the compressed airspace, as determined by local factors such as hypoxic vasoconstriction and vascular compression.

The reduction in lung volume induced by a pleural effusion can be largely attributed to collapse of the dependent portions of the lung most prominent at end expiration. However the change in lung volumes is less than the volume of the pleural effusion and is depended on the compliance of the lungs and chest wall. The more compliant the lung the greater the change in lung FRC; the more compliant the chest wall the greater the thoracic cage adjustment with a smaller impact on lung volume. A number of studies in spontaneously breathing patients with unilateral pleural effusion show a disproportionably small increase in lung volumes after large volume thoracentesis and no or poor relationship between the volume of fluid removed and the increase in lung volume. In mechanically ventilated patients the effect of pleural fluid drainage on lung volumes and gas exchange has been variable, with some studies demonstrating little improvement in PaO_2/FiO_2 while others have demonstrated a significant increase in the PaO_2/FiO_2 ratio [5–7]. The response to fluid drainage may depend on the applied airway pressure. Alveolar pressure generated during the respiratory cycle may not be enough to reopen collapsed lung (see lung recruitment below). Recruitment maneuvers (including Bilevel ventilation) should therefore be considered after drainage of a pleural effusion.

Drainage of Pleural Effusion

Pleural fluid may be drained by either thoracentesis or placement of a small bore catheter (pig-tail catheter) [5–9]. A pig-tail catheter is recommend for large effusions. A pig-tail catheter may also obviate the need to repeated thoracentesis Pleural fluid drainage should always be performed under ultrasound guidance. Ultrasound allows estimation of the size of the effusion [10, 11]; attempts at thoracentesis should be aborted in patients with small effusions (less than 750–1,000 mL). Furthermore ultrasound allows the procedure to be performed safely, particularly in ventilated patients [8, 9, 12]. Not all patients with a pleural effusion require drainage. This should only be considered in patients with a low PaO_2/FiO_2 and in patients who have failed a spontaneous breathing trial. Goligher et al. reviewed 19 observational studies that evaluated pleural fluid drainage in patients undergoing mechanical ventilation [13]. In this study the mean PaO2:FiO2 ratio improved by 18 %. Reported complication rates were low with the pooled risk of post-thoracentesis pneumothorax being 3.4 %.

Hepatic Hydrothorax

Hepatic hydrothorax is defined as the presence of pleural fluid (usually greater than 500 cm^3) in a patient with cirrhosis in the absence of primary cardiac or pulmonary disease. This complication occurs in approximately 6–10 % of patients with advanced cirrhosis and has a predilection for the right hemithorax. The incidence of pleural effusion is much higher with the concomitant presence of ascitic fluid. However, isolated hepatic hydrothorax (usually on the right) may occur. The direct passage of peritoneal fluid via diaphragmatic defects appears to be the most plausible cause in most cases [14]. The composition of the pleural fluid from hepatic hydrothorax, as expected, is similar to that of ascitic fluid and is always transudative.

A diagnostic thoracentesis is indicated in all cases to exclude spontaneous bacterial empyema (SBEM) and other causes including [15]:

- Tuberculosis
- Adenocarcinoma
- Parapneumonic empyema
- Undiagnosed exudates

SBEM is defined as an infection of pre-existing pleural fluid (hydrothorax) in a patient with cirrhosis. The pathogenesis, bacteriology, diagnostic criteria and treatment is similar as that for SBP. Diagnostic criteria include:

- PMN count >500 cells/mm^3
- Or positive culture with PMN >250 cells/mm^3

The treatment of a hepatic hydrothorax is similar to that of ascites; sodium restriction, cautious diuresis and treatment of portal hypertension. However, in most patients this is ineffective and liver transplantation remains the only definitive treatment. Tube thoracostomy (and pig-tail drainage) is considered a contraindication for the treatment of hepatic hydrothorax; this may lead to massive fluid shifts, significant protein and electrolyte losses, hemodynamic compromise and death. A fistulous tract which continues to leak fluid may also develop [14, 16].

Alelectasis

Mechanically ventilated patients have an ineffective cough reflex and are unable to adequately deal with their respiratory sections. Atelectasis is therefore a common problem in these patients. The risk of atelectasis may be increased with the widespread use of a lung protective strategy utilizing low tidal volumes (6 mL/kg IBW) [17]. Atelectasis may worsen hypoxemia through shunting and may predispose to nosocomial pneumonia. Traditionally the treatment of atelectasis in mechanically ventilated patients has centered on chest therapy (slapping, beating and vibrating) and endotracheal suctioning [18]. When this fails, bronchoscopy and/or recruitment maneuvers are attempted [19].

Respiratory Therapy

Respiratory therapy refers to "treatments" provided by the respiratory therapist to aid in lung expansion and mobilizes retained secretions. This includes techniques to loosen and mobilize secretions including saline instillation, endotracheal suctioning and chest clapping/vibration and recruitment (hyperinflation) maneuvers. Manual hyperinflation delivers a large tidal volume breath over a prolonged inspiratory time, followed by an inspiratory hold and a rapid release of pressure [18]. The goal is to stimulate cough and propel mucous cephalad. There is limited data with respect to the efficacy of manual hyperinflation, however, high airway pressure and large lung volumes may produce adverse homodynamic effects and injure the lung via barotrauma and/or volutrauma. Maa and colleagues performed a randomized controlled trial in which ventilated patients with atelectasis were randomized to manual hyperinflations three times a day or to "standard" care [18]. The manual hyperinflation technique used a rate of 8–13 breaths/min for a period of 20 min each session. The manual hyperinflations were performed by a single investigator using a predefined protocol which limited peak airway pressure to 20 cmH_2O. Spontaneous tidal volumes, oxygenation, sputum volume and the chest radiographic score increased in the treatment group whereas these indices remained largely unchanged in the standard care group. The mechanical ventilator can be used to achieve hyperinflation with similar results [20, 21]. This approach may be safer as the inflation volumes and pressures can be preset. High frequency chest wall vibration/compression/oscillation, rib cage compression (or squeezing) and chest wall "clapping/slapping" have been used to loosen and mobilize secretions. There is however no evidence that any of these interventions have any beneficial effects and they are currently not recommended in mechanically ventilated patients [22, 23].

Mucolytics

Dornase alfa, a nebulized recombinant human deoxyribonuclease I (rhDNase), formulation (Pulmozyme; Genentech, South San Francisco, CA) is a safe and noninvasive therapy, which is FDA approved for the treatment of cystic fibrosis patients. Their notoriously thick sputum, rich in neutrophil DNA, becomes less viscous in response to Dornase alfa therapy, resulting in improved lung function. It has therefore been postulated that this agent may have a role in the treatment of mechanically ventilated patients with atelectasis. Zitter et al. performed a RCT of nebulized Dornase vs nebulized placebo given twice daily in mechanically ventilated patients with new onset atelectasis [24]. In this study Dornase alfa did not improve the appearance of atelectasis on chest radiographs, or the "Total Chest X-Ray Score" over the first 5 days of treatment in mechanically ventilated patients. Similarly, there is no evidence that nebulized n-acetylcysteine or other "mucolytics" have any beneficial effect.

Bronchoscopy

Bronchoscopy is a commonly performed treatment of atelectasis, with reports indicating that more than 50 % of bronchoscopies performed in the ICU are for retained secretions and/or atelectasis [25, 26]. However, the utility of fiberoptic bronchoscopy for the treatment of atelectasis is unclear. Olopade and Prakesh reviewed the experience at the Mayo Clinic over a 4 year period from 1985 to 1988 [26]. During this period 90 fiberoptic bronchoscopies were performed for atelectasis and retained secretions, with only 17 (19 %) of patients demonstrating an improvement in oxygenation or radiographic changes following the procedure. Stevens and colleagues reported their experience with 297 fiberoptic bronchoscopies in 223 ICU patients [27]. Of the 118 patients in whom FOB was performed for atelectasis 93 (79 %) showed an improvement in aeration on examination, oxygenation, or chest radiographic appearance. However, of the 70 patients in whom bronchoscopy was performed for retained secretions, only 31 (44 %) improved following the procedure. Marini and colleagues, in the only randomized controlled study reported to date, compared an aggressive chest therapy regimen with that of fiberoptic bronchoscopy in 31 patients with acute lobar atelectasis [19]. Forty-three percent of the patients in this study were intubated at the time of treatment. Chest therapy was performed 4 hourly in both groups and included deep breathing (non-intubated patients) or manual inflations and endotracheal suctioning, as well as nebulization and chest percussion. In this study, approximately 65 % of the volume loss on the chest radiograph was restored by 24 h (and 80 % at 48 h) with no difference between groups (ventilated, bronchoscopy vs. chest therapy and non-ventilated, bronchoscopy vs. chest therapy).

Bilevel/APRV

Non-invasive modes of ventilation which provide positive pressure including, continuous positive airway pressure (CPAP), bilevel positive airway pressure and pressure support ventilation have been used successfully in surgical patients to both prevent [23, 28, 29] and treat [30] postoperative atelectasis. We have demonstrated APRV (Bilevel ventilation) to be very effective in re-expanding atelectatic lung in patients who have failed traditional approaches [31]. We use a Pressure-high of 20–25 cm H_2O, a pressure–low of 5 cm H_2O, and a time-low of 1–1.4 s. Although recruitment maneuvers may be effective in improving gas exchange and compliance, these effects are not sustained; APRV may be viewed as a nearly continuous recruitment maneuver. Ventilation modes such as APRV are likely to be more successful than conventional recruitment maneuvers as they provide a more gradual and prolonged recruitment of alveoli. We believe that endotracheal suctioning and APRV may be the preferred approach to the recruitment of collapsed lung in intubated patients.

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Chapter 27
Venous Thromboembolic Disease: DVT and PE

Deep venous thrombosis (DVT) and pulmonary emboli (PE) are usually considered the same disease, namely, ***thromboembolic disease*** (TED), as a large proportion of patients with DVT have "asymptomatic" PE and about 40 % of patients with PE have "asymptomatic DVT". Furthermore, in most instances the treatment is the same. TED is a common disorder that carries a high mortality rate. In a population based study performed in Canada, Tagalakis and colleagues reported an incidence of venous thromboembolism of 0.90 per 1,000 person-years; the 30-day and 1-year case-fatality rates were 10.6 % and 23.0 % respectively [1]. The 1-year survival rate was 47 % in patients with cancer, 93 % in patients with unprovoked venous thromboembolism and 84 % in patients with venous thromboembolism secondary to a major risk factor. In this study 62 % of cases were associated with a major risk factor, with cancer, hospitalization, and surgery being the most common. In the International Cooperative Pulmonary Embolism Registry (ICOPER), all-cause mortality rate at 3 month was 17 % [2]. PE was considered to be the cause of death in 45 % of patients. Important prognostic factors associated with death from pulmonary embolism were age older than 70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, systolic arterial hypotension, tachypnea, and right ventricular hypokinesis on echocardiography.

Pregnancy, Venous Thromboembolism and Thrombophilias

TED is one of the leading causes of maternal morbidity and mortality. The incidence of VTE is estimated at 0.76–1.72 per 1,000 pregnancies [3, 4] In the United Kingdom, VTE accounts for a third of all maternal deaths [5, 6]. In women of reproductive age, over half of all TED thrombotic events are related to pregnancy [7]. The risk of venous thrombotic events is increased fivefold during pregnancy and 60-fold in the first 3 months after delivery compared with non-pregnant women [7]. Similarly the risk of PE is increased two fold during pregnancy and up to 30-fold in the

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Table 27.1 Estimated prevalence rates for congenital thrombophilia and the risk (odds ratio) of thromboembolism during pregnancy in a European population [10–12]

Thrombophilic defect	Prevalence (%)	OR (95 % CI)
Factor V Leiden heterozygous	2–7	8.3 (5.4–12.7)
Factor V Leiden homozygous	0.5–0.25	34.4 (9.9–120.1)
Prothrombin G20210A heterozygous	2	6.8 (2.5–18.8)
Prothrombin G20210A homozygous	Rare	26.4 (1.24–559.3)
Antithrombin deficiency (<80 % activity)	0.02–0.55	4.7 (1.3–16.9)
Protein C deficiency (<75 % activity)	0.2–0.33	4.8 (2.2–10.6)
Protein S deficiency (<65 % activity)	0.03–0.13	3.2 (1.5–6.9)
Methyltetrahydrofolate reductase mutation (homozygous)	–	0.74 (0.22–2.48)
Antiphospholipid antibodies	1–8	15.8 (10.9–22.8)

post-partum period [7]. DVTs occur with equal frequency during each trimester. Approximately, one third of pregnancy related DVT and half of pregnancy related PE occur after delivery. Regardless of the type of event, the postpartum period carries the highest daily risk of VTE. Most cases of postpartum DVT occur within the first 4 weeks with the highest number of cases occurring in the second week [7]. However, the risk remains increased for up to 3 months postpartum.

Up to 50 % of cases of VTE in pregnancy are associated with an inherited or acquired thrombophilia [8, 9]. A thrombophilia is defined as a disorder of hemostasis that predisposes an individual to a thrombotic event [10]. The relative prevalence of the inherited thrombophilias is variable and depends upon the population studied (see Table 27.1) [10–12]. Although in combination the described inherited thrombophilias are common (affecting 15 % of Western populations) and underlie approximately 50 % of VTE in pregnancy, VTE complicates only 0.1 % of pregnancies. Therefore, the presence of a thrombophilia alone, even in the context of the hypercoagulable state of pregnancy, does not consistently result in a thrombotic event. This suggests that multiple interacting prothrombic factors are responsible for VTE in pregnant patients.

Site of Venous Thrombosis

Venous thrombosis may involve the lower limb, upper limb, iliac vein and in rare circumstances other veins. Thromboses of the limbs may be further classified as proximal or distal and superficial or deep [13]. The location of the venous thrombosis is critically important, particularly in the lower limb, as it determines the therapeutic approach. It is believed that most lower extremity deep venous thromboses originate in the distal lower limb leg with about a third of these clots extending above the knee into the proximal veins. The risk of PE is high with proximal lower extremity DVT, whereas the risk of PE is believed to be exceedingly low with

isolated lower extremity DVT. It is therefore important to distinguish between a proximal and distal lower extremity DVT (see below). The risk of PE appears to be lower with upper extremity DVT and superficial venous thrombosis of the extremities. The incidence of isolated DVT in the iliac vein is thought to be relatively higher in pregnant women [14, 15].

The Veins of the Lower Limb

In managing patients with lower limb venous thrombosis it is of utmost importance to have a good understanding of the venous system of the lower leg (see Fig. 27.1). A source of ongoing confusion and a "potentially lethal misnomer" is the term "superficial femoral vein" which describes a vein that is not superficial [16]. The femoral vein is contained within the deep muscle compartments bound by the muscle fascia and is a "deep" vein. DVTs above the knee (but including involvement of the popliteal vein) are considered proximal deep venous thromboses of the lower extremity.

Critically ill ICU patients have many factors which increase the risk of DVT. The risk of DVT can be quantified according to the modified Caprini score (see Table 27.2) [17–19]. Using this risk assessment tool most ICU patients fall into the high risk or very high risk group. Consequently ALL ICU patients require DVT prophylaxis (mechanical, pharmacologic, or both) on admission to the ICU. Despite universal guidelines recommending DVT prophylaxis in all ICU patients, in the XPRESS trial only 50 % of the patients were receiving DVT prophylaxis [20]. Ho et al. demonstrated that omission of thromboprophylaxis within the first 24 h of ICU admission was associated with an increased risk of mortality (OR, 1.22; CI 1.15–1.30, $p = 0.001$) [21].

While few head-to-head randomized studies have been performed, sequential compression devices (SCDs), unfractionated heparin (UFH) and low molecular weight heparin (LMWH) appear to be equally effective in reducing the risk of DVT in low to moderate risk patients [22–25]. In high risk patients (orthopedic patients) SCDs appear to be as effective as LMWH in preventing DVTs [26–28]. In high risk patients LMWH and fondaparinux appear to be more effective in preventing *asymptomatic* DVT than UFH [29–31]. The combination of SCDs and LMWH appear to act additively in reducing the risk of DVT [31–33]. Graduated compression stockings, however, appear to have no role in preventing DVT [32]. These data suggest that in high to very high risk patients a combination of pharmacologic prophylaxis (if not contraindicated) together with SCD's are indicated [19]. As is evidenced from Table 27.2 trauma patients are at a very high risk of DVT. LMWH has been demonstrated to be safe and effective in trauma patients and is the approach recommended by the East Surgical Group and the current ACCP guidelines [34, 35]. In trauma patients at high risk of bleeding the placement of a removal IVC filter may be a suitable strategy [36].

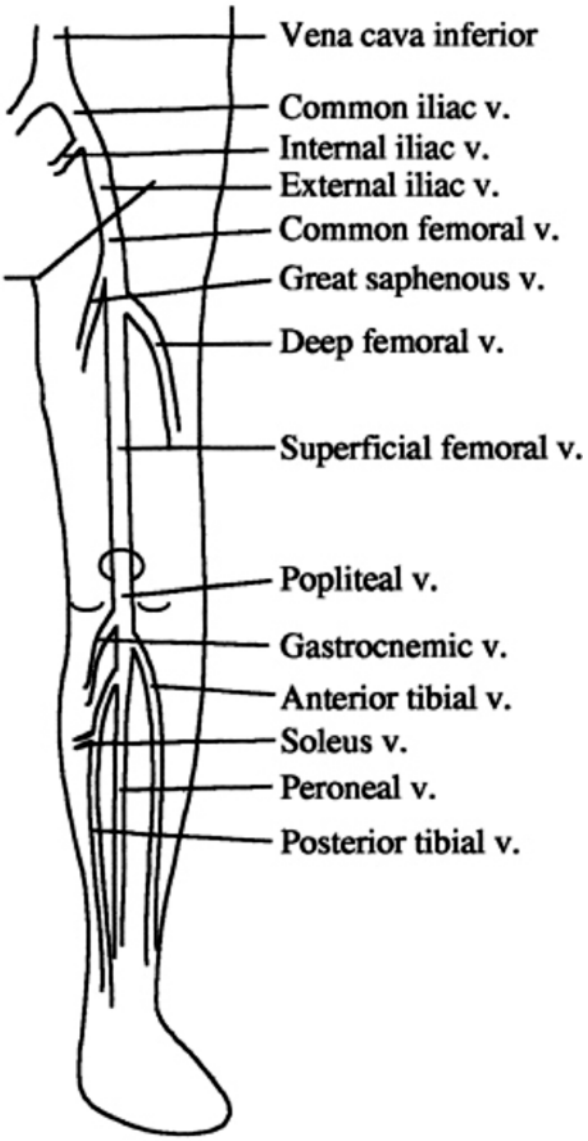

Fig. 27.1 Deep veins of the lower limb

In a meta-analysis comparing any heparin formulation to placebo the risk of DVT and PE was 50 % lower with heparin [37]. Trials testing UFH used only bid dosing. Although there are no direct comparisons of bid versus tid UFH in any population, indirect comparisons suggest that their effects are similar on thrombosis and bleeding. The Canadian Critical Care Trial group performed a multi-center trial, in which they compared dalteparin (a LMWH) to unfractionated heparin (at a dose of 5,000 IU twice daily) in 3,764 patients [22]. There was no significant difference

Table 27.2 Modified Caprini DVT risk assessment score

1 point	2 points	3 points	5 points
Age 41–60	Age 61–74	Age over 75 years	Elective arthroplasty
Minor surgery	Major surgery or laparoscopic surgery (>45 min)	History of VTE	Hip, pelvis or leg fracture
Varicose veins or swollen legs	Arthroscopic surgery	Any thrombophilia	Acute spinal cord injury
Inflammatory bowel disease	Malignancy		Stroke
Obesity (BMI > 25)	Confined to bed >72 h		Multiple trauma
Congestive heart failure	Immobilizing plaster cast		
Sepsis	Central venous access		
Chronic lung disease			
Medical patient at bed rest			
Pregnancy or postpartum			
Oral contraceptive or hormone replacement			

0–1 points low risk, *2 points* moderate risk, *3–4 points* high risk, ≥*5 points* very high risk

between the rates of proximal DVT, which occurred 5.1 % of patients receiving dalteparin versus 5.8 % receiving UH. The proportion of patients with PE was significantly lower with dalteparin (1.3 %) than with UH (2.3 %); the explanation for this finding and its implications are unclear. There was no significant difference in the rates of major bleeding or death in the hospital.

The use of sequential compression devices (SCDs) and graduated compression stockings (GCS) in the prevention of DVT has been controversial. However, as discussed above SCDs appear to be as effective as UF and LMWH in reducing the risk of DVT. In an observational propensity adjusted study Arabi et al. demonstrated that the use of SCDs was associated with a significantly lower VTE incidence compared with no mechanical thromboprophylaxis (RR 0.45; 0.22–0.95; p = 0.04) [38]. In this study GCS were not associated with a lower risk of VTE. Vignon randomized 407 patients with a high risk of bleeding to receive SCDs and GCS or GCS alone for 6 days during their ICU stay [39]. By day 6, the incidence of TED was 5.6 % in the SCD + GCS group and 9.2 % in the GCS group (RR 0.60; CI 0.28–1.28; p = 0.19). Lacut et al. randomized 151 patients who had suffered an intracerebral bleed to SCD + GCS or GCS alone [40]. Asymptomatic DVTs were detected in 4.7 % in the SCD + GCS group and 15.9 % in the GCS group (RR 0.29; CI 0.08–1.00). The CLOTS 3 trial randomized 2,876 immobile patients who had suffered a stroke to SCDs or no SCDs [41]. The primary outcome (DVT in the proximal veins

Table 27.3 Bleeding risk score

Bleeding risk factor	Points
Moderate renal failure, GFR 30–59	1
Male vs. female	1
Age > 40–84	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
ICU/CCU	2.5
Severe renal failure, GFR < 30	2.5
Hepatic failure (INR > 1.5)	2.5
Age ≥ 85	3.5
Platelet count <50	4
Bleeding in the 3 months before admission	4
Active peptic ulcer	4.5

detected on a screening CDU or symptomatic DVT in the proximal veins within 30 days of randomization) occurred in 8.5 % of patients allocated SCD and 12.1 % of patients allocated no SCD; an absolute reduction in risk of 3.6 % (95 % CI 1.4–5.8). The CLOTS 1 study randomized 2,518 patients who had suffered a stroke to thigh-length GCS or no GCS [42]. The primary outcome occurred in 10.0 % patients allocated to thigh-length GCS and in 10.5 % who did not receive GCS. These studies provide robust data that SCD reduce the risk of DVT while GCS do not.

The current *American College of Chest Physicians* (ACCP) guidelines suggest "For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with LMWH, UH bid, UH tid, or fondaparinux (Grade 1B)" [43]. Furthermore, they recommend "For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with SCD. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis" (Grade2B). The reader is referred to the "*American College of Chest Physicians evidence-based clinical practice guidelines on the Prevention of venous thromboembolism (9th Edition)*" for a comprehensive review on this topic [43]. Decousus et al. evaluated the independent risk factors for bleeding in a large cohort of medical patients [44]. These authors then developed a bleeding score risk to quantitate the risk of bleeding (see Table 27.3). Patients with a bleeding risk score ≥7 were at an increased risk of bleeding. While this scoring system has not been independently validated it provides a useful tool to weigh the risks and benefits of pharmacological DVT prophylaxis in medical patients [45].

It is important to note that LMWHs and fondaparinux are renally excreted (and therefore should not be used when GFR < 35 mL/min), will accumulate in renal failure, and that the anticoagulant activity of these drugs are not easily reversed. Prophylactic vena-caval filters have very limited utility for DVT prophylaxis; their

use is associated with significant long term sequela (recurrent DVT and post-phlebitic syndrome). Vena-caval filters are frequently placed in trauma patients, because of the perceived risk of pharmacologic prophylaxis. However, a large randomized clinical trial supports the fact that pharmacologic prophylaxis is both safe and effective in these patients [34]. Furthermore, there are no randomized prospective evaluations of the use of vena-caval filters in this setting.

Despite adequate prophylaxis, DVTs develop in between 5 and 10 % of ICU patients [20, 22, 46]. Furthermore, these DVTs' are frequently "clinically silent". These observations have led to the idea of routinely screening ICU patients for DVT with compression ultrasound. However, an economic and decision analysis by Sud and colleagues concluded that "*appropriate prophylaxis provides better value in terms of costs and health gains than routine screening for deep vein thromboses*" [47]. In this study weekly screening Doppler compression ultrasound cost more than $200,000 per QALY gained.

Suggested DVT Prophylaxis Protocols

- Enoxaparin (or equivalent LMWH) 40 mg SC once daily OR fondaparinux 2.5 mg SC once daily OR UH 5,000 U BID. UH should be avoided in patients at high risk of HIT. See dosing adjustments in Tables 27.4 and 27.5.
- Very high risk for DVT (cancer, paralytics, previous DVT, morbid obesity, etc): Enoxaparin 40 mg SC once daily OR fondaparinux 2.5 mg SC once daily PLUS SCD's
- Reduce dose of Enoxaparin to 30 mg SC once daily with renal impairment
- In patients with renal failure (GFR < 35 mL/min) UFH 5,000 U BID PLUS SCD's
- Neurosurgical patients/Intracerebral hemorrhage: SCD's. Add UFH 5,000 U BID if no hematoma expansion at 48 h.

Diagnosis of DVT

Compression ultrasound (CUS) is a non-invasive test with a sensitivity of 97 % and a specificity of 94 % for the diagnosis of symptomatic, proximal lower extremity DVT in the general population [48]. Compression ultrasound is less accurate for

Table 27.4 Fondaparinux dosing

Fondaparinux dosing (kg)	Prophylaxis	Treatment (mg)
<50	Heparin 500 U SC BID	5
50–100	2.5 mg daily	7.5
>100	2.5 mg daily	10

Table 27.5 Enoxaparin dosing with renal dysfunction and obesity

Indication	Creatinine Cl (mL/min)	Standard dose	Adjust for obesity BMI > 40 kg/m^2 [90, 91]
Prophylaxis Medical	>30	40 mg SC daily	0.5 mg/kg SC daily
	<30	30 mg SC daily	Heparin 5,000 U SC BID + SCDs
	<10	Heparin 5.000 U SC BID	As above
Prophylaxis Surgery	>30	30 mg SC q 12	40 mg SC q 12 + SCDs
	<30	30 mg SC daily	Heparin 5000 U SC BID + SCDs
	<10	Heparin 5,000 U SC q 12	As above
VTE treatment	>30	1 mg/kg SC q 12 or 1.5 mg/kg SC daily	Body Weight <190 kg
			1 mg/kg SC q 12
			Body Weight > 190 kg
			1 mg/kg SC q 12+
			Monitor anti-Xa
			Or heparin infusion
	<30	1 mg/kg SC daily	Heparin infusion
	<10	Heparin infusion	Heparin infusion

isolated calf and iliac vein thrombosis [49]. Magnetic resonance direct thrombus imaging (MRDTI) which has no radiation exposure and is not deleterious to the fetus, has a high sensitivity and specificity for the diagnosis of iliac vein thrombosis [15, 50]. Pulsed Doppler of the iliac vein and CT scanning may be useful for detecting iliac vein thrombosis when MRI is not available [51, 52].

Distal Lower Extremity DVT

The ACCP guidelines suggest; "In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation" [53]. Furthermore, "In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension, we suggest initial anticoagulation" [53]. Anticoagulation is preferable in the immobilized ICU patient, particularly if there is extensive clot burden.

Upper Extremity DVT

Upper extremity DVT (UEDVT) is not uncommon in the ICU. Risk factors include central venous catheters, malignancy, previous lower extremity DVT and inherited disorders of coagulation [54–56]. Malinoski et al. screened 862 surgical and trauma

ICU patients for an UEDVT using duplex ultrasound [57]. In this study 15 % of patients had an UEDVT. The internal jugular vein was the most common site (52 %), 72 % were non-occlusive and 64 % were associated with a central venous catheter. The CVC was removed in 73 of the 79 catheter associated UEDVT. Line removal was associated with a significantly greater occurrence of clot improvement on the follow up duplex. Lamontague and colleagues screened a cohort of 3,746 medical-surgical ICU patients who were receiving pharmacologic thromboprophylaxis for the presence of non-leg DVT (NLDVT) [13]. In this study 2.2 % of patients developed one or more NLDVT. Cancer was the only independent predictor of NLDVT. NLDVT increased the risk of PE (HR 11.83) but did not increase the risk of death. In this study 94.5 % of NLDVT's occurred in the upper extremity.

As is the case with lower extremity DVT most cases of upper extremity DVT are asymptomatic. Presenting features include pain and swelling of the extremity. These features should prompt a Doppler ultrasound examination. Complications of upper extremity DVT include PE and the postthrombotic syndrome [55]. While there are no RCT's to guide the management of this condition, the recommended treatment is anticoagulation with UFH or LWMH followed by 3 months of Coumadin [58]. In patients with a catheter associated UEDVT it is advisable to start anticoagulation before removal of the catheter to limit the risk of clot embolization.

Superficial Phlebitis

Superficial phlebitis refers to the clinical findings of pain, tenderness, induration and/or erythema in one of the superficial veins due to inflammation, infection and/or thrombosis. The term "superficial venous thrombosis" is preferred when the presence of clot is confirmed (by ultrasonography) and the term "superficial phlebitis" in the absence of venous thrombosis. Patients with inherited thrombophilic states have an increased risk of superficial venous thrombosis [59, 60]. In addition, obesity and immobilization increase the risk of superficial venous thrombosis. The differential diagnosis includes DVT, cellulitis, lymphangitis, insect bite and erythema nodosum. Superficial and deep venous thrombosis can occur together because of direct extension of the superficial venous clot into the deep venous system; therefore, all patients with suspected superficial venous thrombosis should undergo CUS examination [61]. Superficial venous thrombosis of the great saphenous vein, particularly when the clot extends to the sapheno-femoral junction, in is associated with an increased risk of DVT [61, 62]. In a large prospective, epidemiologic study, Decousus and coauthors reported that among 844 patients with superficial venous thrombosis 25 % had concomitant DVT or PE [63]. Furthermore, among the 600 patients without DVT or PE at enrollment, 10 % developed thromboembolic complications at 3 months despite the fact that 90 % received anticoagulants.

A systemic review which included 24 studies involving almost 2,500 cases concluded that treatment with LMWH should be considered to prevent thromboembolic events and the extension and/or recurrence of superficial venous thrombosis [64].

This review suggested treatment with an "intermediate dose of LMWH for at least a month." Furthermore, the review concluded that "the optimal dose and duration of anticoagulation requires further investigation and the role of NSAIDS alone or in combination with LMWH remains uncertain" [64, 65]. In patients with thrombosis of the great saphenous vein it may be prudent to repeat CUS before stopping treatment with LMWH.

Pulmonary Embolism

Patients may be admitted to the ICU with hypoxemic respiratory failure with the diagnosis of PE or in whom a PE is suspected. The diagnosis of PE should always be entertained in patients who present to the ICU with hypoxemic respiratory failure in whom the diagnosis is uncertain. In addition, PE may be the cause of a "COPD exacerbation" or worsening heart failure [66]. PE may develop in ICU patients admitted to the ICU for other reasons. In the ICU setting, PE may cause acute episodes of hemodynamic instability or hypoxia and may contribute to failure of weaning from mechanical ventilation. However, in many instances PE is "clinically silent" and unsuspected. Consequently, PE is one of the most common unexpected autopsy findings in the critically ill, being reported in between 7 and 27 % of autopsies [67, 68]. PE is considered massive when it causes hemodynamic compromise (hypotension) and sub-massive when it is associated with tachycardiac and RV dysfunction.

Diagnosis of Pulmonary Embolism

The diagnosis of PE is one of the more challenging dilemmas in clinical medicine. Scoring systems have been used to stratify patients as having a high or low risk venous thromboembolism. For suspected pulmonary embolism, two scores are widely used: the Wells score [69] and the revised Geneva score [70]. The Wells score can be used to diagnose suspected deep vein thrombosis [71]. These scoring system are presented in Tables 27.6, 27.7, and 27.8. These rules have similar predictive accuracy [72]. While an arterial blood gas analysis, electrocardiogram (ECG) and chest radiograph (CXR) should be performed in all patients suspected of having a PE, these tests have a low specificity for the diagnosis of PE. Fibrin D-dimer is a degradation product of cross-linked fibrin, and its concentration increases in patients with acute venous thromboembolism. When assayed by a quantitative ELISA or by automated turbidimetric assays, D-dimer is highly sensitive (more than 95 %) in excluding acute DVT or PE, usually below a threshold of 500 μg/L; i.e. D-dimer has a very high negative predictive value [73]. In elderly patients (50 years and older) a threshold of *age x 10* allows for a larger number of patients to be ruled out for PE with a low likelihood of false negative tests [74]. Compression ultrasonography

Table 27.6 Wells score for DVT

Wells Score for DVT	Points
Cancer	+1
Paralysis or recent plaster cast	+1
Bed rest >3 days or surgery <4 weeks	+1
Pain on palpation of deep veins	+1
Swelling of entire leg	+1
Diameter difference on affected calf > 3 cm	+1
Pitting edema (affected side)	+1
Dilated superficial veins (affected side)	+1
Alternative diagnosis at least as probable as DVT	−2

Score of 0 low risk; 1–2 intermediate risk; ≥3 high risk

Table 27.7 Wells score for PE

Wells Score for PE	Points
Previous PE or DVT	+1.5
Heart rate > 100/min	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3
Hemoptysis	+1
Cancer	+1

Score: 0–1 low risk; 2–6 intermediate risk; and ≥7 high risk

Table 27.8 Revised Geneva Score for PE

Revised Geneva Score for PE	Points
Age > 65	+1
Previous DVT or PE	+3
Surgery or lower limb fracture within 1 month	+2
Active malignancy	+2
Unilateral leg pain	+3
Hemoptysis	+2
Heart rate 75–94/min	+3
Heart rate > 95 beats/min	+5
Pain on deep vein palpation in leg and unilateral edema	+4

Score: 0–1 low risk; 2–6 intermediate risk; and >6 high risk

(CUS) has largely replaced venography as the main imaging procedure to diagnose DVT. Ultrasound has a lower sensitivity and specificity for the detection of calf vein thrombosis than it does for proximal DVT.

Pulmonary angiography has traditionally been considered the gold standard with which to compare other methods, however, angiography is invasive, costly and not

readily available in most hospitals. Ventilation/perfusion scanning (V/Q) currently has a limited role in the diagnosis of PE. While a completely normal V/Q scan rules out a PE and a high probability scan effectively rules in PE, most V/Q scans are of indeterminate probability and neither rule in or rule out a PE. CT pulmonary angiography (CTPA) has largely replaced V/Q lung scintigraphy as the main imaging modality in suspected PE. CTPA has the additional advantage of allowing visualization of the lung parenchyma allowing the formulation of alternative diagnoses. Single detector CTPA has a sensitivity of only about 70 %. Multidetector CTPA is more sensitive than single-detector CT angiography. In the PIOPED II study (conducted between 2001 and 2003) multidetector CTPA had a sensitivity 83 % and a specificity 96 %; this increased to 90 % and 95 % respectively with CT venography (of the lower limbs) [75]. Consequently, CUS of the lower extremities was recommended in patients with a negative CTPA to improve the diagnostic sensitivity. However, more recently the added benefit of CUS with a negative CTPA has been questioned [73]. Righini et al. compared two diagnostic strategies: clinical probability assessment and either D-dimer measurement and CTPA (DD-CT strategy) or D-dimer measurement, CUS and CTPA [76]. In the DD-US-CT strategy, D-dimer was measured only in patients with a low or intermediate clinical probability on the revised Geneva score. In these patients, pulmonary embolism was ruled out by a negative D-dimer test without further testing. When the D-dimer concentration was greater than 500 ng/mL, CUS was performed in both legs, and patients with a proximal DVT were given anticoagulant drugs without further testing. Patients without proximal DVT underwent CTPA and were treated if positive for PE. The DD-CT strategy was similar except that a CUS was not performed. The primary outcome was the 3-month thromboembolic risk in patients who were left untreated on the basis of the exclusion of PE by diagnostic strategy; the primary outcome occurred in 0.3 % in the DD-US-CT group and 0.3 % in the DD-CT group. These data suggest that CUS may not be necessary in all patients with a suspected PE and a negative CTPA. However, it would appear prudent to perform a CUS in those patients who are admitted to hospital and require further diagnostic workup. Isolated subsegmental abnormalities, which are reported in 10–20 % of CTPA's may be due to PE causing symptoms or incidental PE that is not responsible for the patient's symptoms or may be a false positive finding [77]. Consequently, it is uncertain if patients with these findings should be treated. Treatment is generally recommended in those patients with clinical evidence of PE (high D-dimer, etc) and a low risk of bleeding [77].

A V/Q scan is indicated in patients with a dye allergy and those with moderate to severe renal dysfunction. A suggested diagnostic algorithm for patients presenting to the ICU with suspected PE is presented in Fig. 27.2, based on the pre-test probability of PE and the result of the D-dimer assay. A positive CUS usually negates the need for further diagnostic testing (as the patient needs to be anticoagulated anyway) and is the suggested first diagnostic step; additional testing is required in patients who may be candidates for thrombolytic therapy or catheter directed thrombolysis/fragmentation (see below). A D-Dimer has limited diagnostic value in ICU patients; however, a negative D-Dimer (below 500 ng/mL) has a negative predictive value of about 90 %.

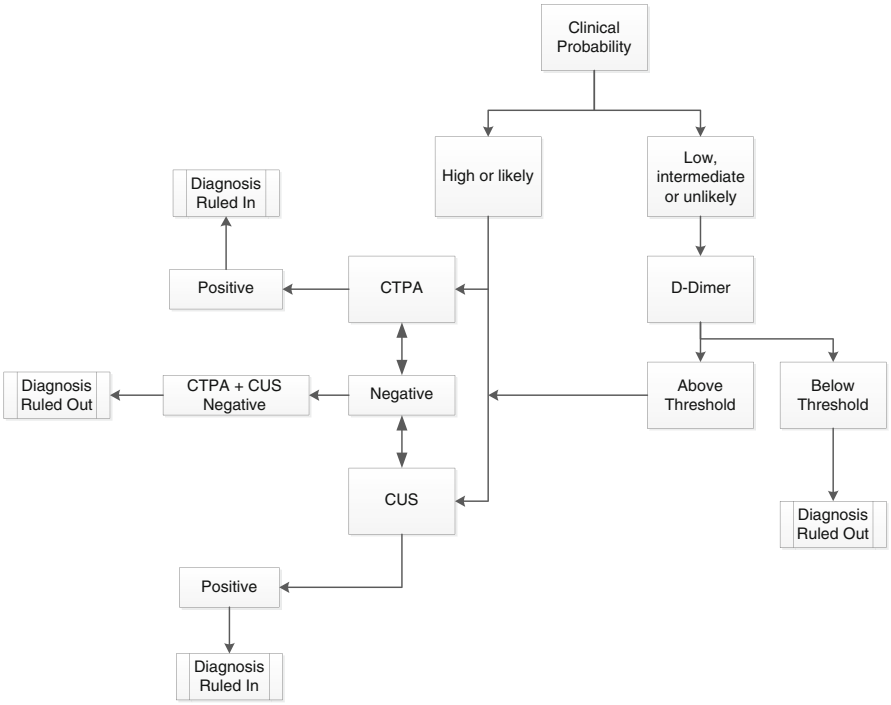

Fig. 27.2 Suggested diagnostic algorithm for DVT/PE

Treatment of Thromboembolic Disease

Patients with PE should be risk stratified according to prognosis. The pulmonary Embolism Severity Index is a useful clinical stratification tool (Table 27.9) [78].

High-risk patients require an urgent ECHO to assess RV function (and ? biomarkers such as BNP and Troponins [79]) and in selected circumstances should be considered for treatment with thrombolytic agents or catheter directed thrombolysis/fragmentation (see below) [73]. Findings of RV dysfunction on ECHO include RV dilatation and hypokinesis, flattening or paradoxical (diastolic) movement of interventricular septum toward the left ventricle, pulmonary hypertension and tricuspid regurgitation. Specific ECHO findings associated with acute PE including McConnell's sign (RV hypokinesis with sparing of apical motion) and the "60/60" sign (pulmonary acceleration time <60 ms in the presence of an echocardiographically derived pulmonary artery pressure <60 mmHg) [80]. RV enlargement with the RV appearing larger than the LV can be detected on the cardiac phase of the CTPA. Data from the ICOPER and French registries have demonstrated that patients with RV dysfunction on ECHO have an increased risk of death [2, 81]. RV function, hypotension and clot burden (on CTPA) are the most important prognostic factors in acute PE.

Table 27.9 Simplified pulmonary embolism severity index according to RIETE [78]

Simplified PE severity index	Points
Age > 80 years	+1
History of cancer	+1
History of heart failure of chronic lung disease	+1
Heart rate >110 /min	+1
Systolic blood pressure <100 mmHg	+1
Arterial saturation <90 % (on room air)	+1

Patients with a score of 0 are low risk those with scores ≥1 are high risk

Immediate anticoagulation with heparin is the treatment of choice in all patients unless heparin is absolutely contra-indicated (see below). Unfractionated heparin (UH) has until recently been considered the treatment of choice. LMWH and fondaparinux are currently considered the agents of choice for the initial treatment for patients with DVT and PE [53]. Meta-analyses have demonstrated that fixed-dose LMWH are at least as effective (if not more effective) and safe as dose-adjusted intravenous unfractionated heparin for the initial treatment of non-massive PE and DVT [82–85]. Furthermore, once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH [86]. Fondaparinux is considered to be at least as efficacious os LMWH [87, 88]. LMWHs and fondaparinux have a number of practical and therapeutic advantages over UH. The advantages of LMWH and fondaparinux include a reduced risk of bleeding, predictable pharmacokinetics allowing weight based dosing without the need for monitoring and reduced risk of HIT. The "disadvantage" of LMWHs and fondaparinux include their long half-life. UFH should be considered in ICU patients who are at risk of bleeding or who will require invasive procedures, as the anticoagulant effects of UFH are much easier to reverse. The following are the standard dosing regimens for DVT and PE [43].

- UFH 80 U/kg IV bolus, 18 U/kg/h infusion; titrated to maintain PTT between 60 and 80s
- Enoxaparin 1 mg/kg every 12 h or 1.5 mg/kg SC daily (see Table 27.4)
- Tinzaparin 175 IU/kg SC daily
- Fondaparinux 5–10 mg daily (see Table 27.9)

In uncomplicated patients with acute VTE, Coumadin should be started on day 1 or 2 of low-LMWH, fondaparinux or UFH therapy rather than waiting for several days to start [43]. For patients treated with Coumadin a therapeutic INR range of 2.0–3.0 is recommended. In ventilated ICU patients it may be preferable to delay the initiation of Coumadin until the patient is weaned from mechanical ventilation. Patients with cancer should be treated for at least 3 months with LMWH rather than with vitamin K antagonists [73, 89]. Several new "novel" oral anticoagulant drugs (NOAC's) have been developed that may replace vitamin K antagonists and heparins in the treatment of patients with TED. These include direct inhibitors of FXa

Table 27.10 Novel oral anti-coagulants (NOAC's) for the treatment of acute thromboembolism

	AMPLIFY [92]		EINSTEIN [93]		RECOVER [94]	
Drug	Apixaban	Enoxaparin-Coumadin	Rivaroxaban	Enoxaparin-Coumadin	UH/LMWH Dabigatran	UH/LMWH Coumadin
Dose	10 mg 7 days	INR adjusted	15 mg BID 3 weeks	INR adjusted	Heparin 9 days	INR adjusted
	5 mg OD		20 mg OD		150 mg BID	
Duration (months)	6	6	3, 6, 12	3, 6, 12	6	6
Recurrent VTE (%)	2.3	2.7	2.1	3	2.4	2.1
Major Bleeds (%)	0.6	1.8	0.8	1.2	1.6	1.9
Cost/day[a]	$16 then $8	pennies	$16 then $8	pennies	$8	pennies

[a]Cost in the US July 2014

(e.g., rivaroxaban, apixaban) or thrombin (e.g., dabigatran). These drugs are administered in fixed doses, do not need coagulation monitoring in the laboratory, and have very few drug–drug or drug–food interactions. The specific indications of these newer anticoagulant drugs remain to be determined. These drugs have been used for the acute treatment of thromboembolism (6–12 months) as well as for extended treatment. These drugs are compared in Tables 27.10 and 27.11.

Thrombolytic Therapy

The role of thrombolytic therapy in patients with massive and submassive (intermediate risk) PE is controversial. Although thrombolytic therapy may result in more rapid clot lysis and improvement in right ventricular (RV) function, its clinical benefit has not been clearly established. The major limitation to the use of thrombolytic therapy is the increased risk of intra-cerebral hemorrhage. A meta-analysis (n = 254) published by Wan et al. in 2004 demonstrated that thrombolytic therapy tended to reduce the risk of death in patients with massive PE (OR 0.47; 95 % CI 0.2–1.1) [97]. Based on this very limited data international guidelines from the American College of Chest Physicians and the European Society of Cardiology recommend thrombolytic therapy for patients with massive PE and hemodynamic instability [53, 98]. However, accepting the limitations of registry data, data from the ICOPER registry showed that thrombolysis for massive PE did not reduce mortality or the rate of recurrent PE at 90 days [99]. In the ICOPER registry 3 % of patients who received lytic therapy suffered an intracerebral bleed as compared to 0.3 % treated with other agents [2]. A retrospective cohort study also revealed no difference in

Table 27.11 NOACs' for extended treatment of venous thromboembolism

	RE-MEDY [95]		RE-SONATE [95]		AMPLIFY-EXT [96]			EINSTEIN-EXT [93]	
Drug	Dabig.	Coumadin	Dabig.	Placebo	Apixaban	Apixaban	Placebo	Rivaroxaban	Placebo
Dose	150 BID	INR adjusted	150 BID	–	2.5 mg BID	5 mg BID	–	20 mg OD	–
Duration (months)	6–36	6–36	12	–	12	12	–	6, 12	–
Recurrent VTE (%)	1.8	1.3	0.4	5.6	1.7	1.7	8.8	1.3	7.1
Major bleeds (%)	0.9	1.8	0.3	0	0.2	0.1	0.5	0.7	0

Table 27.12 Pulmonary artery systolic pressures (mmHg) in patients randomized to thrombolytic therapy versus standard care in the MOPPETT trail after a mean follow up of 28 months

	Thrombolysis	Standard Rx	p value
On admission	50 ± 6	51 ± 7	0.4
End of study	28 ± 7	43 ± 6	<0.001

outcomes among patients with massive PE treated with thrombolytics and heparin versus heparin alone [100]. More recently Stein and Matta evaluated the use of thrombolytic therapy in unstable patients discharged from short-stay hospital in the US from 1999 to 2009 using data from the Nationwide Inpatient Sample [101]. In this retrospective cohort study the case fatality attributable to PE was 8.4 % with thrombolytic therapy compared to 42 % with standard care ($p < 0.001$). The mortality was even lower (2.7 %) in those patients treated with thrombolytic therapy and a vena caval filter.

The role of thrombolytic therapy in intermediate risk (submassive) PE is no less controversial. The MOPETT trail investigated the effect of low-dose thrombolysis (50 mg rt-TPA) versus standard therapy on the reduction of pulmonary artery pressures in patients with intermediate risk PE [102]. In this study "moderate PE" was based on clot burden as defined by CTPA findings and not echocardiography. RV enlargement on the initial echocardiogram was noted in only 20 % of patients. The pulmonary artery systolic pressures at a mean of 28 months are presented in Table 27.12. While the pulmonary artery systolic pressures were significantly lower in the thrombolytic group, the clinical implications of this finding are unclear.

Recently the results of the PEITHO study were published [103]. This is the largest and most robust study published to date to investigating the role of thrombolysis in this group of patients [103]. In this randomized, double-blind trial, 1,006 normotensive patients with intermediate-risk PE we randomized to receive tenecteplase plus heparin versus placebo plus heparin. Intermediate risk PE was defined by the presence of RV dysfunction on echocardiography or CT together with myocardial injury as indicated by a positive cardiac troponin I or troponin T. At least one of the following echocardiographic criteria were needed to confirm right ventricular dysfunction: (i) Right ventricular end-diastolic diameter >30 mm (parasternal long-axis or short-axis view); (ii) right-to-left ventricular end-diastolic diameter >0.9 (apical or subcostal four-chamber view); (iii) hypokinesis of the right ventricular free wall (any view); and (iv) tricuspid systolic velocity >2.6 m/s from the apical or subcostal four-chamber view. Patients with a systolic blood pressure <90 mmHg for at least 15 min or the requirement for catecholamines to maintain a systolic blood pressure >90 mmHg were excluded. The 30 day mortality was 2.4 % in the tenecteplase group and 3.2 % in the placebo group ($p = 0.42$). Stroke occurred in 2.4 % in the tenecteplase group and in 0.2 % in the placebo group. Recurrent pulmonary embolism between randomization and day 7 occurred in 0.2 % of the tenecteplase patients compared to 1 % of the placebo group. Major extracranial bleeding tended to occur more commonly in patients over the age of 75 years

Table 27.13 Number need to treat to save one life and the number need to treat to cause one ICH in the PEITHO and Chatterjee studies

	PEITHO	Chatterjee et al.
NNT	161	59
NNH	47	78

(p = 0.09) It should be noted that (only) 4.6 % of patients in the placebo group received open label thrombolytic therapy for hemodynamic instability; this suggests that an expectant approach may be appropriate in intermediate risk patients with thrombolysis reserved for the small percentage who develop hemodynamic compromise [104]. Furthermore, it should be noted that the mean systolic blood pressure and pulse rate were 130 mmHg and 95/min respectively; according to the RIETE score these patients were on average not "high risk" (see Table 27.9). This favorable hemodynamic profile may explain the relatively low mortality of these intermediate risk patients, suggesting that a patients hemodynamic profile may be a better prognostic indicator (and indication for thrombolytic therapy) than the presence of RV dysfunction alone. This suggests that patients with RV dysfunction should be further risk stratify according to the presence or absence of unfavorable hemodynamic signs.

Against the background of the PEITHO study, Chatterjee et al. published a meta-analysis of the use of thrombolytic therapy in PE [105]. The study included 16 trials performed over the last 40 years, using different thrombolytic agents, in different patient populations and using different trial designs (i.e. a high bias meta-analysis better known as a paella meta-analysis; paella is a free-style combination of land animals, seafood, vegetables, and beans—you add a lot of crap into a bowel and see what comes out). The meta-analysis included 2,115, of whom 47.5 % came from the PEITHO study. In this meta-analysis thrombolysis was associated with a lower all cause morality; 2.17 % vs. 3.89 % (OR 0.53; 95 % CI 0.32–0.88). Thrombolysis was associated with a greater risk of ICH 1.46 % vs. 0.19 %; OR 4.63; 95 % CI 1.78–12.04. In the subgroup of patients older than 65 years there was a non-significant association with a lower mortality (OR 0.55; 95 % CI 0.29–1.05); however, there was an association with a greater risk of major bleeds (OR 3.10; 95 % CI 2.1–4.56). In the patients 65 years and younger the risk of major bleeding was not increased with thrombolytic therapy. In the eight trials enrolling patients who were hemodynamically stable with RV dysfunction, thrombolysis was associated with a lower mortality; 1.39 vs. 2.92; OR 0.48, 95 % CI 0.25–0.92. The Number Needed to Treat (NNT) to save one life and the Number Needed to Harm (NNH) to cause one ICH between the PEITHO study and Chatterjee et al. meta-analysis are provided in Table 27.13. This analysis demonstrates a less favorable risk/benefit ratio in the PEITHO study compared to the Chatterjee et al. study.

Thrombolytic therapy should be considered in patients with acute massive PE who are hemodynamically unstable (SBP < 90 mmHg), who have no contraindication to thrombolysis and where catheter directed interventions are not available

(see below). The most recent ACCP guidelines make the following recommendation "*In patients with acute PE associated with hypotension (SBP < 90 mmHg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy* (Grade 2C)" [53]. Wang et al. demonstrated that a 50 mg/2 h TPA infusion resulted in similar efficacy and perhaps better safety than the traditional 100 mg/2 h dosing regimen in patients with acute PE [106]. This dosage regimen may therefore be preferable particularly in high risk patients (age > 65 years). This lower dosing strategy was used in the MOPPETT study. Right heart thromboemboli (large mobile clots in the right atrium) may occur as a complication of venous thromboembolism [107, 108]. This condition carries a high mortality. Retrospective cohort studies suggest an improved outcome with thrombolytic therapy in patients with right heart thrombi [107, 108].

Thrombolytic treatment in patients with acute sub-massive PE (echocardiographic evidence of RV dysfunction without hypotension) appears to offer limited survival benefit but may prevent clinical deterioration and the need for escalation of care. It would be appropriate to observe these patients in the ICU and offer thrombolytic therapy to those when develop hemodynamic compromise [104]. Alternatively it may be appropriate to further risk stratify this group and consider thrombolytic therapy in the "higher" risk patients with abnormal hemodynamics but without overt hypotension (see Fig. 27.3).

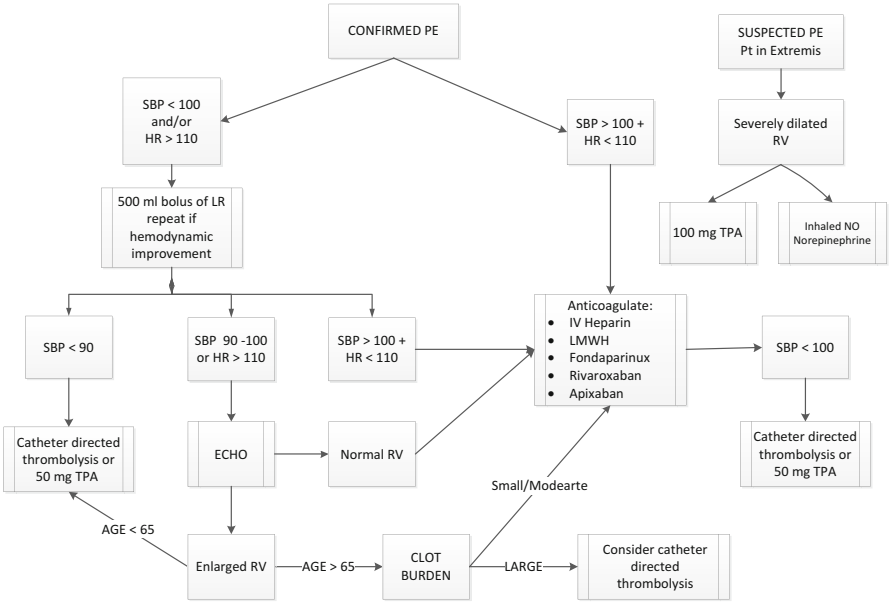

Fig. 27.3 Proposed treatment algorithm for pulmonary embolism

Catheter Directed Clot Fragmentation and Aspiration

Due to the disappointing results with systemic thrombolytic therapy alternative techniques have emerged. In patients with massive and sub-massive PE, catheter directed clot fragmentation and aspiration may be a viable alternative to systemic thrombolysis in centers that have the expertise to perform this procedure [109–115]. In patients with massive PE pulmonary vascular pressure increases with an elevation of RV afterload, leading to RV dilation and ultimately RV failure. Progressive RV failure leads to reduced forward cardiac output and is the cause of death from acute PE in most cases. Rapid restoration of the pulmonary artery blood flow can improve pulmonary perfusion, reduce pulmonary pressure, and prevent cardiac failure. Mechanical techniques and direct catheter directed thrombolysis will result in much more rapid clot dissolution than systemic thrombolysis potentially allowing the salvage of patients who would otherwise have died. A number of percutaneous catheter-tipped interventional techniques are available which attempt to restore pulmonary blood flow, including aspiration thrombectomy, fragmentation thrombectomy and rheolytic thrombectomy and a hybrid combination of these techniques [109–115]. Catheter directed mechanical thrombectomy/thrombolysis as the primary treatment of massive and submassive PE has been demonstrated to have a high rate of technical and clinical success in high-risk patients [109–117]. The most recent innovation is the EkoSonic Endovascular System (EKOS, Bothell, WA). This system utilizes an ultrasound-accelerated catheter directed thrombolytic treatment (USAT) strategy that emits low-intensity, high-frequency ultrasound that dissociates fibrin strands without causing thrombus fragmentation [116, 117]. In vitro studies have demonstrated that vascular blood clots dissolve more rapidly when exposed to the combination of ultrasound and a thrombolytic agent [118–120]. A small RCT demonstrated that this approach was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 h, without an increase in bleeding complications [121]. Although very promising, large multicenter outcome studies are required to determine the role of these techniques in the management of patients with massive and sub-massive PE.

Inhaled Nitric Oxide

Inhaled Nitric Oxide (iNO) has been shown to preferentially lower resistance in the pulmonary vasculature. The relative selectiveness of iNO in accomplishing this effect makes it an attractive drug to administer as salvage therapy in patients with acute right ventricular failure secondary to PE. iNO has been was used as a temporizing agent to decrease right ventricular after-load following massive near-fatal pulmonary embolism [122].

Vena Caval Interruption

No randomized controlled trial has been conducted which has compared heparin to vena caval interruption (alone) in the management of thromboembolic disease. However, the available evidence suggests that venal caval interruption is associated with a higher incidence of complications; particularly recurrent DVT and post-phlebitic syndrome [123]. Because of "presumed contraindications" to heparin, vena-caval filters have become commonplace for the primary and secondary prevention of pulmonary embolism. This is in spite of a lack of data on the relative safety and efficacy of venal caval interruption as compared with anticoagulant therapy [123]. Furthermore, most of the presumed contraindications have never been subject to rigorous analysis to determine whether they are associated with a worse outcome than those treated with vena caval interruption. For example intracranial neoplasms have been considered an "absolute" contraindication to anticoagulation. However, studies have suggested a high complication rate with IVC filters in these patients. Furthermore, in this patient population, anticoagulation is well tolerated, is associated with a low risk of intracerebral bleeding (if excessive anticoagulation is avoided) and results in a better quality of life than an IVC filter [114].

"Absolute Contraindications" for Anticoagulation with Heparin

- recent intracerebral bleed (2–3 weeks)
- recent significant gastro-intestinal bleeding (2 weeks)
- patients with heparin associated thrombocytopenia; these patients can be treated with direct thrombin inhibitors which do not cross react with heparin

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Part III
Cardiac

Chapter 28
Hypertensive Crises

Hypertensive emergencies and hypertensive urgencies (see definitions below) are commonly encountered by a wide variety of clinicians. It is estimated that 1–2 % of patients with hypertension will develop a hypertensive crises at some point in their lifespan. The epidemiology of hypertensive emergencies parallels the distribution of essential hypertension with a higher incidence among the elderly and African-Americans [1, 2]. Prompt recognition, evaluation and appropriate treatment of these conditions are crucial to prevent permanent end organ damage.

Definitions

The classification and approach to hypertension undergoes periodic review by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure with the most recent report (JNC 8) having been released in 2014 [3]. This most recent report is quite controversial and unlike previous reports did not provide a classification of hypertension. The previous report published in 2003 (JNC 7) recognized two stages of hypertension (compared to the previous four stages in JNC 6), namely, Stage 1 with a Systolic BP (SBP) of 140–159 and a diastolic BP (DBP) of 90–99 and Stage II hypertension with a SBP $\geq$ 160 or a DBP $\geq$ 100 mmHg [4]. Although not specifically addressed in the JNC 7 report, patients with a systolic blood pressure of greater than 179 mmHg or a diastolic that is greater than 109 mmHg are usually defined as having a "hypertensive crisis". The 1993 report of the JNC proposed an operational classification of hypertensive crises as either "hypertensive emergencies" or "hypertensive urgencies" [5]. This classification remains useful today. Severe elevations in BP were classified as:

- *Hypertensive emergencies* in the presence of acute end-organ damage or
- *Hypertensive urgencies* in the absence of acute target-organ involvement.

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Distinguishing hypertensive urgencies from emergencies is critically important in formulating a therapeutic plan. Patients with hypertensive urgency should have their BP reduced within 24–48 h (with PO medication), whereas patients with hypertensive emergencies should have their blood pressure lowered immediately (in the ICU), although not to "normal" levels. The term "malignant hypertension" has been used to describe a syndrome characterized by elevated BP accompanied by encephalopathy or acute nephropathy. This term, however, has been removed from National and International Blood Pressure Control guidelines and is best referred to as a hypertensive emergency.

Hypertensive urgencies are treated with oral antihypertensive agents usually on an outpatient basis

Hypertensive emergencies are treated in the ICU with a rapidly acting, titratable, intravenous antihypertensive agent

The vast majority of patients presenting with a hypertensive emergency to an emergency department (ED) have previously been diagnosed with HTN and have been prescribed antihypertensive agents [6, 7]. However, in many of these patients BP control prior to presentation was inadequate [7]. The lack of a primary care physician as well as the failure to adhere to prescribed antihypertensive regimens has been associated with the development of a hypertensive emergency [6, 8]. In the prospective study by Saguner and colleagues, female sex, high grades of obesity, coronary artery disease and non-adherence to medications were associated with hypertensive crisis [9]. In both major metropolitan areas and smaller communities, illicit drug use has been reported to be a major risk factor for the development of hypertensive emergencies [8].

The Studying the Treatment of Acute hypertension (STAT) is a 25-institution US registry of 1,588 patients with severe acute hypertension enrolled between January 2007 and April 2008 who were treated with intravenous therapy [10]. The mean age of the patients was 53 years, 49 % were women and 56 % were African American with a median admission BP of 200/100 mmHg. In the STAT registry the hospital mortality was 6.9 % with an aggregate 90-day mortality of 11 % and a 90-day readmission rate of 37 %.

Pathophysiology

The factors leading to the severe and rapid elevation of BP in patients with hypertensive emergencies are poorly understood. The rapidity of onset suggests a triggering factor superimposed on pre-existing hypertension. Hypertensive emergencies are thought to be initiated by an abrupt increase in systemic vascular resistance likely related to humoral vasoconstrictors [11]. The subsequent increase in BP generates mechanical stress and endothelial injury leading to increased permeability, activation of the coagulation cascade and platelets, and deposition of fibrin (See Fig. 28.1). With severe elevations of BP, endothelial injury and fibrinoid necrosis of the arterioles ensue. This process results in ischemia and the release of additional

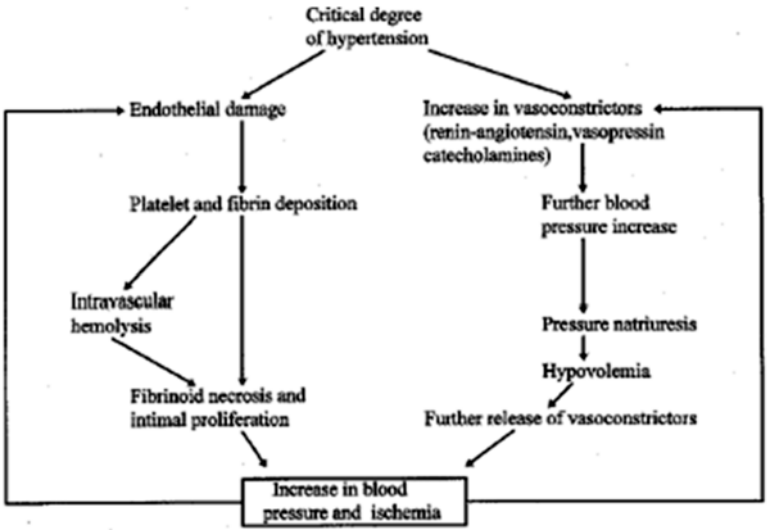

Fig. 28.1 Proposed pathophysiology of hypertensive emergency

vaso-active mediators generating a vicious cycle of on-going injury. The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifests as a hypertensive emergency.

Clinical Presentation

The clinical manifestations of a hypertensive emergency are directly related to the particular end-organ dysfunction that has occurred, and includes:

- Hypertensive encephalopathy (and PRES)
- Acute aortic dissection
- Acute myocardial infarction
- Acute coronary syndrome
- Pulmonary edema with respiratory failure
- Severe pre-eclampsia, HELLP syndrome, eclampsia
- Microangiopathic hemolytic anemia
- Acute postoperative hypertension

The signs and symptoms of a hypertensive crisis vary from patient to patient. In the STAT registry the most common presenting symptoms included shortness of breath (29 %), chest pain (26 %), headache (23 %) altered mental status (20 %) and focal neurologic deficit (11 %) [10]. Microangiopathic hemolysis has been reported

in up to 27 % of patients presenting with a hypertensive crisis [12]. It is important to make this diagnosis as it is usually associated with reversible renal insufficiency. No particular BP threshold has been associated with the development of a hypertensive emergency. However, organ dysfunction is uncommon with a DBP less than 130 mmHg (except in children and pregnancy) [13]. The absolute level of BP may not be as important as the rate of increase [14–16]. For example, in patients with long-standing hypertension, SBP of 200 mmHg or a DBP up to 150 mmHg may be well tolerated without the development of hypertensive encephalopathy, whereas in children and pregnant women encephalopathy may develop with a DBP of only 100 mmHg [17].

Initial Evaluation

Patients with hypertensive emergency usually present for evaluation as a result of a new symptom complex related to their elevated BP. Patient triage and physician evaluation should proceed expeditiously to prevent ongoing end organ damage.

A focused medical history should include:

- History of hypertension, previous control, current anti-hypertensive medications with dosing, compliance, and time from last dose
- The use of any prescribed or over-the-counter medications
- Use of recreational drugs (amphetamines, cocaine, phencyclidine) or monoamine oxidase inhibitors should be made.

Physical examination should:

- Confirm the elevated BP by measuring the BP in *both* arms with an adequately sized cuff.
  - The appropriate size cuff is particularly important as the use of a cuff too small for the arm size has been shown to artificially elevate BP readings in obese patients.
- Identify evidence of end-organ damage by assessing
  - pulses in all extremities
  - auscultating the lungs for evidence of pulmonary edema, the heart for murmurs or gallops and the renal arteries for bruits and
  - perform a focused neurologic and funduscopic examination.

Headache and altered level of consciousness are the usual manifestations of hypertensive encephalopathy. Focal neurological findings, especially lateralizing signs, are uncommon in hypertensive encephalopathy being more suggestive of a cerebrovascular accident. Subarachnoid hemorrhage should be considered in patients with a sudden onset of a severe headache. The ocular exam may show evidence of advanced retinopathy with arteriolar changes, exudates, hemorrhages or papilledema assisting in the identification of hypertensive encephalopathy.

Cardiac evaluation should aim to identify angina or myocardial infarction with the focus on clarifying any atypical symptoms such as dyspnea, cough, or fatigue that may be overlooked. Severe renal injury may result in hematuria or oliguria. On the basis of this evaluation, the clinician should be able to distinguish between a hypertensive emergency or an urgency and to formulate the subsequent plan for further diagnostic tests and treatment.

Initial objective evaluation should include:

- A metabolic panel to assess electrolytes, creatinine and blood urea nitrogen
- A complete blood count (and smear if microangiopathic hemolytic anemia is suspected)
- A urinalysis to look for proteinuria or microscopic hematuria,
- An electrocardiogram to assess for cardiac ischemia
- Radiographic studies such as a chest radiograph in a patient with cardiopulmonary symptoms or a head computed tomography scan in a patient with neurologic symptoms should be obtained in the appropriate clinical scenario
- If the physical examination or clinical picture is consistent with aortic dissection (severe chest pain, unequal pulses, widened mediastinum), a contrast computed tomography scan of the chest should be obtained promptly to rule out aortic dissection. Although trans-esophageal echocardiography has excellent sensitivity and specificity for aortic dissection, this study should not be performed until adequate blood control has been achieved.
- In patients presenting with pulmonary edema it is important to obtain an echocardiogram to distinguish between diastolic dysfunction, transient systolic dysfunction or mitral regurgitation. Many patients, particularly the elderly, have a normal ejection fraction and in such patients heart failure is due to isolated diastolic dysfunction. The management these patients differs from those patients with predominant systolic dysfunction and those with transient mitral regurgitation.

Initial Management of Blood Pressure

The majority of patients in whom severe hypertension (SBP > 160, DBP > 110 mmHg) is identified on initial evaluation will have no evidence of acute end-organ damage and thus have a *hypertensive urgency*. Since no acute end-organ damage is present, these patients may present for evaluation of another complaint and the elevated BP may represent an acute recognition of chronic hypertension. In these patients, oral medications to lower the BP gradually over 24–48 h is the best approach to management [11]. Rapid reduction of BP may be associated with significant morbidity in hypertensive urgency due to a rightward shift in the pressure/flow auto-regulatory curve in critical arterial beds (cerebral, coronary, renal) (see Fig. 28.2). Rapid correction of severely elevated BP below the autoregulatory range of these vascular beds can result in marked reduction in perfusion causing ischemia and infarction.

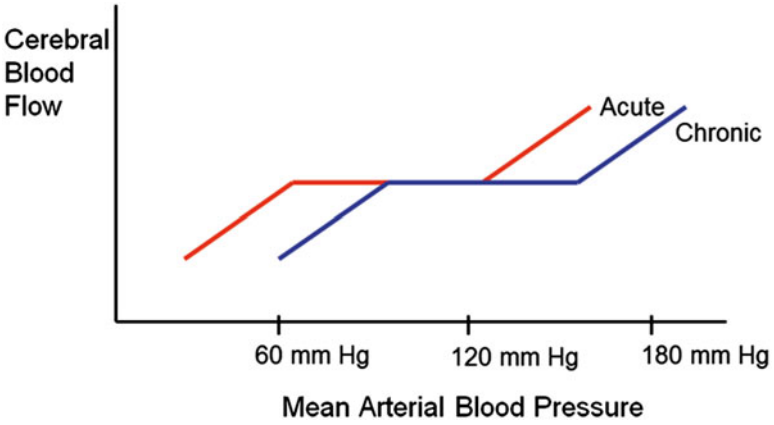

Fig. 28.2 The autoregulatory range is shifted to the right in chronic hypertension. Overzealous BP reduction below the autoregulatory rang eof the brain, heart or kidney will predictably result in organ infarction

Therefore, although the BP must be reduced in these patients, it must be lowered in a slow and controlled fashion to prevent organ hypoperfusion.

Patients with hypertensive urgency should NOT receive intravenous antihypertensive agents. If you feel compelled to treat with an IV agent give yourself or the bed-side nurse some Ativan!

Resident (or Hospitalist) Called to the Floor for High Blood Pressure: What to Do?

- Check BP yourself (in both arms with an adequately sized cuff)
- Review chart
  - Hx of HTN, CAD, drug or alcohol use
  - Current anti-HTN meds

- Examine patient
- Hypertensive EMERGENCY—call ICU
- Hypertensive urgency
  - Treatable causes of high BP
    Pain, anxiety, distended bladder, hypothermia, hypoxic, volume depletion, drug or alcohol withdrawal
  - Calm and reassure nurse
  - PO anti-HTN medication: metoprolol, lisinopril, etc

Altered autoregulation also occurs in patients with hypertensive emergencies and since end-organ damage is already present, rapid and excessive correction of the BP can further reduce perfusion and propagate further injury. Therefore, patients with a hypertensive emergency are best managed with a *continuous infusion of a short-acting, titratable antihypertensive agent*. Due to unpredictable pharmacodynamics, the sublingual and intramuscular route should be avoided. Patients with a hypertensive emergency should be managed in an ICU with close monitoring. For those patients with the most severe clinical manifestations or with the most labile BP, intra-arterial BP monitoring may be prudent. There are a variety of rapid-acting intravenous agents that are available for use in patients with hypertensive emergency; the agent of choice depends on the organ system involved (see Table 28.1):

Table 28.1 Preferred antihypertensive agents for hypertensive emergency

Condition	Preferred agents
Acute pulmonary edema-systolic dysfunction	Nicardipine or clevidipine in combination with nitroglycerin and a loop diuretic
Acute pulmonary edema-diastolic dysfunction	Esmolol, metoprolol, labetalol or verapamil in combination with low dose nitroglycerin and loop diuretic
Acute myocardial ischemia	Esmolol or labetalol in combination with nitroglycerin
Hypertensive encephalopathy and PRESS	Nicardipine, clevidipine or labetalol
Acute aortic dissection	Labetalol or combination of nicardipine and esmolol or nitroprusside with esmolol/metoprolol
Eclampsia	Labetalol or nicardipine
Acute renal failure/microangiopathic hemolytic anemia	Nicardipine or clevidipine
Sympathetic crisis/cocaine	Verapamil, diltiazem, nicardipine or clevidipine in combination with benzodiazepine
Acute postoperative hypertension	Esmolol, labetalol, clevidipine or nicardipine
Ischemic stroke (SBP > 200)	Nicardipine, clevidipine or labetalol
Hemorrhagic stroke (SBP > 140)	Nicardipine, clevidipine or labetalol

Management Principles of Hypertensive Emergency

- Admission to ICU
- Controlled reduction of BP to limit further organ damage using a continuous infusion of *titratable, short-acting intravenous antihypertensive agent*
- NO PLACE for S/L or IM route
- 15 % reduction in DBP or to 110 mmHg over 1 h
  - aortic dissection 10 min
    Type A—Surgery
    Type B—SBP < 140 mmHg
- Must set a target BP range
- After first hour, further gradual reduction to lower BP by 25 % over 24 h
- Volume depleted—IV crystalloids (except pulmonary edema)

Rapid-acting intravenous agents should not be used outside of a monitored ICU setting to prevent precipitous falls of BP which may cause significant morbidity or mortality. The immediate goal is to reduce DBP by 10–15 % or to about 110 mmHg over a period of 30–60 min. In aortic dissection, this goal should be achieved within 5–10 min. Once there is stable BP control with intravenous agents and end-organ damage has ceased, oral therapy can be initiated as the intravenous agents are slowly titrated down. An important consideration prior to initiating intravenous therapy is to assess the patient's volume status. Due to pressure natriuresis, patients with hypertensive emergencies may be volume depleted and restoration of intravascular volume with intravenous saline will serve to restore organ perfusion and prevent a precipitous fall in BP when anti-hypertensive regimens are initiated.

Drugs to AVOID

- ACE inhibitors are long acting and poorly titratable; however, this agent may be useful in the management of hypertensive urgencies.
- Clonidine. A relic from the past.
- Hydralazine is a direct acting vasodilator. Following intramuscular or intravenous administration there is an initial latent period of 5–15 min followed by a progressive and often precipitous fall in BP that can last up to 12 h. Although hydralazine's circulating half-life is only about 3 h, the half-time of its effect on BP is about 10 h. Because of hydralazine's prolonged and unpredictable anti-hypertensive effects and the inability to effectively titrate the drugs' hypotensive effect, hydralazine SHOULD BE AVOIDED in the management of hypertensive crises.
- Sublingual and intranasal nifedipine may cause a precipitous drop in blood pressure with cerebral and myocardial infarction, renal failure and death. These complications are best avoided and therefore this approach to BP control is strongly "discouraged".

- Furosemide, is a no-no. Volume depletion is common in patients with hypertensive crises and the administration of a diuretic together with a hypertensive agent can lead to a precipitous drop in BP. Diuretics should be avoided unless specifically indicated for volume overload as occurs in renal parenchymal disease or coexisting pulmonary edema.
- Nitroglycerin is a potent venodilator and only at high doses affects arterial tone. It causes hypotension and reflex tachycardia which are exacerbated by the volume depletion characteristic of hypertensive emergencies. Nitroglycerin reduces BP by reducing preload and cardiac output; undesirable effects in patients with compromised cerebral and renal perfusion. Low dose (≤60 mg/min) nitroglycerin may, however, be used as an adjunct to intravenous anti-hypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary edema.
- Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload. Nitroprusside decreases cerebral blood flow while increasing intracranial pressure, effects that are particularly disadvantageous in patients with hypertensive encephalopathy or following a cerebrovascular accident. Nitroprusside is a very potent agent, with an onset of action of seconds, a duration of action of one-to-two minutes and a plasma half-life of three to four minutes. Nitroprusside is a *toxic drug*. Data suggests that nitroprusside infusion rates in excess of 4 μg/kg/min, for as little as 2–3 h, may lead to cyanide levels which are in the toxic range [18]. The usual "recommended" dose of nitroprusside of up to 10 μg/kg/min results in cyanide formation at a far greater rate than human beings can detoxify. Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other intravenous anti-hypertensive agents are not available and then only in specific clinical circumstances and in patients with normal renal and hepatic function. The duration of treatment should be as short as possible and the infusion rate should not exceed 2 μg/kg/min.

Recommended Antihypertensive Agents

The pharmacokinetics and dosages of the recommended intravenous antihypertensive agents are listed below and summarized in Table 28.2.

- Labetalol is a combined selective α-1 and non-selective β-adrenergic receptor blocker with an α- to β-blocking ratio of 1:7. The hypotensive effect of labetalol begins within 2–5 min after its intravenous administration, reaching a peak at 5–15 min following administration, and lasting for about 2–4 h. Due to its β-blocking effects the heart rate is either maintained or slightly reduced. Unlike pure β-adrenergic blocking agents which decrease cardiac output, labetalol maintains cardiac output. Labetalol may be given as loading dose of 20 mg, followed by repeated incremental doses of 20–80 mg given at 10 min intervals until the desired BP is achieved. Alternatively, after the initial load-

Table 28.2 Dosing and pharmaco-kinetics of the most commonly used intravenous anti-hypertensive agents

	Medications	Dosage	Onset	Duration	Adverse effects
Beta Blockers	Esmolol	*Bolus:* 500 mcg/kg	60 s	10–20 min	• Bradycardia
		Continuous: 25–300 mcg/kg/min			
		Titration: Increase by 50 mcg/kg/min every 4 min			
	Labetalol	*Bolus:* 10–20 mg, double dose at 10 min intervals to max of 80 mg	2–5 min	2–6 h	• Bradycardia
		Continuous: 2–10 mg/min			
		Titration: Increase by 1 mg/min every 10 min			
	Metoprolol	*Bolus:* 2.5–20 mg	20 min	3–4 h	• Bradycardia
Calcium Channel Blockers	Clevidipine	*Continuous:* 1–21 mg/h (max due to lipid restriction)	2–4 min	5–15 min	• Reflex tachycardia
		Titration: Double rate every 90 s until close to goal, then increase rate 5–10 min			• Acute renal failure
	Diltiazem	*Bolus:* 0.25–0.35 mg/kg	1–3 min	1–3 h	• Bradycardia
		Continuous: 5–20 mg/h			
	Nicardipine	*Continuous:* 2.5–15 mg/h	5–15 min	4–6 h	• Tachycardia
		Titration: Increase by 2.5 mg/h every 5–15 min			• Local Phlebitis
	Verapamil	*Bolus:* 0.075–0.15 mg/kg	3–5 min	0.5–6 h	• Bradycardia
Vasodilators	Enalaprilat	*Bolus:* 1.25–5 mg every 6 h	0.5–4 h	6 h	• Variable response
		Give over 5 min			
	Nitroglycerin	*Continuous:* 10–200 mcg/min	2–5 min	10–20 min	• Tachyphylaxis
		Titration: Increase by 5–10 mcg/min every 5–10 min			• Reflex tachycardia
	Sodium Nitroprusside	*Continuous:* 1–4 mcg/kg/min	3 s	1–2 min	• Tachyphylaxis
		Titration: Increase by 0.25–0.5 mcg/kg/min every 2–3 min			• Muscle twitching

Table 28.3 Characteristics of the intravenous calcium channel blocking agents

Compound	Coronary vasodilatation	Suppression of cardiac contractility	Suppression of SA node	Suppression of Av node	Systemic vasodilatation
Verapamil	++++	++++	+++++	+++++	+
Diltiazem	+++	++	+++++	++++	0
Nicardipine	+++++	0	+	0	++++
Clevidipine					

Note: The relative effects are ranked from no effect (0) to most prominent (+++++)

ing dose, an infusion commencing at 1–2 mg/min and titrated up to until the desired hypotensive effect is achieved is particularly effective. Bolus injections of 1–2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided. FDA approved maximal daily dose is 300 mg.

- Nicardipine is a second generation dihydropyridine derivative calcium channel blocker with high vascular selectivity and strong cerebral and coronary vasodilatory activity (see Table 28.3). The onset of action of intravenous nicardipine is between 5 and 15 min with a duration of action of 4–6 h. Nicardipine' s dosage is independent of the patient's weight, with an initial infusion rate of 2.5 mg/h, increasing by 2.5 mg/h every 5–10 min to a maximum of 15 mg/h until the desired BP reduction is achieved.
- Clevidipine is third generation dihydropyridine calcium channel blocker that has been developed for use in clinical settings where tight BP control is crucial. Clevidipine is an ultra-short acting selective arteriolar vasodilator (see Table 28.3). Similar to esmolol, it is rapidly metabolized by red blood cell esterases, thus its metabolism is not affected by renal or hepatic function. The starting diose is 2 mg/h which is doubled every 3 min up to a dose of 32 mg/h until control is achieved. Clevidipine has proven particularly useful in the management of peri-operative hypertension.
- Esmolol is an ultra-short-acting cardioselective, β-adrenergic blocking agent. The onset of action of this agent is within 60 s with a duration of action of 10–20 min. Typically, the drug is given as a 0.5–1 mg/kg loading dose over one minute, followed by an infusion starting at 50 μg/kg/min and increasing up to 300 μg/kg/min as necessary.

Acute Postoperative Hypertension

Acute postoperative hypertension (APH) has been defined as a significant elevation in BP during the immediate postoperative period that may lead to serious neurologic, cardiovascular or surgical-site complications and that requires urgent management. While APH is widely recognized, there is no standardized definition to define this disorder. We consider an increase in the SBP by more than 20 % or an increase in the DBP to above 110 mm/Hg to be indicative of APH [19]. APH usually

develops within 2 h of surgery and resolves within a few hours. The complications associated with APH include myocardial ischemia, myocardial infarction, cardiac arrhythmias, congestive cardiac failure with pulmonary edema as well as hemorrhagic stroke, cerebral ischemia and encephalopathy. APH will increase bleeding at the surgical site and compromise vascular anastomoses. The pathophysiologic mechanism underlying APH is uncertain and may vary with the surgical procedure and other factors. However, the final common pathway leading to hypertension appears to be activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in patients with APH. The primary hemodynamic alteration observed in APH is an increase in afterload with an increase in SBP and DBP with or without tachycardia. Although APH may occur following any major surgery, it is most commonly associated with cardio-thoracic, vascular, head and neck, and neurosurgical procedures.

In cardiac surgery patients treatment is usually suggested for a BP > 140/90 mmHg or a MAP > 105 mmHg. In these patients meticulous blood pressure control is recommended. In the non-cardiac surgery patient there is no consensus regarding the treatment threshold. Treatment of these patients is usually a clinical decision based on the degree of blood pressure elevation, the nature of the surgery, the patients' comorbidities and the risks of treatment.

Pain and anxiety are common contributors to BP elevations and should be treated before administration of antihypertensive therapy. The patients' volume status should be carefully assessed. Intravascular volume depletion will increase sympathetic activity and increase vasoconstriction; in this setting a volume challenge should be considered. Other potentially reversible causes of APH include hypothermia with shivering, hypoxemia, hypercarbia and bladder distension.

Short-term administration of a short acting intravenous agent is recommended when there is no identifiable treatable cause of hypertension. As increased sympathetic activity underlies the pathophysiology of APH, an alpha/beta blocker or β-blocker alone would appear to be a rational agent to use. The short acting intravenous calcium channel blocking agents also have a role. Labetalol, esmolol, nicardipine and clevidipine are generally considered the agents for choice for the treatment of APH. Several trials have shown clevidipine to be very effective in the control of postoperative hypertension [20]. The recently completed ECLIPSE trial demonstrated the efficacy and safety of this agent in the treatment of APH [21]. ECLIPSE randomized 1,964 cardiac patients who required treatment for perioperative hypertension to clevidipine or a comparator agent (nitroprusside or nicardipine). Clevidipine was more effective than nitroprusside in controlling BP, with a lower mortality (1.7 versus 4.7 %; $p = 0.045$) with similar efficacy and safety to nicardipine.

Pre-operative Hypertension

Although preoperative hypertension has been found to be a significant predictor of postoperative morbidity no data has definitively established that preoperative treatment of hypertension reduces postoperative complications. However, ideally, all

patients with cardiovascular risk factors undergoing elective surgery should undergo aggressive preoperative optimization, including control of blood pressure, correction of electrolytes, glucose control, cessation of smoking and nutritional optimization (in high risk patients). Hypertensive patients should continue to receive all their antihypertensive drugs preoperatively, except for ACE inhibitors (ACEI) and angiotensin II receptor antagonists (ARA). ACEI's and ARA's should be discontinued at least 10 h before surgery

Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES) first described by Hinchey and colleagues in 1996, is a *clinico-neuro-radiological entity* characterized by headache, vomiting, altered mental status, blurred vision and seizures with neuroimaging studies demonstrating white-gray matter edema involving predominantly the posterior region of the brain [22]. PRES is most commonly associated with pre-eclampsia, hypertensive encephalopathy and immunosuppressive/cytotoxic drugs [23–27]. One of the distinctive characteristics of PRES is the reversibility of the clinical and radiological abnormalities once treatment is instituted. Most patients usually make a complete recovery within few weeks. A delay in the recognition and treatment of the syndrome may result in permanent neurological sequela. The exact pathogenesis of PRES remains incompletely understood but is probably related to the failure cerebral autoregulation and endothelial damage. The favored pathogenetic theory suggests autoregulatory disturbance with hyperperfusion, resulting in blood–brain barrier breakdown with reversible edema, without infarction [23]. In particular, in conditions accompanied by high blood pressure (e.g., hypertensive encephalopathy) it has been suggested that the increased systemic pressure exceeds the autoregulatory mechanisms of the cerebral vasculature, sufficient to overcome the blood–brain barrier, and hence allowing extravasation of fluid and blood into the brain parenchyma.

Computed tomography (CT) scan findings are negative in almost all cases of PRES and when positive, it is difficult to distinguish between PRES and acute stroke. Therefore the image study of choice is the magnetic resonance image (MRI) [23–26]. The most common MRI findings are those of bilateral edema in the white matter of posterior portions of the brain, particularly occipital and parietal areas. Other area may also be involved including the postfrontal cortical, subcortical white matter, cortex, brainstem, basal ganglia and cerebellum. Covarrubias et al. reported that the occipitoparietal areas were involved in 100 % of the cases of with involvement of anterior structures (i.e., temporal and frontal lobes) in more than 80 % [28].

Pregnancy-Induced PRES

Pre-eclampsia is the commonest cause of PRES. Patients may present with PRES post-partum without the classic pre-eclamptic signs [23, 27]. Furthermore, status epilepticus has been reported to occur in these patients.

Drugs Associated with PRES

A number of drugs have been implicated in the causation of PRES, including: [23]

- Cyclosporin
- Tacrolimus
- Sirolimus
- Oxaliplatin
- Bevacizumab (a recombinant humanized monoclonal antibody)
- Sunitinib (a tyrosine kinase inhibitor)
- Gemcitabine (a pyrimidine nucleoside analogue)

Management

It is important to treat patients with PRES as soon as the condition is recognized to avoid the risk of irreversible brain injury. The treatment of PRES includes the following:

- Removal/significant reduction in the causative factors/medications
- Delivery or cesarean section in pregnant women
- Lowering of blood pressure, with not more than 15–20 % reduction within the first hour
- Treatment of status epilepticus
  - Lorazepam 0.1 mg/kg over 2–5 min
  - Pregnant women: magnesium sulfate

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Chapter 29
Acute Decompensated Cardiac Failure

Heart failure (HF) is a serious condition affecting an estimated two million Americans and is a common reason for hospitalization. The prognosis of patients admitted to hospital with HF is poor with up to 64 % being re-admitted within the first 90 days after discharge and with a 1 year mortality approximating 20 % [1]. HF can present in patients without previously recognized cardiac dysfunction or as the acute decompensation of chronic congestive HF. Acute Decompensated Heart Failure (ADHF) refers broadly to new or worsening of signs and symptoms of HF that is progressing rapidly, whereby unscheduled medical care or hospital evaluation is necessary. A number of national registries have been developed in the last few decades which have provided invaluable epidemiological and clinical information to help guide the management of patients with ADHF. Currently the total number of patients in the Acute Decompensated Heart Failure National Registry (ADHERE), [2] the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) [3] and the EuroHeart Failure Survey (EHFS) [4] exceeds 250,000. The mean age of the patients in these registries is around 72 years with 50 % being women. Evidence of mild or no impairment of systolic function was found in approximately 45 % of patients. The most common co-morbid conditions were hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD) and diabetes. In-hospital mortality was approximately 4 % and the median hospital length of stay was 4.5 days.

Patients presenting with an acute deterioration of cardiac function are often admitted to the ICU. These patients are likely to benefit from treatment. However, patients with “end-stage” cardiac failure whose condition has progressed slowly and inexorably despite maximal medical therapy are poor candidates for admission to the ICU, unless they are candidates for cardiac transplantation or have suffered from an acute medical complication. The following patients with cardiac failure may benefit from admission to an ICU:

- Worsening pulmonary edema with acute respiratory failure
- Acute myocardial ischemia

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- Acute hemodynamic compromise due to arrhythmias
- Severe complicating disease e.g. pneumonia

Confirm the Diagnosis of Cardiac Failure

An important priority in the management of patients with suspected ADHF is to confirm the diagnosis as well as to establish the presence of co-morbidities and precipitating medical factors. Once the diagnosis of HF has been established the causative factors should be established (i.e. ischemic heart disease, diabetes, hypertension, etc) as well the determination of whether the patient has HF with systolic dysfunction or heart failure with preserved systolic function. In the ADHERE Registry dyspnea occurred in about 89 % of all patients presenting with cardiac failure [5]. Dyspnea on exertion was the most sensitive symptom and paroxysmal nocturnal dyspnea the most the most specific (positive likelihood ratio 2.6). However, many other diseases may cause symptoms that mimic cardiac failure. Dyspnea can be caused by a wide range of conditions. It may be particularly difficult to distinguish dyspnea caused by HF from that caused by chronic respiratory diseases (such as COPD), and in many patients both conditions may coexist [6]. Wuerz and Meador compared the outcome of patients with suspected HF who received pre-hospital treatment with furosemide, morphine and nitroglycerine versus those given no medications [7]. In this study, the patients with asthma, COPD, pneumonia or bronchitis who were erroneously diagnosed with and treated for HF had as a higher than expected mortality. It is important to recognize that ADHF occurs due to left ventricular (LV) dysfunction whereas cor-pulmonale is a manifestation of right ventricular failure due to pulmonary hypertension. Both conditions may present with dyspnea, an elevated jugular venous pressure (JVP) and peripheral edema. However the management of these conditions is vastly different and cor-pulmonale should not be diagnosed or treated as "heart failure."

Physical examination has a low accuracy for diagnosing HF [8–10]. While widely considered a reliable sign of volume overload [11, 12], the JVP is a "measure" of right atrial pressure and provides no useful clinical information about left ventricular function or intravascular volume status [13, 14]. An elevated JVP has a very low sensitivity for the diagnosis of HF (0.22) [10]. Patients with severe chronic HF frequently lack pulmonary rales on examination or alveolar edema on chest radiograph despite high pulmonary venous pressure. This observation is explained by reduced pulmonary microvascular permeability as well as increased lymphatic flow in these patients. Furthermore, rales do not distinguish between a cardiac and respiratory cause of dyspnea [9]. Patients with peripheral edema may be inappropriately diagnosed as having HF when there is another cause for the edema [11]. Mueller and colleagues reported the sensitivity and specificity of rales for the diagnosis of HF to be 0.599 and 0.672, while those for lower extremity edema were 0.46 and 0.76 respectively [10]. This information suggests that physical examina-

tion alone has limited utility in the evaluation of patients presenting to the ED or a physician's office with dyspnea and in establishing the diagnosis of HF. However, in patients with established HF, hypotension (SBP < 90 mmHg) is an important clinical sign which is associated with a low cardiac output state and which carries a poor prognosis [15].

Evaluation of the Patient with Cardiac Failure

B-Type Natriuretic Peptides

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are useful biomarkers to assist in the diagnosis of heart failure. BNP belongs to the natriuretic peptide family, which also includes atrial natriuretic peptide, C-type natriuretic peptide, and urodilantin. Although present in the human brain, BNP is mainly synthesized and secreted by ventricular myocardium. Myocardial wall stress is the most important stimulus for increased synthesis and secretion of BNP. It is released into the circulation as a pro-hormone and cleaved into the biologically active 32 amino acid BNP and the biologically inactive 76 amino acid NT-proBNP. The half-life of BNP is 20 min whereas NT-proBNP has a half-life of 120 min, which explains why NT-proBNP serum values are approximately six times higher than BNP values, even though both molecules are released in equimolar proportions [16, 17].

A large number of studies have demonstrated that BNP and NTproBNP are elevated in patients with heart failure, and the values were found to be related to disease severity as assessed by New York Heart Association (NYHA) functional class, left ventricular ejection fraction, and left ventricular diastolic function [16, 17]. In the Breath Not Properly (BNP) trial 1,586 patients presenting to the emergency department with shortness of breath were investigated [18]. The main finding of this study was that BNP testing provided high test accuracy for the detection of heart failure, being superior to clinical judgement. At a cut-off value of 100 pg/mL BNP had a very high negative predictive value, thus making it especially applicable as a rule-out test for heart failure in this setting. Thus, the particular strength of these markers is their ability to rule out the diagnosis of heart failure. In general, heart failure is unlikely at BNP values < 100 pg/mL and is very likely at BNP values > 500 pg/mL. Independent of their diagnostic value, several large scale studies have shown that BNP and NT-proBNP provide strong prognostic information for an unfavorable outcome (death, cardiovascular death, readmission or cardiac events) in patients with heart failure or asymptomatic left ventricular dysfunction [19].

It should be appreciated that acute right ventricular failure as occurs with acute pulmonary embolism and acute cor pulmonale (ARDS etc) will result in increased BNP and NT-PROBNP levels [20, 21]. BNP levels therefore have little utility in distinguishing cardiogenic from non-cardiogenic pulmonary edema [21].

Echocardiography

Assessment of LV function is a critical step in the evaluation and management of patients with HF. With limited training, ED physicians, hospitalists, critical care physicians and medical residents can become competent in performing a focused, goal-directed echocardiographic (ECHO) examination at the time of presentation [22–25]. An immediate ECHO at the bedside makes it possible to visualize dilatation of the heart chambers, diffuse or regional abnormalities in contraction, functional mitral regurgitation as well as LV hypertrophy. The bedside ECHO examination should allow the clinician to rapidly assess LV function and make the distinction between HF due to systolic versus diastolic dysfunction. Once therapy has been initiated all patients with HF should undergo a complete formal ECHO examination, unless this investigation or angiography has been performed recently (within the last few months). ECHO can accurately assess systolic function, ejection fraction and detect wall motion abnormalities while tissue Doppler can accurately quantitate the degree of diastolic dysfunction. Doppler Quantitative assessment of left ventricular function is important in patients with systolic heart failure as the EF is the most important predictor of the 5 year survival rate in these patients.

Laboratory Testing

Laboratory testing should include serum electrolytes and a complete blood count. In the ADHERE registry, a serum urea nitrogen (BUN) of greater than 43 mg/dL was the single best predictor for in hospital mortality, with a systolic blood pressure of less than 115 mmHg being second, and a creatinine of 2.75 mg/dL being third [5]. A high BUN is a poor prognostic marker in cardiac failure; this is often a consequence of over-diuresis and/or the cardio-renal syndrome (see below). Hyponatremia in a patient with cardiac failure is a sign of failing circulatory homeostasis and is associated with longer length of stay and higher in-hospital and early postdischarge mortality [26]. Anemia is also a poor prognostic marker [27].

Hemodynamic Monitoring

Invasive hemodynamic monitoring in cardiac failure has come under close scrutiny, and its value has been questioned, especially after the results of the ESCAPE trial [28] In this study, patients were randomized to routine care or treatment guided by a PAC. In-hospital adverse events were more common among patients in the PAC group, however, there were no significant differences in 30-day mortality or clinical outcomes or adverse events at 6 months between the two groups of patients. This study, in keeping with the general critical care literature has demonstrated the PAC to be of limited clinical utility [29].

Precipitating Factors

It is important to determine the precipitating factor(s) that have led to a deterioration of cardiac function. The most important include:

- myocardial ischemia
- poorly controlled hypertension
- arrhythmias, particularly atrial arrhythmias
- poor compliance with medication
- drug reactions/side effects
- fluid overload due to deterioration of renal function
- anemia
- intercurrent illness, particularly infections (pneumonia)

Treatment

The treatment of ADHF involves both rapid relief of symptoms and treatment of pulmonary edema, hemodynamic stabilization, management of comorbidities and precipitating factors and initiation of long-term therapy.

Acute Phase of Treatment

While the management and outcome of patients with chronic systolic heart failure has improved in recent years largely due to a number of large well conducted RCT's, the management of ADHF remains problematic with few evidence based interventions available. Indeed, emerging data suggests that the "conventional" therapeutic interventions for ADHF including morphine, high dose furosemide and inotropic agents may be harmful. The treated of ADHF centers on the use of nitroglycerin, oxygen/NIPPV and low dose diuretics.

Oxygen

Patients require supplemental oxygen, this should be titrated by pulse oximetry to target an arterial saturation between 92 and 96 % (see Chap. 17). Strong evidence supports the use of NPPV to treat acute cardiogenic pulmonary edema (see Chap. 20). Positive pressure ventilation is "good for the left ventricle"; it reduces the work of breathing, reduces preload and reduces LV afterload. Both CPAP and BiPAP lower intubation and mortality rates compared to conventional therapy with oxygen [30, 31]. However, CPAP should be considered as the first line intervention as it is as efficacious as BiPAP and CPAP is cheaper and easier to implement in clinical practice [30, 31].

Morphine

Morphine sulfate has long been used to treat ADHF on the basis that it is a potent venodilator with additional anxiolytic properties. However, data from the ADHERE registry suggests that the use of morphine is associated with an increased risk for intubation and is an independent predictor of mortality (OR 4.84) [32]. Based on this data morphine should be avoided in patients with ADHF.

Diuretics

It is important to recognize that patients with "congestive heart failure" have volume overload due to sodium retention primarily as a result of activation of the renin-angiotensin-aldosterone system (RAAS). Agents which improve cardiac performance and renal blood flow, decrease activation of the RAAS and result in a diuresis. Indeed in 1776, William Withering described a patient who was "cured from dropsy" after she self-administered an old cure of a garden plant called foxglove (Digitalis purpurea). Withering conducted experiments in patients with dropsy (congestive heart failure) and showed that foxglove increased urination [33]. It was believed at the time that digitalis was a diuretic which removed "poisons" from the blood stream.

Diuretics have been the mainstay for the treatment of ADHF for the past four decades; indeed these drugs (particularly furosemide) are still widely used and recommended for this indication [11, 34]. The ADHERE study reported that 89 % of patients presented with symptoms of volume overload and that 88 % received intravenous diuretics. However, although patients are volume overloaded with features of "congestion" there is little data to support the use of loop diuretics; indeed high dose furosemide is associated with worse outcomes. It is important to note that loop diuretics are associated with a *fall in GFR*, this may further compromises renal function in patients with cardiac failure. High dose diuretics have a number of adverse effects in patients with heart failure which include:

- Activation of the renin-angiotensin system
- Increased AVP
- Increased heart rate
- Increased norepinephrine levels
- DECREASED GFR
- Increased SVR

It is widely (although incorrectly) believed that diuresis improves cardiac function in patients with congestive cardiac failure. It has been postulated that diuretic induced changes in preload increase ventricular performance by two mechanisms; either by shifting the ventricle to a "more optimal position on the descending limb on the Starling Curve" or by reducing left ventricular size and thereby reducing systolic wall stress (afterload) by the LaPlace effect. However, it has been clearly demonstrated that in the physiological range there is NO descending limb of the left

ventricular stroke volume-pressure curve (Frank-Starlings curve) in the mammalian heart (this includes humans). Furthermore, there is currently no evidence to support the contention that diuresis increases stroke volume or cardiac output in patients with congestive cardiac failure. Braunwald and colleagues demonstrated an average fall in cardiac output of 20 % following diuresis in patients with impaired cardiac function both at rest and during exercise [35]. Nelson and coworkers compared the hemodynamic effects of intravenous furosemide (1 mg/kg) with that of intravenous isosorbide dinitrate (50–200 μg/kg/min) in patients with LV failure following myocardial infarction [36]. The pulmonary artery occlusion pressure (PAOP) fell in both groups of patients' however, the cardiac output was maintained in the nitrate group whereas it fell by about 10 % in the furosemide group. Similarly, Hutton and colleagues compared the effects of intravenous furosemide (0.5 mg/kg) and isosorbide 5-mononitrate (15 mg) at the time of cardiac catheterization in patients with LV dysfunction [37]. In this study furosemide induced acute vasoconstriction with a reduction in cardiac output. In contrast, isosorbide 5-mononitrate maintained cardiac output while reducing the PAOP.

It should therefore be no surprise that the use of high dose loop diuretics in patients with ADHF has been associated with adverse outcomes. Analysis of the ADHERE registry has provided compelling evidence regarding the harm of high dose diuretics in patients with ADHF [38]. Patients in the registry were stratified into a low-moderate (<160 mg) and high-dose group (≥160 mg) according to the cumulative dose of intravenous furosemide (or equivalent) administrated during the first 24 h of hospitalization. Patients in the high-dose group had a significantly greater decline in renal function, a longer length of stay and a higher in-hospital mortality rate (OR 0.87; 95 % CI 0.78–0.97, $p=0.01$) when compared to the low-moderate group, even after adjustment for confounding factors. Similarly, in the ESCAPE trial, high dose furosemide was an independent predictor of hospital mortality and 6-month outcome [39]. Cotter et al. randomized 110 patients with cardiogenic pulmonary edema to either high dose nitrates or high dose furosemide (80 mg iv every 15 min until improvement) after receiving an initial 40 mg dose of furosemide [40]. Mechanical ventilation was required in seven (13 %) patients in the nitrate group and 21 (40 %) in the furosemide group ($p=0.0041$). Myocardial infarction occurred in 9 (17 %) and 19 (37 %) patients ($p=0.047$) and death in one and three patients ($p=0.61$), respectively. One or more of these endpoints occurred in 13 (25 %) and 24 (46 %) patients, respectively ($p=0.041$). Worsening renal function during hospitalization is a powerful independent prognostic factor for adverse outcomes. Metra and colleagues demonstrated that the daily furosemide dose was an independent predictor for worsening renal function, which itself was a predictor of death and rehospitalization [41]. The initial daily dose of furosemide was 82 mg in the group whose renal function remained stable as compared to 160 mg in those with worsening renal function. In a nested case-control study of 382 ADHF patients, Butler and colleagues showed that higher doses of loop diuretics were associated with an increased risk of worsening renal failure independent of the amount of fluid loss [42]. In a long term follow-up study Abdel-Qadir et al. demonstrated that in

elderly patients with HF a dose of furosemide ≥120 mg/day was associated with worsened outcomes and was broadly predictive of death and morbidity [43].

Diuretics however may improve renal function in patients with cardio-renal syndrome and high venous pressures (see Chap. 12, Dangers of a high CVP). A high central venous pressure is transmitted backwards where it increases renal venous pressure and renal interstitial pressure; these effects markedly reduce renal blood flow and GFR. In patients with ADHF, Mullens et al. demonstrated a near linear relationship between increasing CVP and worsening renal function [44]. In this study worsening renal function occurred significantly less frequently in patients with a CVP < 8 mmHg. Furthermore, the CVP was the only hemodynamic parameter that predicted worsening renal failure, with the CI, systolic blood pressure and PCWP being similar between those patients who maintained renal function as compared to those with worsening renal function. The effect of diuresis on renal function likely depends on the balance of reduced stroke volume (following diuresis) which decreases renal function versus reduced central venous pressure which will reduce renal venous and interstitial pressure and may improve renal function. It is difficult to predict which patients will benefit or be harmed by diuresis. However, it is possible that renal function may improve following diuresis in patients with a high CVP. Renal function should be closely monitored in all patients with ADHF receiving diuretics and the dose reduced or stopped in those with worsening renal function. Based on this data patients with ADHF should receive no more than 40–80 mg furosemide per day and that this dose should be reduced in patient with worsening renal function. Administration of the diuretic as a continuous infusion does not appear to have any advantages over giving the drug as bolus doses [45].

Diuretics are appropriate therapy in patients with symptomatic cardiogenic pulmonary edema. However, it is important to realize that patients with failing hearts (chronic) are able to tolerate high pulmonary venous pressures without developing pulmonary edema. Patients with severe chronic left heart failure frequently lack pulmonary rales on examination or alveolar edema on chest x-ay, despite high pulmonary venous pressure (and features of pulmonary venous hypertension on chest x-ray); these patients may have pulmonary venous pressures > 30 mmHg. This observation is explained by reduced pulmonary microvascular permeability as well as increased lymphatic flow in these patients.

Vasodilators

Nitroglycerin is the most commonly used vasodilator in the setting of acute heart failure; however it should be used with caution in hypotensive patients. Nitroglycerin's effects are mediated through the relaxation of vascular smooth muscle; it reduces preload and afterload. Nitroglycerine increase cardiac output, decreases systemic vascular resistance and improves microcirculating perfusion [46]. Nitroglycerin can be given orally, topically, or intravenously, as long as blood pressure is maintained. This is one of the few agents which has been shown to

improve outcome in ADHF, [40] and it is likely that this agent is underutilized for the treatment of this condition. The IV route is recommended in patients admitted to the ICU. The dosing of nitroglycerin is often suboptimal and may need to reach doses of about 160 mg/kg/min to achieve optimal effects. Headache is a common adverse effect but is generally ameliorated with acetaminophen.

Due to its toxicity nitroprusside is best avoided. The role of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in ADHF has not been studied. Intravenous ACE inhibitors should be avoided [47]. A low dose of an oral ACE inhibitor can be considered in patients with stable renal function but should be avoided in patients with declining renal function.

Nesiritide is identical to the endogenous BNP produced by the body. It acts as a vasodilator (arterial and venous) and antagonizes the renin-angiotensin-aldosterone and sympathetic nervous systems. Nesiritide is given as a 2 mg/kg bolus, followed by an infusion of 0.01 mg/kg/min. Pooled analyses have raised concerns about the safety of this agent, with the drug being linked to worsening renal function and increased mortality [35, 48]. Chen et al. compared low-Dose Dopamine, Low-Dose Nesiritide and placebo in patients with ADHF and renal dysfunction (The ROSE Acute Heart Failure Randomized Trial). Neither dopamine nor nesiritide improved urine output or renal function (primary end-points) nor there was there any benefit on the secondary end points reflective of decongestion, renal function, or clinical outcomes. Based on this data nesiritide cannot be recommended in patients with ADHF.

Beta-Blockers

Multiple large, randomized controlled trials have demonstrated that certain beta-blockers (carvedilol, metoprolol succinate and bisoprolol) reduce mortality by about 35 % in patients with chronic HF and systolic LV dysfunction [49, 50]. Until recently it has been unclear if beta-blocker therapy should be continued, withdrawn or the dose reduced in patients admitted to hospital with ADHF. An analysis of the OPTIMIZE-HF registry and the Carvedilol or Metoporlol European Trial (COMET) demonstrated a longer hospital length of stay and a higher risk of death in patients in whom beta-blocker therapy was discontinued or the dose reduced as compared to those patients in whom the beta-blocker was continued or therapy with a beta-blocker initiated [51, 52]. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study beta-blocker therapy reduced the risk of death and hospitalization in the subgroup of patients with recent or recurrent decompensation [50]. This data suggests that all patients with ADHF should continue to be treated with a beta-blocker unless specifically contraindicated. It should be noted that beta-blockers are not contraindicated in patients with concomitant COPD; indeed, evidence suggests that beta-blockers may improve survival even in those COPD patients without overt cardiovascular disease [53]. In patients not previously treated with a beta-blocker initiation of low dose treatment should be considered.

Inotropic Agents

Dobutamine may have a role in patients with acute left ventricular failure due to myocardial ischemia. In this setting dobutamine may recruit hibernating myocardium and improve cardiac function. Furthermore, dobutamine should be considered in patients with sepsis induced acute systolic dysfunction. The role of dobutamine in patients with chronic heart failure is unclear. Chronic heart failure is characterized by sympathetic hyper-activation and β-receptor downregulation. Short term infusions or continuous β-stimulant therapies have not been demonstrated to be beneficial in these patients [54]. Tacon et al. performed a meta-analysis of RCT that evaluated the role of dobutamine in patients with ADHF [55]. In this study the odds ratio for mortality for patients treated with dobutamine compared with standard care or placebo was 1.47 (CI 0.98–2.21, p=0.06). This meta-analysis demonstrated that dobutamine is not associated with improved outcome in patients with heart failure, but was associated with a strong trend towards increased mortality. β-blockers have been demonstrated to improve outcome in patients with compensated heart failure and it therefore appears counterintuitive that β-stimulant therapy would have a role in ADHF.

Milrinone acts by inhibiting the phosphodiesterase III isoenzyme, which leads to increased cyclic adenosine monophosphate (cAMP) and enhanced inotropy. It differs from dobutamine, because it elevates cAMP by preventing its degradation as opposed to dobutamine, which increases cAMP production. In the OPTIME-CHF study the use of milrinone in patients with an ischemic cardiomyopathy was associated with an increase in the composite of death or rehospitalization (42 vs. 36 % for placebo, p=0.01) [56]. Furthermore, in the ESCAPE heart failure trial, the use of an inotrope was associated with an increased risk of death; RR of 2.14, (95 % CI 1.10–4.15) [57]. This data suggests that both dobutamine and milrinone have a limited role in the management of patients with ADHF.

Vasopressin Antagonists

Vasopressin levels are inappropriately high in both acute and chronic HF [58]. Along with activation of the sympathetic nervous system and the RAAS, non-osmotic release of vasopressin is thought to represent a maladaptive response that is central to the pathophysiology of HF. Vasopressin antagonists has been investigated in patients with both acute and chronic heart failure. Although these agents are associated with a greater net fluid loss than placebo and normalization of the serum sodium they have not been associated with improved clinical outcomes [59].

Ultrafiltration

Peripheral ultrafiltration is an alternative to diuretics for sodium and water removal. The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial enrolled 200 patients with ADHF and showed that ultrafiltration compared with diuretics increased weight loss at 48 h

(5.0 vs. 3.1 kg; $p<0.001$), decreased the need for vasoactive drugs (3 vs. 13 %; $p=0.02$) and reduced the rate of readmission to hospital at 90 days (18 vs. 32 %; $p=0.02$) [60]. More recently, Bart et al. tested the efficacy and safety of ultrafiltration in patients with ADHF complicated by persistent congestion and worsened renal function [61]. They randomized 188 patients to a strategy of stepped pharmacologic therapy or ultrafiltration. Ultrafiltration was inferior to pharmacologic therapy with respect to the end points of the change in the serum creatinine level and body weight 96 h after enrollment. A higher percentage of patients in the ultrafiltration group had serious adverse events. The changes from baseline in the creatinine level remained significantly different between the groups up to 60 days. While these two studies provide contradictory results they suggest that ultrafiltration should be avoided in patients with cardio-renal syndrome.

Management of Atrial Fibrillation (AF)

AF may occur in up to 50 % of patients with severe heart failure. If AF causes sudden severe worsening of heart failure immediate cardioversion may be necessary. However, most patients can be stabilized by using amiodarone or digoxin to control heart rate. Approximately 60 % of patients with acute AF (less 1 week) will spontaneously revert back to sinus rhythm. A randomized placebo controlled study demonstrated that the rate of conversion of acute AF to sinus rhythm was similar in a group of patients treated with amiodarone compared to the group receiving placebo [62]. It had previously been assumed that the prognosis of patients with heart failure and AF was improved if these patients were converted to sinus rhythm. However a recent RCT demonstrated that a strategy of rhythm control does not reduce the rate of death or cardiovascular complications as compared to a rate-control strategy [63].

Management of Hypertension

Reduction of blood pressure may in itself have a beneficial effect on the signs and symptoms of heart failure. Hypertension is a relative concept in patients with heart failure. Although a blood pressure of 135/85 mmHg may be acceptable for a patient with a normal EF, that same blood pressure may be harmful for patients with left ventricular systolic dysfunction. Intravenous nicardipine or fenoldopam (see Chap. 28) followed by treatment with on oral ACE inhibitor, ARB's or amlodipine is recommended for blood pressure control in these patients.

Anticoagulation

Routine anticoagulation is not recommended. Patients with a history of systemic or pulmonary embolism, recent atrial fibrillation, or mobile left-ventricular thrombi should be anticoagulated aiming to achieve a prothrombin time ratio of 1.2–1.8 times control (INR 2.0–3.0).

Anemia

Anemia is common and a poor prognostic indicator in HF [27, 64]. Multiple factors contribute to the anemia of HF including decreased erythropoietin production due to kidney injury, ACE inhibitors (inhibit erythropoietin production), increased levels of pro-inflammatory mediators, GI blood loss due to anti-platelet drugs, as well as iron deficiency [64]. Blood transfusions, however, do not improve outcome. Blood transfusion should only be considered in patients with a Hb < 7 g/dL (see Chap. 38). Intravenous iron (200 mg ferric carboxymaltose) has been demonstrated to improve symptoms in NYHA class II or III patients who had an ejection fraction of less than 45 % and had an iron deficiency anemia (ferritin < 100 μg/L and a hemoglobin less than 13.5 g/dL) [65]. Intravenous iron should therefore be considered in patients (non-septic) with ADHF who have an iron deficiency anemia. Erythropoiesis-stimulating agents (ESA's) appear to have limited clinical benefits in anemic patients with heart failure [66].

Treatment of ADHF: Summary

- CPAP + oxygen
- Intravenous nitroglycerin, titrate up to 160 mg/kg/min (hold/stop for hypotension)
- Furosemide 40–80 mg initially (on presentation) and then 40–80 mg daily. Stop if BUN increases.
- Treat complications
- Low dose beta-blocker (carvedilol)
- ? low dose oral ACE inhibitor
- Intravenous iron for iron deficiency (not if septic)
- DVT prophylaxis
- Nutritional optimization (thiamine etc)
- NO morphine, nitroprusside, nesiritide or inotropic agents
- Avoid blood transfusion
- Anticoagulation for chronic AF

Long-Term Management

Once the patients' condition has stabilized (i.e. resolution of features of pulmonary edema and the patient is normotensive with stable renal function) chronic therapy can be reinstated or initiated. At this point it is important to determine if the patient has predominantly systolic (low EF) or diastolic (normal EF) heart failure, as this has some impact of the long term therapeutic plan. While a considerable number of large RCT's have evaluated the utility of various interventions in patients with systolic heart failure the optimal management of patients with diastolic heart failure is somewhat less clear [34].

Diuretics do not improve heart function and they should be used with great caution in the chronic phase of heart failure (both systolic and diastolic); and only in the lowest dose to control symptoms of congestion (pulmonary edema). Patients nutritional status should be optimized (with iron and vitamin supplementation) and comorbidities aggressively treated.

Systolic Heart Failure

ACE Inhibitors

ACE inhibitors have been shown to decrease mortality and hospitalizations in patients with systolic heart failure [67]. It is recommended that all patients with cardiac failure be on an ACE inhibitor before hospital discharge unless there is a contraindication [11].

ACE inhibitors are contraindicated in patients with moderate to severe aortic stenosis, bilateral renal artery stenosis, hypertrophic obstructive cardiomyopathy and pericardial tamponade. Oliguria and serum creatinine levels above 3 mg/dL are also contraindications to the use of ACE inhibitors. In addition, ACE inhibitors should be avoided in patients whose renal function has acutely declined. ACE inhibitors should not be started (or be discontinued) in patients with a serum potassium greater than 5.5 mEq/L. ACE inhibitors should be used very cautiously in patients with poorly controlled angina, as ACE inhibitors may cause an increase in angina in these patients.

Use of ACE inhibitors is associated with an expected increase in sCr of up to 30 %, especially in patients with a baseline sCr greater than 1.4 mg/dL. This increase is the physiologic result of renal efferent arteriole dilation and subsequent decrease in GFR, and the value usually stabilizes within the first 2 months of treatment [68]. A rapid rises in the serum creatinine should prompt a consideration of bilateral renal artery stenosis. Patients should be started on low doses and titrated up to target levels. Even lower than target doses have been shown to decrease mortality, although higher doses are more cost-effective.

ARBs block the angiotensin II receptors, thereby reducing LV remodeling, arterial vasoconstriction, and renal damage. They seem to have a more favorable adverse effect profile with less cough and angioedema; they are reserved for patients who are intolerant of ACE inhibitors.

Beta Blockers

Beta-blocker therapy is effective in reducing sympathetic nervous system activity, symptoms, and mortality in patients who have HF. The hyperadrenergic state of HF, as measured by increases in norepinephrine levels, leads to myocardial hypertrophy, increases in afterload, coronary vasoconstriction, and mortality. Both carvedilol and

long-acting metoprolol have been shown to reduce mortality in heart failure [49, 69]. Carvedilol, however, is a unique beta-blocker exerting vasodilatory and antioxidant activity. In a metaanalysis which compared carvedilol with atenolol, bisoprolol, metoprolol and nebivolol, carvedilol was associated with a significantly greater reduction in all-cause mortality in patients with systolic heart failure than the other beta-blockers [70]. This data suggests that carvedilol is the beta-blocker of choice in patients with systolic heart failure.

Aldactone

The aldosterone-receptor antagonist, Aldactone (12.5 mg up to 50 mg daily) when used in conjunction with an ACE inhibitor, has been demonstrated to reduce the risk of death from progressive heart failure and sudden death from cardiac causes in patients with severe heart failure [71]. The drug is well tolerated with few side-effects. It has been suggested that the beneficial effect of Aldactone may be mediated by preventing myocardial and vascular fibrosis associated with increased circulating levels of aldosterone. Aldactone should therefore be added to the regimen of an ACE inhibitor in patients with severe heart failure due to left ventricular systolic dysfunction. The serum potassium level should be closely monitored and the dose reduced (or stopped) should hyperkalemia develop.

Hydralazine + Isosorbide-dinitrate

Data from the 1990s suggested that heart failure in blacks was associated with worse outcomes. An analysis of the Studies of Left Ventricular Dysfunction data revealed that after adjustment for multiple confounders, blacks had higher all-cause mortality, pump failure mortality, and combined death or heart failure hospitalizations [72]. On the basis of these differences, it was postulated that the response to therapy might differ among races also. A retrospective analysis of the VHeFT trials suggested that blacks had a survival benefit with the addition of hydralazine and isosorbide-dinitrate that was not apparent in whites [73]. The A-HeFT trial enrolled blacks with class III to IV symptoms and evidence of left ventricular dysfunction (EF < 35 %) to receive a fixed dose of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for heart failure [74]. Patients were on optimal therapy as tolerated, including ACEI, ARBS, beta-blockers, aldosterone blockade, digoxin and diuretics. The initial dose was one tablet containing 37.5 mg of hydralazine hydrochloride and 20 mg of isosorbide dinitrate three times daily. The dose was increased to two tablets three times daily, for a total daily dose of 225 mg of hydralazine hydrochloride and 120 mg of isosorbide dinitrate The study was terminated early owing to a significantly higher mortality rate in the placebo group than in the group given isosorbide dinitrate plus hydralazine (10.2 vs. 6.2 %, P = 0.02).

In patients followed for up to 500 days patients allocated to hydralazine/isosorbide dinitrate had a 37 % improvement in event-free survival ($P<0.001$) and a 39 % reduction in the risk for first hospitalization for HF ($P<0.001$) [75].

Digoxin

Digoxin inhibits the Na+K+ATPase of the myocardial cellular membrane and has been used for years to control ventricular response in atrial fibrillation. Digoxin has a very narrow therapeutic index and unless the patient is dosed precisely and the serum levels monitored the patient is likely to suffer significant toxicity. A serum level greater than 1.2 ng/mL offers very little therapeutic advantage but increases the risk of toxicity. The patient's age, weight and renal function must be taken into account when dosing (loading and maintenance) the patient. Because digoxin does not improve survival in patients with heart failure, this drug has a limited role in heart failure patients in sinus rhythm [76].

Calcium Channel Blocking Drugs

First generation calcium channel blocking drugs such as verapamil, diltiazem and nifedipine should be avoided in patients with left ventricular systolic dysfunction as these agents have been demonstrated to increase morbidity and mortality. The PRAISE study demonstrated that amlodipine does not adversely affect the natural history of chronic heart failure [77]. This drug should be considered second line therapy for the management of hypertension or angina in patients with left ventricular dysfunction.

AICD's and Resynchronization Therapy

Sudden cardiac death is the mode of death in approximately half of all patients with HF. Patients with both an ischemic and non-ischemic cardiomyopathy with an $EF<35$ % benefit from placement of an automated implantable cardioverter-defibrillator (AICD) [78, 79]. Mechanical dyssynchrony, defined as nonsynchronous contraction between the walls of the left ventricle or between the ventricular chambers, impairs systolic function, adversely affects ventricular filling, increases wall stress, and worsens mitral regurgitation [80]. Dyssynchrony is most readily defined by the presence of QRS widening on the electrocardiogram and can be visualized on 2-dimensional echocardiography. Cardiac resynchronization therapy (CRT) with biventricular pacing results in more synchronous ventricular contraction, reverses remodeling, improves ventricular function and is associated with a significant reduction in morbidity and mortality in patients with an $EF<30$ % and a

QRS duration ≥130 msec [81–84]. CRT with an implantable pacemaker-defibrillator appears to offer greater benefit than CRT with a pacemaker alone [85]. At this time, CRT should not be used as salvage therapy in patients with ADHF, but should be considered in suitable candidates once the patient's condition has stabilized [80].

Evaluation of Patients for Revascularization

Coronary artery disease is currently the most common cause of heart failure in the US, and some heart failure patients may benefit from revascularization. Patients with a history of angina or AMI should undergo physiologic testing for ischemia, followed by coronary artery angiography if ischemic regions are detected. Patients with heart failure who have significant angina (exercise limiting, occurring at rest, and recurrent episodes of pulmonary edema) should undergo coronary arteriography as the initial test for operable coronary lesions.

Surgical Options

With advances in myocardial protection and preoperative imaging, coronary revascularization has become an option in selected patients with HF. In patients with symptomatic disease and viable myocardium that can be correlated with ischemic disease, CABG can offer improvement in symptoms and survival [86]. Surgical ventricular reconstruction when added to CABG appears to offer little advantage [87]. Patients with left ventricular systolic dysfunction frequently develop mitral regurgitation (MR) as consequence of left ventricular remodeling (secondary or functional MR). Moderate to severe MR occurs in between 15 and 30 % of patient with HF. In selected patients with severe MR, surgical correction may improve symptoms and quality of life [88]. Surgical correction of secondary MR typically consists of placement of a prosthetic annular ring and in some cases correction of the mitral apparatus. Percutaneous repair of the mitral valve using the MitraClip system (Evalve Inc., Menlo Park, CA) appears to be a safe and effective alternative that has produced promising results [89].

Mechanical Support Devices

With technological advances in mechanical devices, non-pharmacologic approaches are now available to supplement the pharmacologic management of HF. Left ventricular assist devices (LVADs) are mechanical blood pumps that serve to augment the function of the LV. In patients with ADHF, LVADs may be used as a bridge to heart transplantation or as permanent therapy, also known as destination therapy. LVADs have been demonstrated to increase survival and improve the quality of life and functional capacity of patients with refractory HF [90]. Most currently available

LVADs are surgically implanted and require cardiopulmonary bypass to implant. The TandemHeart (CardiacAssist, Inc, Pittsburgh, PA) device is a left atrial to femoral arterial bypass system that can be inserted percutaneously and is able to provide active flow via a centrifugal pump independent of native heart rhythm [91]. LVADS should be considered in suitable patients who are not candidates for heart transplantation.

Management of Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

Many patients with features of cardiac failure have a preserved ejection fraction (>40 %); this syndrome is referred to as diastolic heart failure or most recently "Heart failure with normal (or preserved) ejection fraction" (HFnEF). The ADHERE registry demonstrated that up to 46 % of patients with ADHF had preserved systolic function [2]. In patients with HFnEF, the left ventricle has increased diastolic stiffness (reduced compliance) and is unable to fill adequately at normal diastolic pressures [92]. This condition results in reduced end-diastolic volume and elevated end-diastolic pressures. The reduced left ventricular filling leads to decreased stroke volume and symptoms of low cardiac output, whereas the increased filling pressure leads to symptoms of pulmonary congestion.

Hypertension is the commonest cause of diastolic dysfunction which can develop even in the absence of left ventricular hypertrophy. Left ventricular compliance decreases with aging, this syndrome is therefore very common in the elderly hypertensive patients. Diabetes results in a cardiomyopathy characterized by the presence of cardiac hypertrophy and myocardial stiffness. Myocardial fibrosis and collagen deposition are the primary structural changes observed in diabetic cardiomyopathy. Both hypertension and diabetes may coexist in many patients with HFnEF. The results of large recent study found 96 % of patients with HFnEF had hypertension and 37 % diabetes [93]. Morbid obesity (usually associated with both hypertension and diabetes) is also associated with HFnEF. The prognosis of HFnEF is almost as poor as the prognosis of heart failure with reduced EF. After a first hospitalization for heart failure, HFnEF patients have a 5-year survival rate of only 43 % [94].

In patients with features of HFnEF it is important to exclude other diagnoses, including:

- Primary valvular disease
- Restrictive cardiomyopathies
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
- Pericardial constriction
- Chronic pulmonary disease with right heart failure

- Heart failure associated with high output state
  - Anemia
  - Thyrotoxicosis
  - AV fistula

In contrast to heart failure with reduced ejection fraction (HFrEF), no treatment has yet been shown to reduce morbidity and mortality in HFnEF. Randomized controlled trials evaluating ACEI, ARBS, beta-blockers, digoxin, phosphodiesterase V inhibitors and aldosterone antagonists have failed to demonstrate a benefit with these agents [95–102]. The lack of favorable evidence from clinical-outcome trials involving patients with HFnEF is reflected in current guidelines, which offer no specific recommendations for the management of these patients [34]. Because patients with HFnEF often have important comorbid conditions, and because these comorbidities strongly influence outcomes, clinicians should aggressively identify and treat conditions such as hypertension, CAD, atrial fibrillation, diabetes and chronic kidney disease [103]. While not based on outcome data the use of β-blockers or ACEI is generally advocated in HFnEF on the premise that they decrease blood pressure and prolong the diastolic filling period. Diuretics are required in the presence of signs of volume overload, but caution is needed to avoid overdiuresis and a precipitous drop in LV stroke volume.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy also known as apical ballooning syndrome (ABS) is a unique reversible cardiomyopathy that is frequently precipitated by a stressful event and has a clinical presentation that is often indistinguishable from an acute myocardial infarction. This distinct cardiac syndrome was originally described in Japan in 1990 and named after the "octopus trapping pot" which has a round bottom and narrow neck, which closely resembles the left ventriculogram during systole in these patients [104]. Approximately 90 % of all reported cases have been in women. The mean age has ranged from 58 to 75 years, with <3 % of the patients being <50 years [105, 106]. The reason for the female predominance is unknown but raises the question as to whether withdrawal from estrogens contributes to the pathogenesis.

Stressors Reported to Trigger Takotsubo Cardiomyopathy [105, 107]

- Emotional stress
  - Death or severe illness or injury of a family member, friend, or pet
  - Receiving bad news—diagnosis of a major illness, daughter's divorce, spouse leaving for war

- Severe argument
- Public speaking
- Involvement with legal proceedings
- Financial loss—business, gambling
- Car accident
- Surprise party
- Move to a new residence

- Physical stress
  - Non-cardiac surgery or procedure—cholecystectomy, hysterectomy
  - Severe illness—SAH, asthma or COPD exacerbation
  - Severe pain—fracture, renal colic, pneumothorax, pulmonary embolism
  - Recovering from general anesthesia
  - Cocaine use
  - Opiate withdrawal
  - Stress test—dobutamine stress echo, exercise sestamibi
  - Thyrotoxicosis

This condition probably accounts for 1–2 % of all cases of suspected acute myocardial infarction. Takotsubo cardiomyopathy occurs predominantly in postmenopausal women soon after exposure to sudden, unexpected emotional or physical stress. In Takotsubo cardiomyopathy left ventricular dysfunction, which can be remarkably depressed, recovers within a few weeks. Although the left ventricular dysfunction is transient, there is no evidence of obstructive epicardial coronary disease.

The most frequent clinical symptoms of Takotsubo cardiomyopathy on admission are chest pain and dyspnea, resembling acute myocardial infarction. The classic presentation is that of a postmenopausal woman presenting with chest pain or dyspnea that is temporally related to emotional or physical stress, with positive cardiac biomarkers or an abnormal electrocardiogram [105]. Takotsubo cardiomyopathy should also be considered in the differential diagnosis of inpatients, including those in the ICU, who develop an acute reduction in left ventricular systolic function in association with the following features:

- Hemodynamic compromise
- pulmonary edema
- troponin elevation
- ECG evidence of ischemia or infarction.
- There may be a higher prevalence of males in the ICU population.

In general, hemodynamic compromise is unusual, but mild to moderate congestive heart failure is frequent. Transient ST elevation may be present on the electrocardiogram, and a small rise in cardiac troponins is invariable. When anterior ST-elevation is present, the magnitude of ST shift is usually less in Takotsubo cardiomyopathy than that seen in a STEMI. Diffuse T wave inversion and a prolonged QTc interval is typical finding (see Fig. 29.1). The T-wave inversion and QT interval

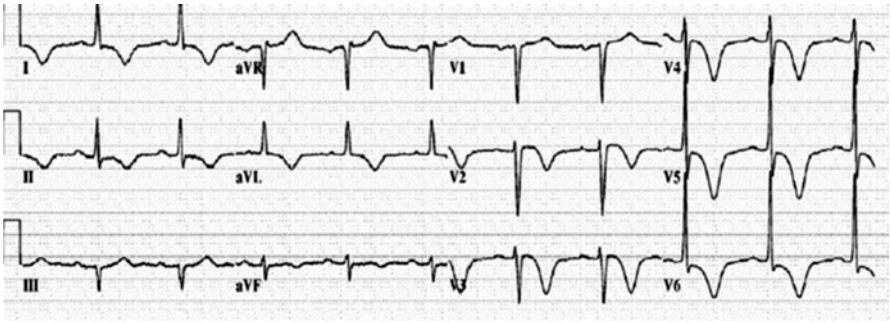

Fig. 29.1 Typical ECG in a patient with Takotsubo cardiomyopathy with diffuse T wave inversion

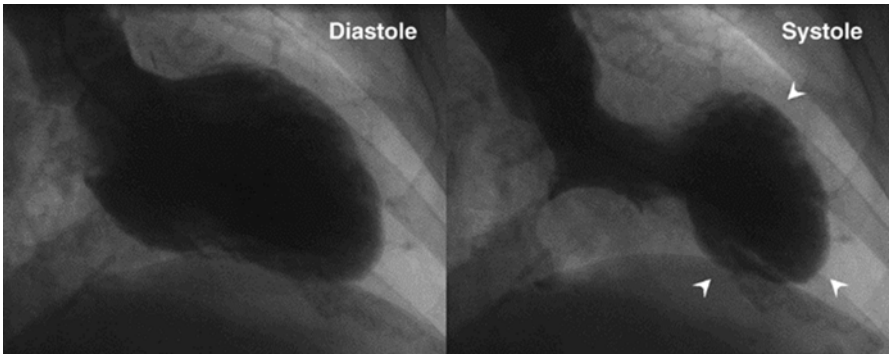

Fig. 29.2 Left ventricular apical ballooning in a patient with Takotsubo cardiomyopathy

prolongation typically resolve over 3–4 months but may occur as early as 4–6 weeks and, in some cases, be present beyond 1 year. Arrhythmias resulting from QT prolongation are commonly observed. Typically, there is hypokinesis or akinesis of the mid and apical segments of the left ventricle with sparing of the basal systolic function (see Fig. 29.2).

Mayo Clinic Criteria for Takotsubo Cardiomyopathy [107]

- Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture

- New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
- Absence of:
  - Pheochromocytoma
  - Myocarditis

Patients with Takotsubo cardiomyopathy on admission have high levels of serum catecholamines and of plasma brain natriuretic peptide (BNP). The myocardial histological changes in Takotsubo cardiomyopathy strikingly resemble those seen in catecholamine cardiotoxicity in both animals and humans. These changes, which differ from those in ischemic cardiac necrosis, include contraction band necrosis, neutrophil infiltration, and fibrosis.

The optimal management of Takotsubo cardiomyopathy has not been established, but supportive therapy invariably leads to spontaneous recovery. Patients have been treated with both β-blockers and ACE inhibitors [105]. Given the findings in animal models, treatment with a combined α- and β-blocker seems rational [106]. Treatment with a catecholamine as a cardiotonic appears contraindicated. It is important to exclude dynamic left ventricular outflow tract obstruction with echocardiography in patients with severe heart failure or hypotension. Dynamic outflow obstruction occurs in up to 20 % of patients. β-blockers have been demonstrated to reverse the obstruction presumably by reducing the hypercontractility of the base of the left ventricle and increasing cardiac filling [108].

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Chapter 30
Acute Coronary Syndromes

Patients with acute coronary syndromes (ACS) are classified as having either:

i) Unstable angina/myocardial infarction without ST-segment elevation (NSTEMI) or
ii) Acute myocardial infarction with ST elevation (STEMI).

The distinction between these two entities is made basis of the 12-lead electrocardiogram and is crucial in formulating the therapeutic plan. As a general rule patients with NSTEMI are treated with aggressive medical therapy followed by coronary angiography (when "cooled down") while patients with STEMI usually undergo immediate coronary angiography and revascularization.

Unstable Angina/NSTEMI

Unstable angina (UA) is characterized by the clinical presentation of angina with or without ischemic ECG changes (ST segment depression or new T-wave inversion). NSTEMI is similar to UA but is characterized by positive biomarkers (troponin or creatine kinase-MB [CK-MB]) in the setting of angina or ECG changes. The presence of myonecrosis as evident by positive cardiac markers portends a higher risk than those presenting with just UA. UA and NSTEMI pathophysiologically and clinically are related and initially may be indistinguishable, as biomarkers may not be elevated at presentation. Rupture of an atherosclerotic plaque and subsequent formation of a thrombus usually is the triggering event in the pathogenesis of most cases of ACS.

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Canadian Cardiovascular Classification of Angina

- Class 1: pain is precipitated only by severe and unusually prolonged exertion
- Class 2: pain on moderate effort. There is slight limitation of ordinary activity
- Class 3: marked limitation of ordinary activity; pain occurs on mild exertion, usually restricting daily chores. Patient is unable to walk two blocks on the level at a comfortable temperature and at a normal pace
- Class 4: chest discomfort on almost any physical activity

Types of Presentations of Unstable Angina

- Rest angina
  - Angina occurring at rest and prolonged, usually >20 min
- New-onset angina
  - New-onset angina of at least CCS class III severity
- Increasing angina
  - Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by ≥1 CCS class to at least CCS class III severity)

Differential Diagnosis

- ST elevation AMI (STEMI)
- aortic dissection
- esophagitis
- pleurisy
- leaking or ruptured thoracic aneurysm
- acute pericarditis
- pulmonary embolism
- pneumothorax
- esophageal rupture

Electrocardiography

Most patients who have unstable angina/NSTEMI have some ECG changes. The ECG is important for diagnostic and risk stratification purposes. Specific characteristics and the magnitude of pattern abnormalities increase the likelihood of

CAD. ST–T-segment depression portends a poorer prognosis than T-wave inversion alone or no ECG changes. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial demonstrated that the 30-day incidence of death or MI was 10.5 % in those who had ST-segment depression versus 5.5 % in patients who had T-wave inversion, and a higher mortality also was seen at 6-month follow-up [1]. The sum of ST depression is a strong independent predictor of short-term mortality and the risk increases with the magnitude of depression [2].

Tropinins

Troponins play a central role in the diagnosis of NSTEMI and risk stratification. The joint statement of the European Society of Cardiology and the American College of Cardiology (ACC) defines myonecrosis as when the peak concentration of troponin T or I exceeds the decision limit (99th percentile for a reference group) on at least one occasion in a 24-h period [3]. This definition has increased the frequency of the diagnosis of NSTEMI in patients who have ACS by 30 %. The troponins are detectable approximately 6 h after myocardial injury and are measurable for up to 2 weeks. Mortality risk is directly proportional to troponin levels and the prognostic information is independent of other clinical and ECG risk factors [4].

Management of UA/NSTEMI

Risk Stratification

Risk stratification plays a central role in determining the treatment strategy of patients with NSTEMI. Two risk-assessment algorithms have been developed for determining whether a patient is at high risk or at relatively low risk for having an ischemic event. Patients with ≥3 TIMI variables are considered to be at high risk. Similarly patients with >110 Total Risk Score Points using the GRACE model have >5 % 6 month mortality.

Thrombolysis in Myocardial Infarction (TIMI) Risk Score [5]

- age >65 years
- ≥3 risk factors for coronary artery disease
- prior coronary stenosis of ≥50 %
- ST segment deviation on electrocardiogram at presentation

- at least two anginal events in prior 24 h
- use of aspirin in prior 7 days
- elevated serum cardiac markers.

Global Registry of Acute Coronary Events (GRACE) Risk Model [6]

- age
- Killip class (a classification of the severity of heart failure)
- systolic arterial pressure
- ST-segment deviation
- cardiac arrest during presentation
- serum creatinine concentration
- elevated serum markers for myocardial necrosis
- heart rate.

Each variable is assigned a numerical score on the basis of its specific value, and the eight scores are added to yield a total score, which is applied to a reference nomogram to determine the patient's risk. The GRACE application tool is available at www.outcomes-umassmed.org/grace.

Treatment Approach for UA and NSTEMI (PER AHA Guidelines) [7]

Class I Recommendations

- Consult cardiology stat.
- Supplemental oxygen in patients with an oxygen saturation less than 90 %.
- Aspirin should be administered as soon as possible. In those intolerant of ASA give loading dose of clopidogrel followed by daily maintenance dose, Patients at medium or high risk in whom an invasive strategy is contemplated should receive dual therapy anti-platelet therapy.
- Patients in whom an initial conservative (i.e., non-invasive) strategy is selected, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible after admission.
- Anticoagulant therapy with enoxaparin or UFH should be added to antiplatelet therapy as soon as possible after presentation (unless contraindicated).
- Ongoing chest discomfort; sublingual NTG (0.4 mg) every 5 min for a total of three doses.
- Intravenous NTG is indicated in the first 48 h for treatment of persistent ischemia, heart failure, or hypertension.

- Oral beta-blocker within 24 h in patients who do not have any of the following:
  - Signs of heart failure
  - Evidence of a low output state
  - Increased risk for cardiogenic shock
  - Heart block etc.
- In patients with ongoing ischemia in whom B blockers are contraindicated a nondihydropyridine calcium channel blocker (i.e., verapamil or diltiazem) should be given.
- An ACE inhibitor should be administered to patients with pulmonary congestion or LVEF < 40 % in the absence of hypotension (SBP < 100 mmHg).
- Based on the patients risk profile the cardiologist may elect an initial conservative approach followed by stress testing/angiography or an initial invasive approach. Among initially stabilized patients with UA/NSTEMI for whom an early invasive strategy of coronary angiography is chosen, optimal timing of angiography has not been well defined.

Class II Recommendations

- Morphine (1–2 mg intravenously) for ongoing chest pain despite IV nitroglycerin
- Patients in whom an initial conservative strategy is selected, enoxaparin or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG is planned within 24 h
- Intravenous B-blocker for patients with hypertension who do not have any of the following (see Chap. 28):
  - Signs of heart failure
  - Evidence of a low output state
  - Increased risk for cardiogenic shock
  - Heart block etc.
- Intraaortic balloon counter pump (IABP) for patients with ongoing ischemia despite aggressive medical therapy.

Treatment Approach to STEMI (PER AHA Guidelines) [8]

Class I Recommendations

- Consult cardiology super-stat
- Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 h

- Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators
- Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI
- Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from AMI onset
- Placement of a stent (bare-metal stent or drug-eluting stent) is useful in primary PCI for patients with STEMI
- ASA 162–325 mg should be given before primary PCI and indefinitely
- A loading dose of a clopidogrel (or equ) should be given as early as possible or at time of primary PCI. Clopidogrel (or equ) should be continued for at least 1 year in patients who receive a stent.
- UFH in patients undergoing primary PCI
- Bivalirudin with or without prior treatment with UFH
- In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 h when it is anticipated that primary PCI cannot be performed in a timely manner.
- ASA and clopidogrel should be given as adjunctive treatment in patients undergoing fibrinolysis
- Patients undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy with UFH or enoxaparin for a minimum of 48 h, and preferably for the duration of the index hospitalization

Class II Recommendations

- Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12–24 h who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population.
- It is reasonable to start treatment with an intravenous glycoprotein (GP) IIb/IIIa receptor antagonist at the time of primary PCI in selected patients with STEMI who are receiving UF
- In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist

Complications Following STEMI

Recurrent Chest Pain Post-AMI

The two most common causes of recurrent chest are acute pericarditis and ischemia. An ECG taken during the recurrent chest pain and compared with the previous ECG's is helpful in distinguishing between these two conditions. Cardiac rupture may also result in recurrent chest pain.

Pericarditis

Pericarditis has been reported to occur in 20 % of patients following AMI and occurs with extension of myocardial necrosis throughout the wall to the epicardium. The pain associated with pericarditis is pleuritic in nature and positional. The ECG features of pericarditis include, J point elevation, concave-up ST-segment elevation and PR segment depression. It is not associated with re-elevation of the CK-MB. Aspirin is the treatment of choice, but high doses (650 mg 4–6 hourly) may be required.

Ischemia

Reinfarction during the first 10 days postinfarction has been reported to occur in about 10 % of patients who have not received thrombolytic therapy compared to approximately 3 % of patients who have been thrombolysed. Coronary angiography is indicated in patients with suspected ischemic-type chest pain. Prompt reperfusion using PCI or additional thrombolytic may be feasible.

Mitral Regurgitation

Acute mitral regurgitation is a life-threatening complication that can occur with or without papillary muscle rupture. It is more common with inferior STEMI, usually because of occlusions of the right coronary or left circumflex arteries. Medical management carries a very high mortality (70 %). Surgical mortality, although high, is still lower (40 %) than medical treatment alone [9]. Diagnosis can be established rapidly by transthoracic and if required transesophageal echocardiography. All patients should be considered for emergent surgery while stabilization is achieved by IABP, inotropes, and vasodilators. Delay in operation increases the risk of myocardial and other organ injury and subsequent death.

Left Ventricular Failure and Low Output States

Heart failure is present in 15–25 % of patients with acute myocardial infarction with an in-hospital mortality rate of 15–40 %. The severity of left ventricular dysfunction is proportional to the extent of myocardial injury. Mortality has been reported to vary from 6 % in patients with clear lung fields and no third heart sound to up to 60 % in patients with cardiogenic shock in the reperfusion era.

Patients with a systolic blood pressure below 90 mmHg and/or who have signs of inadequate tissue perfusion together with pulmonary congestion have significant LV dysfunction with elevated left sided filling pressures. Intravenous norepinephrine should be administered and titrated to increase the mean arterial pressure (MAP) above 65–70 mmHg. Dobutamine 5–20 μg/kg/min should be added to improve cardiac function. In addition, consideration should be given to initiating intra-aortic counter pulsation. Reperfusion by PCI or CABG may improve the outcome of these patients.

Right Ventricular Infarction

Right ventricular infarction (RVI) commonly occurs in patients with an inferior myocardial infarction (and very rarely with anterior myocardial infarction). Although RVI is evident in approximately 25 % patients with an inferior STEMI, hemodynamic compromise is evident in fewer than 10 % of these patients. EKGs with right-sided precordial leads should be monitored in all patients with an inferior STEMI. Fluid administration (despite a raised JVP) is the cornerstone of therapy. High degree heart block is common in these patients. AV sequential pacing improves right ventricular filling and increase in cardiac output (even in patients who have not improved with ventricular pacing alone)

Atrial Fibrillation

Atrial fibrillation (and flutter) in STEMI is an independent predictor of 30-day mortality. Atrial fibrillation associated with AMI most often occurs within the first 24 h and is usually transient but may recur. The incidence of AF in AMI ranges from 10 to 16 %. In the patient with AMI, the appearance of atrial fibrillation is often a manifestation of extensive LV systolic dysfunction. If its occurrence causes hemodynamic compromise or ongoing ischemia, direct-current cardioversion should be performed. In the absence of CHF, bronchospastic disease, or AV block the most effective means of slowing the ventricular rate in AF is the use of intravenous-adrenoceptor blocking agents such as atenolol or metoprolol.

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Chapter 31
Arrhythmias

Sustained arrhythmias occur in approximately 10–15 % of general ICU patients [1, 2]. As a general rule the development of arrhythmias is a reflection of the severity of the underlying disease and they do not appear to be independent predictors of death, although they increase the risk of neurological sequela. Atrial arrhythmias (atrial fibrillation/flutter) are the most common arrhythmia. AF/Aflutter are usually secondary to the underlying disease process (respiratory failure), while ventricular arrhythmias are usually due to preexistent cardiac disease or acute ischemia. Atrial arrhythmias are usually the consequence of acute respiratory failure (acute cor pulmonale-pulmonary hypertension, right ventricular failure and atrial distension) [3]. Left ventricular systolic and diastolic dysfunction (sepsis, ARDS, etc.) as well as abnormalities in fluid balance and electrolytes may contribute to the development of sustained arrhythmias in critically ill ICU patients. The management of arrhythmias in acutely ill ICU patients differs from that of patients with primary cardiac disease. Unfortunately, there is little (if any) evidence based literature to guide the management of these arrhythmias in the ICU.

Arrhythmias and Electrolyte Disturbances

Intravenous magnesium has been used to prevent and treat many different types of cardiac arrhythmia. It has diverse electrophysiological actions on the conduction system of the heart; including prolonging sinus node recovery time, and reducing automaticity, atrioventricular nodal conduction, antegrade and retrograde conduction over an accessory pathway, and His-ventricular conduction. Intravenous magnesium can also homogenize transmural ventricular repolarization. Because of its unique and diverse electrophysiological actions, intravenous magnesium has been reported to be useful in preventing atrial fibrillation and ventricular arrhythmias after cardiac and thoracic surgery; in reducing the ventricular response in acute

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onset atrial fibrillation, including patients with Wolff-Parkinson-White syndrome; in the treatment of digoxin induced supraventricular and ventricular arrhythmias, multifocal atrial tachycardia, and polymorphic ventricular tachycardia or ventricular fibrillation from drug overdoses [4]. In addition magnesium has synergistic activity when combined with other rate and rhythm controlling drugs [5]. Magnesium sulfate, when used to supplement other standard rate-reduction therapies, enhances rate reduction and conversion to sinus rhythm in patients with rapid atrial fibrillation [6]. Magnesium has a relatively wide toxic/therapeutic window; the most common reported side effects are a transient sensation of warmth and flushing. Magnesium should be considered the "first line" agent for control of arrhythmias in the ICU even in patients with normal serum magnesium (1.6–2.5 mg/dL)… aim to achieve a serum magnesium level of about 2.8–3.0 mg/dL.

Magnesium is the Intensivists anti-arrhythmic agent of first choice!

Hypokalemia causes cellular hyperpolarity, increases resting potential, hastens depolarization, and increases automaticity and excitability. Hypokalemia appears to be a risk factor for the development of both atrial and ventricular arrhythmias. In the Study of Prevention of Postoperative Atrial Fibrillation (SPPAF), the rate of postoperative AF was 51 % in patients with a serum potassium <3.9 mmol/L compared to 33 % in patients with a serum potassium >4.3 mmol/L ($p < 0.05$) [7].

Acute Atrial Fibrillation/Flutter

Atrial tachyarrhythmias are the commonest arrhythmias occurring in ICU patients, with a reported prevalence of between 6 and 28 % [1, 2, 8, 9]. Atrial fibrillation is the commonest atrial arrhythmia, followed by atrial flutter and multifocal atrial tachycardia (MAT). Since the etiology and management strategies of atrial fibrillation and atrial flutter overlap, for the purposes of this discussion they will be considered one entity (AF). Patients who develop AF have a worse prognosis than those who remain in sinus rhythm (SR); however, the attributable mortality of AF is unclear [8]. Loss of atrioventricular synchrony will compromise stroke volume and cardiac output to a variable degree depend upon ventricular compliance, venous filling pressure, ventricular rate, and other hemodynamic factors. In the study by Annane and colleagues the presence of a supraventricular arrhythmia doubled the risk of a neurological sequelae (OR 2.64; 95 % CI 1.19–5.84) [1].

AF is particularly common in ICU patients with cardiovascular disorders, respiratory failure and sepsis. The etiology is largely multifactorial with hypoxia, electrolyte disturbance, myocardial ischemia, increased sympathetic tone and atrial distention being implicated. Pulmonary hypertension with right atrial distension may be an important precipitant in patients with respiratory failure and sepsis.

The components of the acute management of AF include;

- assessment of the need for urgent cardioversion
- correct treatable precipitating factors

- control the ventricular response rate
- prophylaxis against thromboembolic events in those patients who remain in AF

Drugs such as dopamine should be stopped. Pain and anxiety, which increases sympathetic activity, should be treated. New onset atrial fibrillation may occur in patients with pulmonary embolism; this diagnosis should be considered.

Urgent Cardioversion

Electrical cardioversion is a time-honored highly effective method for converting AF to sinus rhythm. Urgent cardioversion is indicated when the ventricular response is greater than 130/beats/min in association with:

- angina/myocardial ischemia on ECG
- acute cardiac failure
- hypotension (MAP < 70 mmHg or fall in MAP > 15 mmHg)
- indices of inadequate tissue perfusion

Rate Control

Rate control can improve hemodynamics even if the patient remains in AF. Digoxin is commonly used in the treatment of AF in ICU patients. Yet, in the critically ill ICU patient digoxin is probably the least effective drug in controlling the ventricular response in AF. Digoxin decreases ventricular response in AF by vagotonic mechanisms. In critically ill patients, AF occurs in the setting of high sympathetic tone and frequently with the use of vasopressors and inotropic agents, a situation in which digoxin is likely to be ineffective. In addition, this drug has a very narrow therapeutic index and should be avoided except in patients with poor LV function.

Diltiazem is an effective agent for rate control in most patients with a response rate of between 93 and 97 %. Diltiazem is given as a 5 mg bolus every 5 min until rate control is achieved or a maximal dose of 15 mg is administered, followed by an infusion of up to 15 mg/h. Esmolol, an ultrashort acting selective beta-blocker has been demonstrated to be effective in controlling the ventricular response in AF. Similarly, IV metoprolol (5 mg boluses) may used for rate control. However, beta-blockers may cause hypotension particularly in patients with poor LV function. Amiodarone (or digoxin) may be used for rate control in patients with poor LV function. Magnesium has been shown to reduce the ventricular response in AF, with a greater effect when combined with digoxin. Magnesium may act by increasing the atrio-His interval and atrioventricular nodal refractoriness.

Digoxin and calcium channel blockers should not be given to patients who have atrial fibrillation with an anterogradely conducting accessory pathway, because blocking atrioventricular nodal conduction may provoke conduction down the accessory pathway, leading to an increase rather than decrease in the ventricular rate and hemodynamic collapse.

Pharmacologic Cardioversion

A number of randomized controlled studies (RCT's) have evaluated procainamide, amiodarone, flecainide, sotalol, propafenone and ibutilide in patients presenting to hospital with acute atrial fibrillation (non-ICU setting). In general these studies have found the rate of conversion to be similar with the antiarrhythmic drug as with placebo, with approximately 60 % of patients spontaneously converting to sinus rhythm within 24 h [10]. The natural history of AF in acutely ill ICU patients has not been studied. However, it is likely that untreated the arrhythmia will persist until the underlying medical condition which precipitated the arrhythmia has improved or resolved. The role of anti-arrhythmic agents in facilitating pharmacological cardioversion is unclear; however it would appear that these agents have a limited role in the critically ill patient. Amiodarone is the agent most commonly used to facilitate cardioversion in the ICU. Amiodarone is not without risks, with hypotension and bradycardia being the most common adverse events, usually occurring during the loading infusion. Acute hepatotoxicity with liver function test abnormalities has been reported in 9–17 % of patients Amiodarone has also been associated with acute pulmonary toxicity presenting as ARDS. High inspired oxygen concentration and pre-existing ARDS may be risk factors for acute amiodarone pulmonary toxicity. Sleeswijk et al. reported the efficacy of a magnesium-amiodarone step-up scheme in critically ill patients with new-onset atrial fibrillation [11]. A $MgSO_4$ bolus (0.037 g/kg body weight in 15 min) was followed by continuous infusion (0.025 g/kg body weight/h) [bolus of 2–3 g followed by infusion at 2 g/h in 70 kg patient]. Intravenous amiodarone (loading dose 300 mg, followed by continuous infusion of 1,200 mg/24 h) was given to those not responding to $MgSO_4$ within 1 h. Clinical response was defined as conversion to sinus rhythm or decrease in heart rate <110 beats/min. Sixteen of the 29 patients responded to $MgSO_4$ monotherapy, whereas the addition of amiodarone was required in 13 patients. Median time until conversion to sinus rhythm after $MgSO_4$ was 2 h while the median conversion time in patients requiring amiodarone was 4 h. The 24-h conversion rate was 90 %. As this approach obviates the need for anticoagulation, it may be the preferable approach to AF in ICU patients. Kanji et al. determined the outcome of patients in a mixed ICU who had preexistent AF (186 pts) or developed new onset AF (139 pts) in the ICU (10.5 % of all patients) [9]. Hemodynamic instability developed in 37 % of patients with new-onset AF with pharmacologic rhythm conversion was attempted in 76 % those with new-onset AF. Although initially successful in 87 % of new-onset cases, 42 % reverted back to AF. Only 18 % of patients with new-onset AF who survived to ICU discharge left the ICU in AF.

Anticoagulation

According to the most recent guidelines on antithrombotic therapy from the American College of Chest Physicians anticoagulation is not required for AF of less than 48 h [12]. This recommendation is supported by the study of Weigner and

colleagues who demonstrated 3 thromboembolic events in 357 patients (1 %) with new onset AF who converted to sinus rhythm [13]. However, in patients in whom the arrhythmia lasts more than 48 h or its duration is uncertain full anticoagulation may be required. In these patients this risks of anti-coagulation must be balanced against the risk of thromboembolic disease. The presence of structural heart disease, chronic/recurrent atrial fibrillation and increased atrial dimensions may increase the risk of embolic events. In patients planned for pharmacological cardioversion in whom the arrhythmia has been present for more than 48 h, require transesophageal echocardiography to exclude the presence of an atrial thrombus before attempts at cardioversion.

Multifocal Atrial Tachycardia (MAT)

MAT has been defined as a rhythm with an atrial rate > 100 beats/min, at least three morphologically distinct P waves, irregular P-P intervals, and an isoelectric baseline between P waves. An exacerbation of COPD is the most common setting in which MAT arises. The treatment of COPD may promote the arrhythmia. A weak relationship exists between MAT and pulmonary embolism. This arrhythmia is typically an epiphenomenon of an underlying disorder and should usually not be treated. MAT is commonly transient and will often resolve after precipitating causes are reversed. MAT should only be treated if it causes hypotension, CHF or myocardial ischemia. Calcium channel blockers, beta-blockers (avoid in acute exacerbation of COPD) and magnesium have demonstrated some utility in treating this arrhythmia. Magnesium may be particularly effective and should probably be the first line of treatment (a loading dose of 2 g in 10 mL dextrose water over 5 min, followed by 10 g in 500 mL dextrose water over 5 h).

Paroxysmal Supraventricular Tachycardia (PSVT)

Atrioventricular nodal re-entrant tachycardia is usually not associated with underlying heart disease and may be precipitated by the same factors as atrial fibrillation/atrial flutter. This arrhythmia is characterized by a sudden onset and sudden termination. The rate may range from 150 to 200 beats/min but most often is 180–200 beats/min. In the common atrioventricular nodal reentrant tachycardia there is antegrade conduction over the slow AV nodal pathway and retrograde conduction over the fast pathway. As there is almost simultaneous excitation of both the atria and ventricles the P wave occurs at the time of the QRS complex and are difficult to appreciate on the electrocardiogram. In 10 % of patients the reentrant pathway is reversed. This tachycardia, referred to as the “uncommon atrioventricular nodal reentrant tachycardia” is characterized by clearly visible P waves that are inverted in leads II, II and aVF.

Management

- Vagal maneuvers are the initial treatment of choice:
  - Valsalva maneuver
  - Muller maneuver—deep inspiration against a closed glottis
  - Carotid sinus massage. Check that the patient has no carotid bruit or history of TIA's.
- Adenosine is the pharmacologic agent of choice in patient who has failed vagal maneuvers. The usual dose is 6–12 mg by slow IV push. After termination of the tachycardia brief periods of asystole are common.
  - due to denervation hypersensitivity adenosine should not be given to heart transplant recipients
- Verapamil is also effective in terminating a PSVT.
- Electrical cardioversion if the patient is hemodynamically unstable

SVT Mediated by Accessory Pathways

Accessory pathways are anomalous bands of conducting tissue that form a connection between the atrium and ventricle. When there is antegrade accessory-pathway conduction during sinus rhythm, ventricular pre-excitation occurs. This results in the combination of a short PR interval and a delta wave, the electrocardiographic features of the Wolff-Parkinson-White (WPW) syndrome. Nearly 25 % of accessory pathways are capable of only retrograde conduction (concealed bypass tracts).

The most common SVT in patients with WPW is the orthodromic atrioventricular reentrant tachycardia; the impulse travels anterogradely over the AV node and then retrogradely through the accessory pathway. In about 10 % of patients with WPW the reentrant circuit travels in the opposite direction (antidromic). This tachycardia is characterized by a wide QRS configuration (exaggeration of the delta wave).

Atrial fibrillation and atrial flutter are frequently seen in patients with the WPW syndrome because most accessory pathways have rapid conduction. These patients may achieve ventricular rates that approach 300 beats per minute; ventricular fibrillation may occur under such circumstances.

A number of acute therapies are available for an orthodromic reciprocating tachycardia:

- electrical cardioversion if the patient is hemodynamically unstable
- Adenosine is the pharmacologic agent of choice (6–12 mg IV)
- Procainamide may be safely used in WPW syndrome
- DIGOXIN and VERAPAMIL should not be administered as these drugs can shorten the refractory period of the by-pass tract.

Adenosine, digoxin and calcium-channel blockers should NOT be given to patients who have atrial fibrillation with an accessory pathway, because blocking AV nodal conduction may provoke conduction down the accessory pathway leading to an increase in the ventricular rate and hemodynamic collapse. The treatment of choice of these patients is procainamide.

Sinus Bradycardia

Sinus bradycardia is not uncommon in ICU patients. This may occur due to myocardial ischemia, digoxin toxicity, sick-sinus syndrome and or beta-blockers, calcium channel blockers and dexmedetomidine. The patient should only be treated if symptomatic and/or hypotensive.

- atropine 0.5 mg repeated up to total of 3 mg
- isoproterenol 1–2 μg/min up to 20 μg/min
- a dopamine infusion, especially in hypotensive patients
- pacing
  - transvenous temporary pacemaker
  - external pacemaker (transcutaneous)

Sick-Sinus Syndrome

This syndrome is also known as the tachycardia-bradycardia syndrome. As the name implies these patients have episodes of both tachycardia and bradycardia. The critically ill patient with this syndrome often requires temporary pacing in order to achieve hemodynamic stability.

Accelerated Idioventricular Rhythm

This rhythm is characterized by a wide QRS complex and a regular ventricular rate, usually 60–110 beats/min. This is a benign rhythm that is usually asymptomatic and should just be observed.

Ventricular Premature Complexes and Bigeminy

These are recognized by wide QRS complexes (>120 ms) with a bizarre configuration. Identify and treat possible precipitating factors; such as hypoxia, and electrolyte disturbances. Ensure that the K+ > 4 meq/L and that the Mg++ > 2.6 mg/dL. Treat the underlying cause and NOT the VPC's.

Nonsustained Ventricular Tachycardia

Defined as from three consecutive PVC's up to 30 s at a rate of > 100 beats/min. This arrhythmia is usually associated with underlying heart disease and is associated with an increased mortality. In the ICU setting precipitating factors should be diagnosed and treated. In the setting of acute myocardial ischemia progressively longer runs of this arrhythmia may herald the onset of VF and should therefore be suppressed. In most other situations, unless the patient is symptomatic this arrhythmia should just be observed. Ensure that the K+ > 4 meq/L and that the Mg++ > 2.6 mg/ dL.

Sustained Ventricular Tachycardia

A wide QRS complex tachycardia: Ectopy or aberration?

Factors favoring ectopy

- AV dissociation
- R or qR in V1 with taller LEFT rabbit ear
- QS or RS in V6
- bizarre frontal plane axis
- concordant V leads
- LBBB pattern with wide r in V1

Factors favoring SVT with aberration

- preceding P wave
- RBBB pattern
- triphasic contour in V1 and V6
- initial vector identical with that of flanking conducted beats
- qRs in V6

If there is any question of doubt the arrhythmia should be considered to be ventricular rather than supraventricular. Adenosine may be used to differentiate between these two arrhythmias. The treatment of a ventricular tachycardia with a calcium channel blocker can result in a fatal outcome.

Sustained ventricular tachycardias usually occur in patients with severe underlying heart disease, usually ischemic heart disease. The prognosis depends largely on that of the underlying heart disease. The treatment of patients with sustained VT is dependent on the hemodynamic consequences. Cardioversion is the treatment of choice in hemodynamically compromised patients. If the patient is asymptomatic or only mildly symptomatic a number of therapeutic options can be pursued (alone and in combination) including:

- elective synchronized cardioversion
- procainamide is considered the drug of choice. Loading dose of 15 mg/kg at rate of 25–50 mg/min followed by an infusion at 1–4 mg/min. Monitor levels and ECG

- amiodarone
- implantable anti-tachycardia device

Polymorphic Ventricular Tachycardia (Torsades De Pointes)

The hallmark of polymorphic ventricular tachycardia (PVT) is a QRS morphology that changes constantly. Torsades de pointes translated means "twisting of the points". Multiple leads may be required to demonstrate this phenomenon. This arrhythmia is classified as being associated with either (i) a normal QT interval or (ii) a prolonged QT interval.

Normal QT interval

- acute myocardial ischemia
- hypertrophic cardiomyopathy
- dilated cardiomyopathy

Prolonged QT interval

- congenital long-QT syndrome
- acute myocardial ischemia
- anti-arrhythmic drugs especially class 1 agents; rarely sotalol (hypokalemia) and amiodarone
- other drugs, including phenothiazines, tricyclic antidepressants, erythromycin, ampicillin, pentamidine
- electrolyte disturbances
  - hypokalemia
  - hypomagnesemia
  - hypocalcemia
- acute intracranial pathology, such as subarachnoid hemorrhage and intracerebral bleed

Management

- electrolyte abnormalities must be aggressively corrected, particularly potassium and magnesium deficiency
- magnesium sulphate (1–2 g) is usually highly successful, even in the absence of magnesium deficiency. 2 g (10 mL of 20 % solution) is given IV over 10 min, followed by 4 g over 4–8 h as an infusion.
- Accelerating the heart rate is a simple and quick method of shortening the QT interval. Transvenous pacing is a safe and effective method of controlling this arrhythmia. As an immediate measure transcutaneous pacing may be used while preparations are being made for electrode placement.

- An infusion of Isoproterenol (2–8 μg/min) titrated to increase the heart rate above 120/min is sometimes used if pacing is not available. Isoproterenol is contraindicated in patients with an acute myocardial infarction, active ischemia, and severe hypertension.
- If the arrhythmia occurs during therapy with a type 1A agent amiodarone may terminate the arrhythmia.
- PVT occurring in the setting of myocardial ischemia does not usually respond to anti-arrhythmic therapy. These patients usually require coronary revascularization. If the QT interval is prolonged standard class I anti-arrhythmic agents should not be used.
- Patients with the congenital long-QT syndrome are usually treated with B-blockers or phenytoin.

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Part IV
Gastrointestinal

Chapter 32
Nutrition in the ICU: It's Whey Cool

The traditional method of continuous tube feeding is illogical, stupid and quite likely harmful

Paul Marik MD, Intensivist, 1958–∞

During the last decade, the seemingly simple task of feeding critically ill patients has become exceedingly complex with much controversy [1]. While many consider nutrition support "an afterthought" current evidence suggests that in critically ill patients the approach to nutritional support directly impacts patient outcome. Furthermore, critically ill patients' loose large amounts of lean body mass (muscle), and this has a dramatic effect on the ability of the patient to wean from mechanical ventilation and long term recovery. Emerging data suggests that a more rational approach to nutrition support (bolus feeding high quality protein) may limit the loss of lean body mass. In reality the approach to nutritional support in the ICU is quite simple (this is not rocket science):

- Route—Enteral nutrition (EN)
  - PO (1st)
  - OG tube (2nd choice)
  - Post pyloric feeding tube (3rd choice)
  - Avoid TPN like the plague (no choice)
- When
  - Within 24 h
- Quantity
  - Day 1: 15 kcal/kg/day
  - Day 2: 20 kcal/kg/day
  - Day $\geq$ 3: 25 kcal/kg/day
- Composition (tube feeds)
  - High quality protein, with branch chain amino acids especially leucine (Whey)

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  - Omega-3 fatty acids and structured lipids
  - Low glycemic index
  - Soluble fiber
- HOW
  - Bolus feeds

The two commandments of nutrition support

- "If The Bowel Works, Use It" (and if it don't work, make it work)
- "There is no disease process that benefits from starvation".

Myths of Nutritional Support [2]

- Starvation is "okay"
- TPN is safe
- EN is contraindicated with vasopressors
- EN contraindicated with mechanical ventilation
- EN is contraindicated with high gastric residual volumes
- Post-pyloric feeding reduces the risk of aspiration
- EN is contraindicated in patients without bowel sounds and/or postoperative ileus
- EN is contraindicated following GI surgery
- EN is contraindicated with an open abdomen
- EN is contraindicated in patients with pancreatitis
- Patients must be fed semirecumbent at 45° The risk of aspiration is equivalent with the head of bed at 20° as compared to 45°
- Bowel rest. In reality there is no such thing, the bowel never stops functioning and trying to "rest the bowel" is akin to inducing cardiac arrest to rest the heart.

All ICU patients should be fed soon after admission to the ICU. The only exceptions include:

- Patients with GI bleed (GIB) who will require endoscopy. Feeding must be resumed after completion of endoscopy
- Patients with ischemic bowel (this is a surgical problem that must be fixed)
- Patients with bowel obstruction (this is a surgical problem that must be fixed)
- Patients in whom extubation is planned within 12 h in whom oral feeding will be resumed
- Patients who are about to die or are dead

The results of a number of RCT's (and meta-analyses of these trials) have established the following principles on which to base nutritional support in critically ill patients [3–10]:

- There is no data that parenteral nutrition (TPN) is of any benefit in critically ill patients. The available evidence suggests that TPN increases complications

and mortality rates [2, 4]. TPN should not be given to supplement the "nutritional deficit" associated with enteral nutrition. PN should therefore be limited to patients, who after 5–7 days of starvation are unable to tolerate even small volumes of enteral nutrition. This includes patients with proximal small bowel fistula, unresolving bowel obstruction and short gut syndrome [11].

- Early enteral nutrition (within 24 h of admission to the ICU) has been shown to reduce complications and improve the outcome of critically ill patients when compared to delayed enteral nutrition [12, 13]. The data is most convincing in postoperative patients. No studies demonstrate an advantage to delaying nutritional support in seriously ill patients.
- In critically ill medical and trauma patients' an initial strategy of permissive underfeeding has been demonstrated to be well tolerated and did not appear to compromise long term outcomes. It is important to note that these studies used continuous tube feeds; this is an outdated and potentially harmful feeding strategy that should be abandoned (see below).
- Overfeeding patients is associated with significant complications including hyperglycemia, hepatic steatosis with hepatic dysfunction, elevated BUN and excessive CO_2 production
- In surgical patients an aggressive approach to peri-operative enteral nutrition including a rapid escalation in volume and the use of immunonutrition has been demonstrated to reduce postoperative complications [14].
- There is no data to suggest that accurately measuring resting energy expenditure (REE) to determine nutritional requirements improves outcome. Measurement of REE may be appropriate in morbidly obese patients.
- Enteral nutritional feeding formulas of low osmolarity and enriched with fibre (nondigestible plant cell wall constituents) reduce the risk of diarrhea and improve feeding tolerance.
- Emerging experimental data suggests that administering enteral nutrition (with high quality protein) as intermittent boluses rather than as a continuous infusion results in a more physiological endocrine profile with greater protein synthesis (see below)
- Whey protein results in greater protein anabolism than soy or casein protein (see below)

Important Points to Digest

- A large number of different enteral nutrition formulations are available (see Table 32.1). While many hospitals have a complex list (with many tables) of formulations in reality only four different formations are required, namely
  - a general all-purpose formula suitable for most patients (whey and omega 3)
  - a formulation with arginine and omega-3 fatty acids for peri-operative and trauma patients

Table 32.1 Composition of common enteral formulas

Product	Type	Kcal/mL	Osmol.	CHO g/L (% cals)	Protein g/L (% cals)	Fat g/L (% cals)	Source of lipid	n-6:n3	Source protein	Added Arg. (g)	Manufacturer
Osmolite 1.2	St w/o fiber	1.2	360	158/53	56/18	39/29	Canola oil MCT oil	6.3:1	Casein Soy	0	Abbott
Jevity 1.2	St w fiber	1.2	450	169/52	55/18	39/29	Canola oil MCT oil	6.3:1	Casein Soy	0	Abbott
Glycerna 1.2	Diabetic	1.2	720	114/35	60/20	60/45	Canola oil Fish oil	3.3:1	Casein Soy	0	Abbott
Vital AF 1.2	S-elemental	1.2	425	110/36	75/25	54/39	Fish, Soy Canola, MCT	0.9:1	Whey Casein	0	Abbott
Nephro	Fluid elect restricted	1.8	745	161/34	81/18	96/48	Canola Safflower	5.2/1	Casein	0	Abbott
Pivot	IMD	1.5	595	172/45	93/25	51/30	Fish, Soy Canola, MCT	1.7:1	Whey Casein	13	Abbott
Replete	St w fiber	1.0	319	113/45	62/25	34/30	Canola oil MCT oil	2.3:1		0	Nestle
Peptamen AF	S-elemental IMD	1.2	390	107/36	75/25	55/39	Fish, MCT, Soy	1.8:1	Whey	0	Nestle
Novosource Renal	Fluid elect restricted	2.0	800	183/37	90/18	100/45	Canola, MCT	–	Soy	0	Nestle
Fibersource HN	St w fiber	1.2	490	160/53	53/18	39/29	Canola oil, MCT	2.7:1	Soy	0	Nestle
Vivonex Plus	Elemental low fat	1.0	650	188/76	45/18	6.6/6	Soy	7.0:1	Free amino acids	6.3	Nestle
Impact	S-elemental IMD	1.0	375	132/53	56/22	28/25	Fish, sunflower, safflower	1.4:1	Casein	12.5	Nestle

IMD immune-modulating diet, *MCT* medium chain triglycerides, *St* standard

  - a volume and electrolyte reduced formulation for patients with renal failure not receiving dialysis when a general all-purpose formula is not suitable
  - a low fat elemental formulation for patients on high dose propofol, the initial formulation for severe pancreatitis and patients with fistula, short gut syndrome, etc.
- There is no specific generic all-purpose formulation which has been proven to improve outcome. However we use a formula with following characteristics:
  - In excess of 70 % of ICU patients develop stress hyperglycemia. Common sense would therefore dictate using a formulation higher in fat than carbohydrate (low glycemic index)
  - As most patients have some degree of inflammation we prefer that the fat content include omega-3 fatty acids
  - As many patients may have issues with lipid absorption and metabolism we prefer a structured lipid with medium chain triglycerides
  - We prefer a formulation that has whey rather than casein or soy as the major protein, as whey contains leucine which is an essential branch chain amino acid that is a prerequisite for protein synthesis
  - The formula should have a low osmolarity to reduce the risk of diarrhoea
- The absence of bowel sounds does not mean that the bowel is not working. In the ICU patient population, neither the presence of bowel sounds nor evidence of the passage of flatus or stool is required for the initiation of enteral feeding [2].
- There is a poor relationship between the gastric residual volume and the risk of aspiration [15–17]. DO NOT hold tube feeds unless the gastric residual volume >400 mL and/or the patient shows signs of intolerance (distended abdomen, vomiting)
- In patient's receiving continuous tube feeds hypoglycemia may occur when tube feeds are suddenly discontinued. The patient should be placed on a D5 or D10 solution (to prevent hypoglycemia) and the blood glucose monitored closely (particularly when the patient is on an insulin protocol). However continuous tube feeding is not recommended (see below)
- Making the patient nil per os (NPO) surrounding the time of diagnostic tests or procedures should be minimized to prevent inadequate delivery of nutrients and prolonged periods of ileus. Ileus may be propagated by NPO status. If the patient is intubated there no need for tube feeds to be stopped hours before a procedure. This issue becomes less of a problem with bolus tube feedings as the boluses can be timed according to the timing of the diagnostic tests or procedure.
- Propofol emulsion contains approximately 0.1 g of fat (1.1 kcal) for every milliliter. An infusion of propofol may therefore provide a significant caloric load. In patients receiving high dose propofol infusions, the enteral feeds need to be adjusted to take into account the added caloric load. A low-fat enteral formulation, such as Vivonex or Vital High Protein may be used.

How Many Calories and How Much Protein to Give?

While no nutrition is bad (starvation) the unresolved question is how much is enough? Adequate nutrition is essential for the critically ill patient in order to ameliorate uncontrolled catabolism, maintain the integrity of the gastrointestinal tract, maintain a competent immune system, and ultimately improve patient outcome. Nutrition support attenuates the metabolic response to stress, limits oxidative cellular injury and favorably modulates the immune response [18–22]. However, the most important goal of nutrition is to promote anabolism and limit protein breakdown; as will be demonstrated further in this chapter none of the current methods of nutritional support have been demonstrated to promote protein synthesis. This would suggest that the amount of protein and calories delivered does not matter; however as reviewed further in this chapter, this is because the standard approach to nutritional support (continuous enteral feeding) does not support anabolism; wrong formula and wrong method of delivery!!

Aberda and colleagues conducted a large observational study to determine the association between the provision of energy and protein and patient outcomes [23]. Data were collected on 2,772 mechanically ventilated patients who received an average of 1,034 kcal/day and 47 g protein/day. An increase of 1,000 cal per day was associated with reduced mortality [OR for 60-day mortality 0.76; CI, 0.61–0.95, $p=0.014$] and an increased number of ventilator free days. The benefit of increased calories was only seen in patients with a BMI < 25 and > 35 (moderate obesity may be protective against critical illness). Similar results were observed when comparing increasing protein intake and its effect on mortality. Furthermore a number of studies have demonstrated that the energy deficit accumulated by underfeeding patients during their ICU is an important factor in increasing the risk of adverse outcomes [24–26]. However, it is important to recognize that these are all observational studies that are likely confounded by severity of illness; less sick patients tolerate enteral nutrition better, are more adequately fed and have better outcomes. Four RCT's support this contention; the first two studies randomized patients to trophic feeds or full nutrition, the third randomized patients to permissive underfeeding or full nutrition while the fourth randomized ICU's to a "PepUP protocol" where additional nutrition was given to reach caloric targets (in the intervention ICU's) compared to control ICU's where patient received usual care. The EDEN study randomized patients ($n=1{,}000$) with acute lung injury to receive either trophic feeding at 20 kcal/h (which is about 7 cal/kg/day) or full feeding at 25–30 kcal/kg/day for the first 6 days [8]. After day 6, all patients who were still receiving mechanical ventilation received the full feeding protocol. There was no difference in the number of ventilator free days (primary outcome), 60 day mortality and other secondary end-points between groups. Follow-up of these patients showed no difference in physical function, psychological and cognitive function as well as quality of life at 12 months [9, 27]. The results of the EDEN trial are similar to a smaller study ($n=200$) conducted by Rice and colleagues with a similar study design and patient population to the EDEN trial [28]. Arabi and colleagues

performed a two by two factorial design study in which 240 ICU patients were randomized to permissive underfeeding or target feeding (caloric goal: 60–70 % compared with 90–100 % of calculated requirement, respectively) and either intensive or conventional glycemic control [10]. Hospital mortality was lower in the permissive underfeeding group than in the target group (30.0 % compared with 42.5 %; RR 0.71; 95 % CI: 0.50, 0.99; $P = 0.04$). Heyland et al. randomized 18 ICU's in the USA and Canada (1,059 patients mechanically ventilated >72 h) to a novel feeding protocol (PEP-uP protocol) which targeted a daily caloric goal or usual care [29]. In the intervention ICU's enteral feeds started at a higher initial rate and they operationally shifted from an hourly rate to target a 24-h volume goal. This intervention allowed the nurses to increase the volume of feeds delivered if there was an interruption for non-gastrointestinal reasons. While patients in the intervention ICU's received more calories and protein there was no difference in any outcome variable between the intervention and control ICU's. These data suggest that achieving target caloric goals (by conventional feeding) does not improve patient outcomes.

The current SCCM/ASPEN guidelines recommend providing 1.2–2.0 g/kg/day of protein [30], with some authorities recommending up to 2.5 g/kg/day to "promote muscle anabolism" [31]. However, increased provision of protein by conventional feeding has not been demonstrated to limit muscle wasting, loss of lean body mass or improve clinical outcomes [29, 32, 33]. Paradoxically, the increased provision of protein either enterally or parentally has been demonstrated to accelerate loss of muscle mass (see below). In a post hoc analysis of the EPaNIC study, Casear et al. demonstrated a strong association between increasing cumulative protein intake with a lower likelihood of an earlier alive-discharge from the ICU [34]. These data suggest that the current guidelines for the provision of protein in critically ill patients are likely to be harmful.

Muscle Wasting in Critical Illness

Survivors of critical illness suffer from marked muscle wasting which may take years (if ever) to recover. The loss of muscle mass is associated with muscle weakness, prolonged mechanical ventilatory support, fatigue and delayed recovery. This disorder is known as Critical Illness Myopathy (CIM). CIM is characterized by a diffuse non-necrotizing myopathy accompanied by fiber atrophy (particularly type-II fast twitch fibers), fatty degeneration of muscle fibers and fibrosis [35]. In the critically ill patient multiple factors are likely to play a role in inducing muscle atrophy including muscle inactivity, inflammation, cellular energy stress, corticosteroids, hyperglycemia, neuromuscular blocking agents and inadequate provision of amino acids (low quality and continuous rather than bolus feeding) [35]. Clinically, patients with CIM may demonstrate weakness, failure to wean or paresis [35]. Creatinine phosphokinase (CPK) levels are relatively normal, consistent with a myopathy and not a myositis. Herridge et al. evaluated 109 survivors of ARDS for up to 5 years after discharge from the ICU. At the time of discharge from the ICU

patient's had lost on average 18 % of their base-line body weight [36]. Seventy-one percent of patients returned to their base-line weight by 1 year. However, it is likely that most of the mass gained was fat mass rather than repletion of the loss of muscle mass [37]. All patients reported poor function and attributed this to the loss of muscle bulk, proximal weakness, and fatigue. At 1 year the distance walked in 6 min was 66 % of predicted which increased to 76 % of predicted at 5 years [38]. The mean score for the physical component of the SF-36 Heath Survey was 25 at 1 year and 41 at 5 years (mean norm score matched for age and sex is 50). At 1 year 48 % of patients had returned to work which increased to 77 % at 5 years. Similarly, Needham and colleagues evaluated the physical performance of patients with ARDS who were enrolled in the EDEN study at 12 months following hospital discharge [9, 27]. At 12 months, the mean 6-min walk test distance was 66 % of predicted while the SF-36 physical health summary score was 39 (mean norm score of 50).

In health, muscle synthesis is stimulated in the post-prandial state while protein breakdown occurs between meals. In healthy individuals muscle mass is maintained through balanced protein breakdown and synthesis. Distinct metabolic pathways are involved in the synthesis and degradation of muscle (see Fig. 32.1). In critical illness, loss of muscle mass results from an imbalance between muscle proteolysis and protein synthesis, with proteolysis overwhelming an inadequate synthetic response. Proteolysis is achieved by several cellular signaling networks, but the predominant proteolytic pathway activated in models of muscle atrophy is the ubiquitin–proteasome system. Two muscle specific E3-ligases belonging to the ubiquitin-proteasome complex, muscle RING-finger 1 (MuRF1) and muscle atrophy F-box (MAFbx) have been identified as key regulators of proteasome-mediated protein breakdown [35, 39–41]. Forkhead box O (FOXO) is a transcriptional factor that plays a major role in muscle wasting primarily by increasing expression of MuRF-1 and MAFbx (atrogen-1) [42, 43]. FOXO dependent gene activation can be regulated by increased overall expression and by posttranslational modification of the transcription factor. Phosphorylation and dephosphorylation of FOXO result in inactivation and activation respectively of the transcription factor. FOXO-1 is activated (dephosphorylated) by inflammation and sepsis. Myostatin, a transforming growth factor-β (TGF-β) protein secreted by muscle induces muscle wasting by directly inhibiting phosphorylation of Akt and thereby increasing the activity of FOXO1 transcription factors and the downstream targets MurF1 and MAFbx. Insulin and insulin growth factor 1 (IGF1) promote net protein synsthesis. In skeletal muscle, the binding of IGF-1 or insulin activates the phosphoinositol-3 kinase/ protein kinase B (PI3K/AKT) pathway inducing muscle hypertrophy by stimulating translation via mTOR kinases. In addition IGF-1 suppresses MuRF1 transcription in part via the phosphatidyl-inositol 3 kinase/AKT pathway. Akt phosphorylates FOXO1 which is then sequestered in the cytoplasm preventing transcription of FOXO target genes [44]. In addition to activation by insulin and AKT, mTOR is controlled by the supply of amino acids and glucose [45].

Puthucheary and colleagues demonstrated a 17 % reduction in the rectus femoris cross sectional area in critically ill patients after 10 days of mechanical ventilation [46]. Loss of muscle mass was greatest in those with multisystem failure and

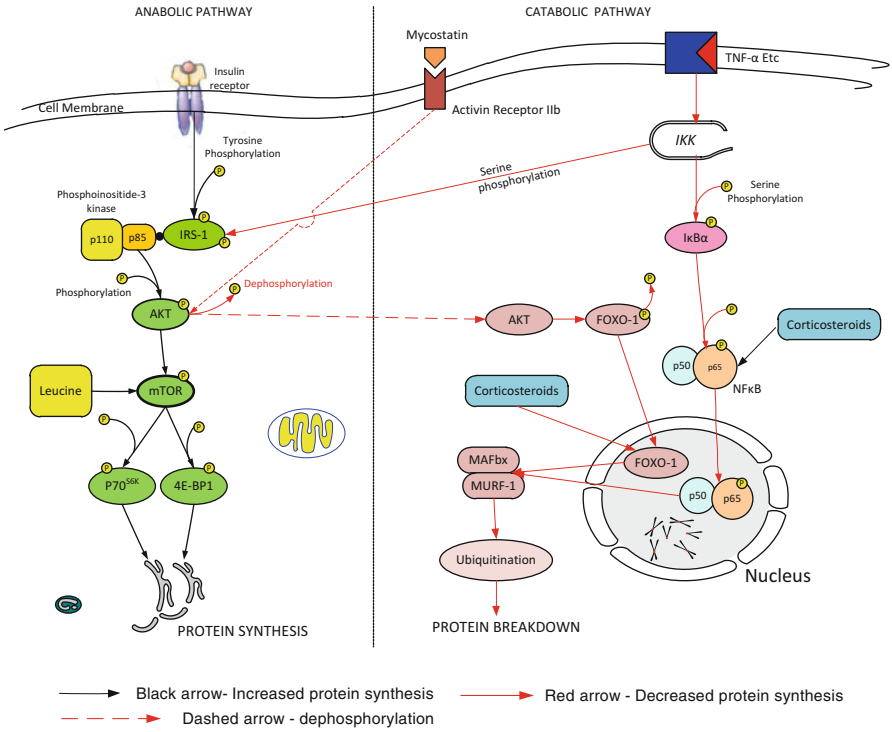

Fig. 32.1 A simplified overview of the anabolic and catabolic pathways in skeletal muscle. *Black arrow*—Increased protein synthesis. *Red arrow*—Decreased protein synthesis. *Dashed arrow*—dephosphorylation. *AKT* protein kinase b, *FOXO-1* forkhead box class O-1, *IRS-1* insulin receptor substrate-1, *MAFBx* muscle atrophy f-box-1, *MURF-1* muscle ring finger protein 1, *NF κB* nuclear factor κB, *IKK* inhibitor of nuclear factor κB kinase, *IκB* inhibitor of nuclear factor κB, *4E-BP1* eukaryotic initiation factor (eIF) 4E binding protein 1, *P70^{S6K}* 70-kDa ribosomal protein S6 kinase, *mTOR* mammalian target of rapamycin, *TNF-α* tumour necrosis factor-α

increased with increasing length of stay. Protein synthesis was depressed on day 1 compared to rates in fasted control subjects but increased by day 7. In this study the pattern of intracellular signalling demonstrated increased breakdown and decreased synthesis. Wollersheim and colleagues investigated the dynamics of myosin degradation in patients requiring mechanical ventilation for at least 15 days [35]. These authors demonstrated decreased gene expression of the myosin heavy chain isoforms with significantly increased expression of MuRF-1, MAFbx and FOXO-1 mRNA. Constantin et al. reported similar findings; in addition these authors reported widespread dephosphorylation (inactivation) of the proteins regulating translation initiation factor activation and protein synthesis (AKt1, mTOR, 4E-BP1) and increased expression of myostatin [47]. In an animal model Smith et al. demonstrated that sepsis upregulated FOXO1 expression, by a glucocorticoid-dependent mechanism [42]. Levine and colleagues demonstrated similar findings in the diaphragms of organ donors [41].

While one could argue that providing carbohydrate and fat intravenously (TPN) is unphysiologic and associated with adverse outcomes one could speculate that the provision of protein (amino acids) would promote muscle synthesis. EPaNIC was a large randomized controlled study that compared the early initiation of TPN (early TPN group) when enteral nutrition was insufficient with delayed parenteral nutrition which was initiated after 7 days, allowing a pronounced nutritional deficit to occur in the late TPN group [4]. Casaer et al. evaluated the impact of early TPN on muscle and adipose tissue compartments in a subgroup of patients enrolled in the EPaNIC study [32]. Over the first week there was a 6.9 % loss of femoral muscle volume in both groups. However, as opposed to near starvation in the late TPN group, early TPN reduced the quality of muscle tissue due to increased water and lipid content. In the study by Puthucheary et al. (referenced above) a higher protein delivery during the first week of critical illness was associated with greater muscle wasting [46]. These studies together with those previously reviewed, suggest that the traditional method of feeding patients whether enterally or parenterally does not preserve muscle mass.

The effect of steroids on muscle wasting is complex. High dose corticosteroids induce ubiquitin-proteasome dependent protein degradation in muscle [48]. However, low dose corticosteroids have not been shown to induce myopathy [49]. Furthermore, the effects of corticosteroids may be more marked in the elderly [48]. In patients with sepsis and ARDS, low dose corticosteroids decrease transcription of NF-κB a potent inducer of MuRF-1 and MAFbx and may thereby limit muscle breakdown. However corticosteroids directly increase the transcription of FOXO1, MAFbx and muRF-1 thereby promoting muscle breakdown [50]. Waddell et al. demonstrated that the MuRF1 promoter is responsive to both the activated glucocorticoid receptor and FOXO1, with coexpression of both dramatically up-regulating MuRF1 expression [51]. It is likely that the balance between these two opposing effects would determine the effect of glucocorticoids on muscle homeostasis. Furthermore, stimulation of the IGF-1 pathway will suppress FOXO-1 and MuRF-1 expression favoring muscle synthesis rather than breakdown [52]. This suggests that septic patients being treated with low dose-corticosteroids should receive a nutritional approach that favors protein synthesis (see below).

Factors That Activate Muscle Synthesis by the mTOR Pathway

Increased rates of protein synthesis require activation of the AKt/mTOR pathway. mTOR exerts a critical role in mediating signal transduction necessary for mRNA translation initiation. Key targets for mTOR activation include the 70-kDA ribosomal protein S6 kinase ($p70^{S6K}$) and the eukaryotic initiation factor 4e-binding protein (4E-BP1) [53]. Ingestion of protein in the form of free amino acids, milk protein or meat stimulates skeletal muscle protein synthesis. A short infusion of amino acids in the absence of exercise increases expression of $p70^{S6K}$ and 4E-BP1 [54]. Similarly, the ingestion of a protein isolate increases muscle protein synthesis

at rest which increases further with exercise [55]. Postprandial muscle protein synthesis depends on the quantity and type of protein ingested. Activation of mTOR pathway is markedly increased following the ingestion of essential amino acids, particularly leucine. Essential amino acids have been described as "priming molecules" whose phosphorylation of mTOR at Ser 2448 is a prerequisite for further phosphorylation by Akt [53, 56]. Both leucine and AKt activate mTOR through phosphorylation of the Ser 2448 site [53, 57]. The activation of translation initiation by essential amino acids is independent of upstream IGF-1 signalling, with mTOR acting as a convergence point for the separate actions of amino acids and resistance exercise [53, 58]. Insulin is a well-known stimulus for muscle protein synthesis. Insulin deficiency leads to a protein catabolic state with loss of muscle mass that can only be reversed by insulin [59]. Insulin increases muscle synthesis by multiple mechanisms including increased AKT/mTOR signalling and endothelial-dependent vasodilatation with an increase in nutritive flow [60].

Whey protein accounts for about 20 % and casein compromises about 80 % of total milk protein. During milk processing the caseins are responsible for making curds while whey remains soluble [61]. Whey protein is a rich source of leucine (14 %) and branched chain amino acids (26 %) [53]. Not only is whey protein a good source of amino acids, but it is also a rich source of bioactive peptides generated during its digestion [61]. Whey protein ingested either immediately prior to or following resistance exercise enhances protein synthesis [53]. However, activation of protein synthesis after acute resistance training is significantly reduced in the absence of essential amino acids [58, 62]. Why protein stimulates postprandial protein synthesis significantly more effectively than does casein [55, 63]. This effect is attributed to wheys faster digestion and absorption and higher leucine content. A 20 g dose of whey protein is required for maximal stimulation of muscle protein synthesis in resistance trained young men [64]. Katsanos and colleagues demonstrated that whey protein ingestion resulted in greater muscle protein synthesis than ingestion of its constituent amino acid content [65]. In this study the insulin response was lower with ingestion of the essential amino acid formulation as compared to whey protein and may partly explain the differential effect on protein synthesis. Furthermore, whey protein is associated with a greater increase in insulin concentration than casein [63]. Whey protein contains aspartate and arginine (non-essential amino acids) which are potent insulin secretagogues, and this may explain the greater insulin response with whey protein [65]. In addition, bioactive peptides generated from whey protein have been demonstrated to stimulate the release of several gut hormones including cholecystokinin, peptide YY, and the incretins glucose-dependent insulinotropic polypeptide 1 (GIP-1) and glucagon-like peptide (GLP-1) that potentiate insulin secretion [61, 66, 67]. Furthermore, these bioactive peptides may inhibit dipeptidyl peptidase-4 (DPP4) preventing incretin degradation [61]. Smith and colleagues demonstrated that dietary omega-3 fatty acid supplementation augments the hyperaminoacidemia-hyperinsulinemia induced increase in the rate of protein synthesis [68]. While the mechanism of this effect is not clear, the authors of this study demonstrated increased activation of the mTOR-p70^{s6k} signaling pathway without an effect on Akt signalling, suggesting increased activation at the level

of mTOR. These data strongly suggest that a whey protein based enteral formula with omega-3 fatty acids would be the preferred nutritional formula to enhance protein anabolism in critically ill and injured patients.

Bolus vs. Continuous Feeding

Vertebrates exhibit diversity in both feeding habits (omnivores, herbivores, carnivores) as well as a feeding frequencies. The structure and function of the gastrointestinal tract is adapted to both the type of feed and its frequency. Herbivores possess large gastrointestinal tracts that are specialized for the fermentation of their plant diet and the absorption of carbohydrates [69]. In contrast, carnivores (humans) have shorter gastrointestinal tracts with a greater capacity to break down proteins and absorb amino acids. Small endotherms (e.g., hummingbirds) feed every few hours while large ectotherms (e.g., crocodilians, boas, and pythons) go months without eating [69]. Medium sized endotherms such as humans seem to fall somewhere between these two extremes. No species eats continuously (day and night) and such an evolutionary design would seem absurd. The alimentary tract and metabolic pathways of humans appears designed for intermittent ingestion of a carnivorous diet a few times a day. Humans have evolved as intermittent meal eaters are not adapted to a continuous inflow of nutrients; normal physiology appears to be altered when this approach is adopted. Continuous enteral feeding of critically ill patients appears to be the standard of care around the world [30]; such an approach is clearly unphysiological and likely to be associated with a myriad of complications.

Muscle protein synthesis requires a pulsatile increase in branch-chain amino acids (particularly leucine) and/or pulses in insulin levels. Pancreatic-substrate clamp studies have demonstrated that insulin and branch chain amino acids independently increase muscle synthesis with the effects of both being additive [70, 71]. Animal data demonstrates that muscle protein synthesis following a meal is rapid (within 30 min) and sustained for about 2 h but then declines toward baseline in parallel with the postprandial changes in circulating insulin and amino acids [72]. This would suggest that continuous tube feeding with continuously low levels of amino acids and low insulin levels would result in significantly less protein synthesis than bolus feeding. This concept has been validated in a remarkable set of experiments performed by Gazzaneo et al. [73]. These authors' randomized neonatal pigs to receive a whey protein diet given as intermittent boluses or as a continuous infusion for 24 h. The authors then measured muscle protein synthetic rate and activation of the muscle intracellular metabolic pathways in both groups. As would be expected branch chain amino acid and insulin levels spiked after each bolus whereas these levels remained flat in the continuously feed animals. Muscle protein synthesis 90 min after a meal in the intermittently fed animals was twice that of the continuously fed animals. Phosphorylation of AKT, $p70^{S6K}$ and 4E-BP1 were significantly increased in the bolus fed group while these biomarkers were at basal levels in the continuously feed animals. This study confirms that a cyclic surge of

amino acids and insulin is needed to maximally stimulate protein synthesis in skeletal muscle. This animal data is supported by a study in humans. Bohe et al. investigated the responses of quadriceps muscle protein synthesis to an intravenous infusion of mixed amino acids given over 6 h [74]. Muscle protein synthesis was measured during the basal period (2.5 h) and at 0.5 h intervals during the amino acid infusion. Muscle protein synthesis increased after 30 min rising rapidly to a peak after 2 h and thereafter declining rapidly to basal values despite ongoing provision of amino acids (replicating the data seen in animal studies). The authors suggested that muscle protein synthesis responds rapidly to increased availability of amino acids but is then inhibited, despite continued amino acid availability (probably switching off mTOR). This suggests that providing a large protein load as a continuous supply of amino acids (enterally or parenterally) may paradoxically switch off protein synthesis. This postulate is supported by the study of Puthucheary and colleagues and Casaer et al. (referenced above) [32, 46].

In addition to adversely affecting protein synthesis continuous enteral feeding has other adverse consequences. The gastrointestinal tract is an important endocrine organ with dozens of regulatory peptides being produced by specialized endocrine cells within the gastrointestinal mucosa. These hormones serve complex roles regulating gastrointestinal motility, gall bladder contraction, pancreatic function and nutrient absorption [75]. The majority of these gut hormones are secreted within minutes of nutrient ingestion, rise transiently in the circulation with levels falling back to basal levels after termination of feeding. This entero-hormonal response to nutrition is almost completely absent following continuous tube feeding.

The incretins GIP and GLP-1 play an important role in preparing the pancreas to handle incoming nutrient load [75]. Both these hormones potentiate insulin secretion from the islet-β cell in a glucose dependent manner and account for up to 70 % of insulin release. In an elegant set of experiments, Stoll et al. studied the kinetics of GIP and GLP-1, insulin receptor phosphorylation and gastro-intestinal function in neonatal pigs who received either continuous enteral feed or a polymeric formula given intermittently [76]. In this study blood GIP and GLP-1 levels as well as insulin receptor phosphorylation and phosphatidylinositol 3 kinase (PI3K) levels in liver and muscle were significantly reduced with continuously feeding as opposed to intermittently feeding. Ileal mass and villus height were significantly less with continuous as opposed to bolus feeds. Furthermore, insulin resistance, hepatic steatosis and hepatic inflammation were greater with continuous feeding. Shulman et al. demonstrated greater small intestinal mucosal weight and ileal mass in new born pigs fed by bolus feeds as compared to continuous feeds [77].

Masko et al. measured cholecystokinin (CCK) levels in children receiving continuous enteral nutrition, discontinuous tube feeding and control subjects' receiving normal alimentation [78]. During continuous enteral feeding the CCK levels were similar to the preprandial levels of the control subjects, however the postprandial CCK levels increased significantly in the patients receiving discontinuous oral feeding reaching level similar to those of normal controls. In a prospective crossover study Jawaheer and colleagues compared the effects of bolus versus continuous feed on gallbladder function in 15 infants [79]. These authors demonstrated that

continuous enteral feeding led to an enlarged noncontractile gall bladder. The gallbladder contraction index was 65 % during bolus feeds. It is likely that continuous (rather than bolus feeding) is the major cause of distended non-functioning gallbladders and acalculous cholecystitis in critically ill patients.

Metabolic Abnormities and Complications Associated with Continuous Enteral Feeding

- Decreased skeletal muscle synthesis
- Decreased secretion of GIP, GLP-1 and CCK
- Decreased insulin release
- Insulin resistance
- Hyperglycemia
- Hepatic steatosis
- Hepatic inflammation
- Enlarged non-contractile gallbladder
- Small bowel atrophy

So! What is the Best Way to Feed Critically Ill Patients?

From the data reviewed above, it is quite clear that the traditional method of continuous tube feeding is illogical, stupid and quite likely harmful. Enteral nutrition should almost always be provided as intermittent boluses. Furthermore an enteral formula with whey protein, omega-3 fatty acids, structured lipids and low in carbohydrate is likely to promote protein synthesis, limit hyperglycemia and have positive immunomodulatory properties. This is the preferred type of enteral formula for almost all critically ill patients. Such a formula should be used in almost all patients the possible exceptions being renal failure patients who are not being dialyzed, patients on high dose propofol and the initial feed in patients with severe pancreatitis. Perioperative and trauma patients should receive an arginine/omega-3/whey formula. All ICU patients should be bolus fed. Previous studies have shown that it is feasible to feed critically ill patients by intermittent boluses [80–83]. These studies have demonstrated that this approach is not associated with an increased risk of aspiration. The boluses should be given no more frequently than every 4 h. Since the standard caloric and protein requirements are based on the continuous method of feeding the ideal nutritional approach to bolus feeding is unknown. However based on current data the following approach is recommended. These recommendations are for an average 70 kg patient using a 1.2 cal/mL formula and an infusion pump which can delivery up to 400 ml/h.

Day 1	150 mL q 4 hourly over 30 min	(step 1)
Day 2	200 mL q 4 hourly over 30 min	(step 2)
Day ≥3	250 mL q 4 hourly over 45 min	(step 3)

The gastric residual volume can be checked prior to the next bolus. If the residual volume is greater than 400 mL or the patient develops abdominal distension or vomiting go back to step 1 and give the patient a prokinetic agent (iv erythromycin 100 mg q 8 is preferred) [84, 85].

The optimal method of insulin and glycemic control in patients receiving bolus feeding is unclear. Critically ill patients usually have some degree of insulin resistance. Bolus feeding is likely to be associated with a more normal pattern of insulin release and less insulin resistance. However, bolus feeding is likely to result in greater glucose variability than continuous feeding. Glucose variability has been demonstrated to be associated with worse patient outcomes [86–88]. Maurya et al. compared continuous versus intermittent bolus feeding in 40 critically ill head injured patients [80]. These authors measured blood glucose 4 hourly for the first 24 h. While the blood glucose levels were slightly higher in the intermittent fed group this was not statistically significant. It is unclear whether patients should be given a small bolus of short acting insulin at the time of the bolus. The insulin spike will act synergistically with the peak in essential amino acids to stimulate protein synthesis. This may also result in less glycemic variability. More research is required to resolve this issue. However, in the absence of additional data we recommend that the glucose be checked initially prior to each bolus of enteral formula (i.e. q 4 hourly), with a meal time injection of S/C short acting insulin in patients with a "fasting" glucose above 140 mg/dL. In those patients with "adequate glycemic control" it may be sufficient to check the blood glucose every 8 h.

The Obese Patient

The notion that obese patients can be starved in incorrect. The ICU is not the place to begin a weight loss program. Obese patients often have severe sarcopenia which will be perpetuated by starvation. In the critically ill obese patient, permissive underfeeding or hypocaloric feeding with EN is recommended. For all classes of obesity where BMI is >30, the goal of the EN regimen should not exceed 60–70 % of target energy requirements or 11–14 kcal/kg actual body weight/day (or 22–25 kcal/kg ideal body weight/day). Traditional recommendations suggest that protein should be provided in a range $\geq$ 2.0 g/kg ideal body weight/day for class I and class II patients (BMI 30–40), $\geq$2.5 g/kg ideal body weight/day for class III (BMI >40) [3]. In the new era of bolus feeding it may be sufficient to provide 1.2–2.0 g/kg ideal body weight/day of high quality protein. However, additional research is required to determine the optimal caloric and protein requirements of the obese critically ill patient.

The Refeeding Syndrome

Protein-calorie malnutrition has been shown to exist in up to 50 % of hospitalized patients. Feeding malnourished patients, particularly after a period of starvation may result in severe metabolic disturbances, most notably hypophosphatemia [89,

90]. Hypophosphatemia developing after initiating parenteral or enteral nutrition has been termed the refeeding syndrome. In addition to hypophosphatemia, changes in potassium, magnesium and glucose metabolism occur during refeeding. Although classically described in cachectic patients after prolonged starvation, this syndrome has been reported to occur commonly in poorly nourished ICU patients who have been starved for as short as 48 h.

The commercially available tube feed preparations contain between 50 and 60 mg/dL of phosphorus (the recommended daily allowance). However, in patients with high metabolic demands and phosphorus depleted patients these formulas may not meet the requirements necessary to accommodate the massive transcellular shifts and possible whole-body depletion of phosphorus found in these patients. Enteral nutrition should therefore be advanced slower in patients at risk of refeeding syndrome and the phosphorus, magnesium and potassium closely monitored and aggressively repleted.

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Chapter 33
Stress Ulcer Prophylaxis

In 1969 Skillman and colleagues reported a clinical syndrome of lethal stress ulceration in 7 of 150 (5 %) consecutive ICU patients. These patients had in common respiratory failure, hypotension and sepsis [1]. Pathological examination demonstrated multiple superficial ulcers which were confined to the gastric fundus. Following this report, these authors performed a randomized controlled study in which 100 critically ill ICU patients at risk of "stress ulceration" were randomized to either antacid prophylaxis (titrated to keep the gastric pH above 3.5) or no prophylaxis [2]. Two of 51 (4 %) treated patients had gastrointestinal bleeding (GIB) as compared to 12 of 49 (25 %) control patients ($p < 0.005$). Subsequent studies confirmed this finding and two meta-analysis published by Cook and colleagues demonstrated that both histamine-2 receptor blockers (H2RB) and sucralfate decreased the risk of bleeding from stress ulceration when compared to placebo [3, 4]. Stress-ulcer prophylaxis (SUP) become regarded as the standard of care in patients admitted to the ICU and this intervention is currently endorsed by many professional bodies [5, 6]. The universal use of SUP has been reinforced with the adoption of "ventilator bundles." Currently the Joint Commission and the Institute for Healthcare Improvement recommend universal stress ulcer prophylaxis as a core "quality" measure for mechanically ventilated patients [7]. Estimates indicate that approximately 90 % of critically ill patients admitted to the ICU receive some form of stress ulcer prophylaxis.

Stress ulcers are superficial erosions in the gastric mucosa that are common in patients with acute, life threatening diseases. These lesions are usually shallow and well demarcated, primarily involving the superficial layers of the gastric epithelium [8]. Endoscopic studies have shown that nearly all critically ill patients develop upper gastrointestinal erosions after critical illness or major surgery. Gastric erosions are present in 10–25 % of patients on admission to the ICU, and in up to 90 % of patients by the third ICU day [9, 10]. Although gastric erosions are common in critically ill patients, they are usually clinically silent. The reported frequencies of clinically significant GIB varies from about 0.6 to 2 % in the absence of SUP and was 1.5 % in the large, prospective multi-center cohort study conducted by Cook

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and colleagues [11]. In the study by Cook and colleagues, the independent risk factors for GIB were respiratory failure requiring mechanical ventilation for more than 48 h (OR 15.6) and a coagulopathy (OR 4.3) [11].

The pathogenesis of stress ulceration remains poorly understood. Various factors and mechanisms, alone or in combination, are probably responsible for the lesions. Despite the multi-factorial mechanisms proposed as contributing to the development of stress-related gastrointestinal erosions, the presence of luminal gastric acid appears essential. However, the majority of patients with stress ulceration have normal acid secretion. Alterations in mucosal blood flow, the mucus layer, protein synthesis, bicarbonate and prostaglandins secretion, and epithelial cell renewal have been postulated to alter the gastric mucosal barrier leading to the back diffusion of acid leading to mucosal damage. In addition, alterations in endothelin-1 and serotonin production as well as infection with Helicobacter pylori may play a role in the development of stress ulceration.

Does SUP Reduce GI Bleeding?

During the early years of critical care, stress related GIB was an important cause of morbidity and mortality. During the past two decades the rate of stress-related GIB has declined probably due to improved resuscitation and early enteral feeding of critically ill patients. To be useful SUP should affect clinical outcome. No clinical trial of stress ulcer prophylaxis has demonstrated a reduction in mortality or length of stay. Surprisingly the effect of SUP on the risk of bleeding is unclear. Cook and colleagues performed a meta-analysis of ten studies which randomized patients to receive a H2RA or placebo. The authors reported that H2RA reduced the risk of clinically significant bleeding (OR 0.44; 95 % CI 0.22–0.88), with a trend towards an increased risk of nosocomial pneumonia (OR 0.25; 95 % CI 0.78–2.0) with no effect on mortality [4]. It should be pointed out that these studies were performed in the 1980s when early enteral nutrition was not encouraged and many patients received parenteral nutrition (see below). Messori and colleagues performed a more recent meta-analysis of studies that compared ranitidine with placebo in ICU patients [12]. These authors concluded that “ranitidine is ineffective in the prevention of gastrointestinal bleeding in patients in the ICU and might increase the risk of pneumonia”.

Zandstra and Soutenbeek reported that 1 of 183 patients (0.6 %) receiving prolonged mechanical ventilation without any SUP developed stress ulcer related bleeding [13]. Erstad and colleagues conducted a prospective study on 543 patients and reported clinically significant GIB rates were similar for those patients with ineffective SUP and those with appropriate SUP [14]. Faisy and colleagues compared the rate of clinically significant GIB during two sequential time periods [15]. During the first phase all patients ($n=736$) received SUP while SUP was withheld during the second period ($n=737$). Although the patients’ during the second phase

of the study were sicker (higher SAPS II score) the rate of overt (1.9 vs. 1.6 %) and clinically significant bleeding (1.4 vs. 1.1 %) as well as the use of blood products was similar between the two time periods. More recently, Kantorova and colleagues performed a randomized, placebo-controlled study in critically ill patients at high risk for stress related GIB (mechanical ventilation >48 h and coagulopathy) in which they compared three SUP regimens (omeprazole, famotidine and sucralfate) with placebo [16]. The overall bleeding rate was 1 % with no significant difference between treatment groups (placebo 1 %). Gastric pH and bacterial colonization was significantly greater in the patients who received acid suppressive therapy with a trend towards a higher incidence of VAP in these patients.

This data suggests that the rate of clinically significant bleeding from stress ulceration in critically ill ICU patients is currently very low and that SUP does not alter this risk or the natural history of this disease.

Enteral Nutrition and Stress-ulcer Prophylaxis

It has been suggested that patients receiving enteral alimentation have a lower incidence of stress ulceration than unfed patients [17]. In animal models, enteral alimentation has been demonstrated to protect the gastric mucosa from stress related gastric mucosal damage [18, 19]. It has been suggested that enteral nutrients buffer acid and may act as a direct source of mucosal energy, induce the secretion of cytoprotective prostaglandins and improve mucosal blood flow [18, 19]. Furthermore, mucosal immunity maybe supported via stimulation of the gut-associated lymphoid tissue. Because of duodenal-gastric reflux of liquid and increase in mesenteric blood flow due to small intestinal delivery, postpyloric feeding may offer protection against the development of stress ulceration.

Bonten and colleagues demonstrated that continuous enteral nutrition was more likely to raise gastric pH to >3.5 than patients receiving H2RA or PPI's [20]. Two rat studies have evaluated the role of enteral nutrition in preventing stress ulceration [21, 22]. The results of both trials showed that continuous intragastric administration of elemental formulas significantly reduced the occurrence of macroscopic mucosal lesions compared with intragastric administration of an antacid or intravenous administration of cimetidine. In a retrospective analysis, Raff and colleagues demonstrated that early (within 12 h post-trauma) enteral nutrition was at least as effective as H2RA and/or antacids as stress-ulcer prophylaxis in a cohort of 526 severely burned patients [23]. Pingleton et al. reported a similar finding in 43 ventilated patients [17]. A review of the "historical" randomized controlled trials that studied the effectiveness of acid suppressive therapy in reducing the risk of bleeding, demonstrates that SUP was beneficial only in those patients who were NPO (received no gastric feeding). However, in those studies in which patients were fed enterally the risk of bleeding was equivalent in the treatment and placebo groups [16, 24–26].

This data suggests that in those patients receiving enteral nutrition SUP is not required and indeed may increase the risk of complications (see below). As early enteral nutrition (as opposed to delayed enteral nutrition or parenteral nutrition) has been demonstrated to reduce the morbidity and mortality of critically ill patients, [27, 28] enteral nutrition should be initiated within 24 h of admission to the ICU unless an absolute contraindication exists (bowel obstruction, short gut syndrome).

Acid-suppressive therapy (PPI's and H2RB's) should be avoided in patients with cirrhosis as acid-suppressive therapy has been demonstrated to increase the risk of SBP [29]. Acid suppressive therapy has been associated with increased colonization of the small bowel. Presumably this leads to increased bacterial translocation with an increased risk of SBP.

Complications Associated with Acid Suppressive Therapy

It would appear to be no accident of natural selection that the gastric mucosa of mammalian species secretes acid. Acid plays an important role in protein digestion, but more importantly sterilizes the upper gastro-intestinal tract. Acid suppressive therapy is associated with increased colonization of the upper gastrointestinal tract with potentially pathogenic organism. This may be of critical importance in ICU patients where protocols of oral and enteric decontamination (with non-absorbable antibiotics/anti-microbials) have been demonstrated to reduce the incidence of ventilator associated pneumonia (VAP) [30, 31]. As an extension of these observations, acid suppressive therapy has been demonstrated to increase the gastric colonization and the risk of VAP [12, 16]. In a large prospective pharmaco-epidemiologic cohort study involving non-ICU hospitalized patients, Herzig and colleagues demonstrated that acid-suppressive medication was associated with a 30 % increased odds ratio of hospital-acquired pneumonia [32]. In a subset analysis, these authors demonstrated that this risk was related to the use of PPI's and not H2RB. Furthermore, the use of gastric suppressive therapy together with the use of broad spectrum antibiotics has been associated with an increased risk of *Clostridia difficile* infection [33–35]. Gastric acidity may be important is destroying ingested *C. difficile* spores while broad spectrum antibiotics reduce colonization resistance. PPI's have been shown to significantly raise gastric pH compared with H2RAs, which may result in a greater risk of *C. difficile* and pneumonia. Dial and colleagues demonstrated that PPI's doubled the risk of hospitalized patients developing *C. difficile* colitis, whereas H2RA did not increase this risk [34]. These authors subsequently demonstrated that the use of both PPI's and H2RA increased the risk of community acquired *C. difficile*, however the risk was greater with PPIs [36]. The rapid increase in the incidence of *C. difficile* colitis in hospitalized patients may be causally related to the exploding use of PPI's. Furthermore the use of a PPI during incident CDI treatment is associated with a significantly increased risk of recurrence [37].

So! What to Do?

MacLaren et al. performed a large pharmaco-epidemiological cohort study in adult patients requiring mechanical ventilation for 24 h or more and who were administered either an H2RA or PPI [38]. In this study PPI's were associated with a greater risks of GI hemorrhage, pneumonia, and *Clostridia difficile* infection than H2RA's. Furthermore, ICU LOS and ICU mortality was higher with PPI's as were hospital costs. Alhazzani et al. performed a meta-analysis comparing the risk of GI bleeding with H2RA's or PPI's [39]. In this study PPI's were more effective than H2RA's in reducing clinically important upper gastrointestinal bleeding (RR 0.36; 95 % CI 0.19–0.68; $p=0.002$). However a meta-analysis by Lin et al. did not find evidence that PPI's were different from H2RA's in terms of stress-related upper gastrointestinal bleeding [40].

Krag and colleagues performed a systematic review and trial sequential analysis comparing SUP versus placebo or no prophylaxis in critically ill patients [39]. Trial sequential analysis and sub-group analysis demonstrated no difference in the risk of bleeding between SUP and no-SUP groups. The authors concluded that "both the quality and the quantity of evidence supporting the use of SUP in adult ICU patients is low".

These data clearly demonstrate that SUP does not reduce mortality or ICU LOS. Furthermore, the risk of significant bleeding from stress ulceration appears to be low and it is unclear if this risk is altered by SUP. SUP with both H2RB's and PPI's increase the risk of pneumonia and *Clostridia difficile* infection. There is conflicting data as to the benefits and risks of PPI's compared to H2RB's. Based on these data ***we do not recommend routine SUP***. However, SUP should be considered in very high risk patient's i.e. on mechanical ventilation for >48 h and DIC. Treatment with a PPI or H2RB is indicated in patients with overt GI bleeding and those with an unexplained drop of hemoglobin of >2 g/dL.

Complications Associated with Specific Drugs

H2 Receptor Antagonists (H2RA)

H2RAs are widely used for SUP. They decrease gastric acid secretion through a reversible, competitive inhibition of histamine stimulated acid secretion. H2RAs have a wide therapeutic index, however, adverse reactions occur on average in 7 % of hospitalized patients [41]. Drug interactions can occur with H2RAs, particularly cimetidine. Ben-Joseph and colleagues demonstrated that the failure to reduce the dose of H2RAs in patients with renal dysfunction doubled the likelihood of the patients experiencing an adverse drug reaction [42]. Those reactions of most concern in critically ill patients include altered mental status, neutropenia and

thrombocytopenia. H2RAs may rarely cause a sinus bradycardia with rapid infusion. The central nervous system reactions include confusion, delirium, disorientation, hallucinations and obtundation. These reactions have been reported to occur in between 2 and 3 % of hospitalized patients [43]. While an altered mental status and cognition is a common problem in ICU patients, treatment with H2RAs is associated with a significant increase in central nervous system dysfunction, having been reported in up to 80 % of patients [43–45]. Considering the frequency of this reaction, the advanced age of most ICU patients and the enormous concerns with ICU related delirium, these agents are therefore best avoided.

Proton Pump Inhibitors (PPIs)

PPIs are substituted benzimidazoles that inhibit gastric secretion in a dose dependent manner. They are the most potent antisecretory agents available and can elevate or maintain intragastric pH above 6, which is necessary to maintain clotting in patients at risk for rebleeding and for ulcer healing (from peptic ulcer disease). PPIs irreversibly inhibit the final step in acid production (the transport of H^+ by the proton pump H^+/K^+ ATPase) providing long-lasting suppression of acid secretion. In addition, because PPIs are activated in the acidic compartments of parietal cells, they only inhibit secreting proton pumps. PPIs have the potential for drug interactions. PPIs are metabolized by hepatic cytochrome (CYP450) isoenzymes and therefore may interfere with the elimination of other drugs cleared by this route. Of the available PPIs omeprazole has the highest potential for drug interaction while pantoprazole has the lowest (low affinity for CYP enzymes). Omeprazole interferes with the metabolism of cyclosporine, diazepam, phenytoin, coumadin and several antipsychotic drugs. Clopidogrel is an antiplatelet drug that is commonly used following acute coronary syndromes. Clopidogrel is a prodrug whose bioactivation is mediated by hepatic cytochrome P450 isoenzymes [46]. As these enzymes are inhibited by PPIs, patients taking clopidogrel together with a PPI have been reported to have a higher incidence of cardiac events than those taking clopidogrel alone [47–49].

Sucralfate

Sucralfate is a basic nonabsorbable aluminum salt of saccharose octasulfate. It is physiochemically an antacid, but it does not lead to significant pH increase. Its mechanism of protection is believed to be multifactorial. Sucralfate forms a protective barrier on the surface of the gastric mucosa, it stimulates the secretion of mucous, bicarbonate, prostaglandins and epidermal growth factor as well as improving mucosal blood flow. Since sucralfate is not systemically absorbed, it may decrease the absorption of other concomitantly administered oral medications

including ciprofloxacin, phenytoin, digoxin and levothyroxine. To minimize these interactions it is recommended that these drugs be administered two hours before sucralfate. Sucralfate may also interact with enteral feeding, resulting in clotted feeding tubes and bezoars. Furthermore, its "pharmacodynamic activity" requires an empty stomach; therefore the use of sucralfate necessitates the interruption of tube feeding. Sucralfate should not be administrated through duodenal or jejunostomy feeding tubes because the medication would bypass its site of action. Toxic levels of aluminum have been reported in critically ill patients requiring continuous veno-venous hemofiltration who were receiving sucralfate [50]. As this drug appears to be less effective than acid suppressive therapy in preventing bleeding from stress ulceration and as it administration requires the interruption of tube-feeds, it would appear that this agent has a limited role in the ICU [51].

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Chapter 34
Acute and Chronic Liver Disease

Chronic Liver Failure

Chronic liver failure (CLF) and cirrhosis accounted for more than 26,000 deaths and more than half a million hospitalizations in the United States in 2004, making liver disease the 12th leading cause of death [1]. Hospital and/or ICU mortality rates of cirrhotic patients admitted to the ICU range from 34 to 86 % [2]. The Child-Turcotte-Pugh (CTP) scoring system classifies CLF into three categories based on severity (see Table 34.1). A total CTP score of 5–6 is Child's class A, well-compensated disease; a CTP score of 7–9 is Child's class B, in which there is significant functional compromise; and a CTP score of 10–15 is Child's class C, advanced decompensated disease [3]. The model for end-stage liver disease (MELD) score provides another classification of the severity of chronic liver failure based on the readily obtainable laboratory values of serum creatinine, total bilirubin, and prothrombin time, expressed as the international normalized ratio [3, 4]. Several variations to MELD that include serum sodium (MELD-Na) and the Integrated Model for End-stage liver disease (iMELD) have been shown to improve mortality prediction in cirrhotic patients awaiting liver transplantation [5, 6].

Cirrhosis is defined histologically as an advanced form of progressive hepatic fibrosis with distortion of the hepatic architecture and regenerative nodule formation. It may be due to a variety of causes. The major clinical consequences of cirrhosis are impaired hepatocyte function, an increased intrahepatic resistance (portal hypertension), and the development of hepatocellular carcinoma. The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and resulting portal hypertension. The clinical picture of chronic liver disease is frequently dominated by the complications of portal hypertension. In addition, infectious complications are common and associated with worsening of hepatocyte function and portal hypertension.

P.E. Marik, *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-11020-2_34

Table 34.1 The Child-Turcotte-Pugh (CTP) scoring system

Parameter	1	2	3
Ascites	Absent	Easily controlled	Poorly controlled
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Causes of Cirrhosis

- Viral/infectious
- Viral/infectious
- Hepatitis B
- Hepatitis C
- Schistosomiasis
- Metabolic/toxic
- Alcohol
- Toxins
- medications
- Hereditary hemochromatosis
- Wilson's disease
- Nonalcoholic steatohepatitis (NASH)
- Autoimmune hepatitis
- Cholestatic
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Secondary biliary cirrhosis
- Vascular
- Right heart failure
- Budd–Chiari syndrome
- Alpha-1-antitrypsin deficiency
- Sarcoidosis
- Cystic fibrosis

Cirrhosis represents a clinical spectrum, ranging from asymptomatic liver disease to hepatic decompensation. Manifestations of hepatic decompensation include

- variceal bleeding
- ascites with spontaneous bacterial peritonitis
- hepatic encephalopathy
- hepatorenal syndrome
- hepatopulmonary syndrome
- portopulmonary hypertension

- hepatocellular carcinoma
- hepatoadrenal syndrome

The liver never fails in isolation…it takes each and every organ system down with it!

Metabolic/Hematologic Derangements in Cirrhosis

- Hyperglycemia (portal to systemic shunting)
- Hypoglycemia (hepatocyte failure)
- Hypoalbuminemia
- Decreased synthesis of clotting factors prolonged INR
- Decreased production of AT, Protein S and C. thrombotic risk
- Increased ammonia
- Cholestasis
- Impaired absorption of fat and fat soluble vitamins
- Anemia
  - Microcytic from iron deficiency
  - Macrocytic folate and B12 deficiency
- Hyponatremia (Na < 135 mmol/l)
  - An independent predictor of mortality [7]
  - From increased ADH due to decreased effective circulating volume
- Thrombocytopenia
  - Hypersplenism
  - Alcohol
  - Marrow suppression
  - "Low level" DIC
- Renal dysfunction
- Impaired immunity

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is seen in up to 30 % of patients with ascites [8]. Patients who have SBP present with fever, diffuse abdominal pain or tenderness, altered mental status, leukocytosis, or worsening renal function. Approximately 15 % of patients do not have any signs or symptoms of SBP. SBP is believed to be a consequence of increased bacterial translocation largely via the lymphatic system. Small intestinal bacterial overgrowth is frequently present in the advanced stages of liver cirrhosis. Furthermore, cirrhosis is associated with structural and functional alterations in the intestinal mucosa that increase permeability to bacteria and bacterial products [8]. Only a few intestinal bacteria are able to translocate to the

mesenteric lymph nodes including *Escherichia coli*, *Klebsiella pneumonia* and other Enterobacteriaceae [8]. These are the species most commonly implicated in SBP. The diagnostic test of choice is abdominal paracentesis. An ascitic fluid neutrophil count higher than 250/mm^3, in the absence of an intra-abdominal surgical source of infection, such as a perforated peptic ulcer or abscess, is diagnostic of SBP. Fluid cultures are positive in approximately half of the cases. An elevated serum procalcitonin (PCT) level is reported to have a high diagnostic accuracy for SBP, and appears to be a useful adjunctive diagnostic aid [9]. Almost all cases of SBP are secondary to a single micro-organism, with *Escherichia coli* and *Klebsiella pneumoniae* accounting for approximately half of the cases [10]. Treatment consists of a 5-day course of a third-generation cephalosporin, such as intravenous ceftriaxone, which usually results in an excellent clinical response with resolution of SBP. For patients unable to take a cephalosporin, intravenous ciprofloxacin, followed by oral administration, is recommended [10].

SBP is associated with the development of hepatorenal syndrome in about 30 % of patients. In 1999, Sort and colleagues reported the results of a RCT in which patients with SBP were randomized to cefotaxime + albumin or cefotaxime alone [11]. 20 % albumin was given at a dose of 1.5 mg/kg at the time of SBP diagnosis and 1.0 mg/kg after 48 h. The study does not report the duration of the albumin infusion. Renal impairment developed in 21 patients in the cefotaxime group (33 %) and 6 in the cefotaxime + albumin group (10 %) ($P = 0.002$). Eighteen patients (29 %) in the cefotaxime group died in the hospital, as compared with 6 (10 %) in the cefotaxime-plus-albumin group ($P = 0.01$); at three months, the mortality rates were 41 % (a total of 26 deaths) and 22 % (a total of 14 deaths), respectively ($P = 0.03$). Salerno and colleagues performed a metaanalysis of studies comparing albumin to placebo in patients with SBP [12]. The meta-analysis included three studies; the incidence of renal impairment in control groups was 44 of 144 (30.6 %), compared with 12 of 144 (8.3 %) in groups given albumin. The pooled odds ratio for a reduction in renal impairment after albumin infusion was 0.21 (95 % CI, 0.11–0.42). Mortality among controls was 51 of 144 (35.4 %), compared with 23 of 144 (16.0 %) among patients who received albumin. The pooled odds ratio for decreased mortality after infusion of albumin was 0.34 (95 % CI, 0.19–0.60). Considering the pharmacodynamics of albumin (reviewed in detail in Chap. 9) we would recommend a "bolus" of 5 % albumin (500–1,000 mL) at the time of diagnosis (given over 1–2 h), followed by a continuous infusion of 20–25 % albumin at a rate of 10–15 mL/h. Alternatively, an infusion of 100 mL of 20–25 % albumin may be given over 3–4 h, followed a continuous infusion at a rate of 10–15 mL/h.

Patients who have had an episode of SBP are at an increased risk of recurrent episodes, hence antibiotic prophylaxis is recommended in these patients. Following an initial episode of SBP, 1-year recurrence rate is 55 % with a 1-year survival is less than 50 %. Norfloxacin has been demonstrated to reduce the recurrence of SBP and is currently regarded as the agent of choice for secondary prophylaxis [13].

Amoxicillin-clavulanate and trimethoprim-sulfamethoxazole are acceptable alternatives in those unable to tolerate quinolones. Primary prophylaxis, defined as antibiotic treatment of patients without prior SBP, has been suggested in patients who have chronic liver failure and ascites who fulfill the following criteria:

- ascitic fluid protein concentration lower than 1 g/dL
- serum bilirubin level higher than 3.2 mg/dL, and
- platelet count higher than 98,000/mm^3, as these patients have a threefold-increased risk of developing SBP within 1 year.

A RCT demonstrated that primary prophylaxis with norfloxacin significantly reduced the 1-year risk of developing SBP when compared with placebo (7 % versus 61 %; $P<0.001$) [14]. A meta-analysis which included both primary and secondary prophylaxis demonstrated a lower incidence of infections (RR 0.32; 95 % CI 0.20–0.51) with an overall mortality benefit (RR 0.65; 95 % CI 0.48–0.88) [15].

Acid-suppressive therapy (PPI's and H2RB's) should be avoided in patients with cirrhosis as acid-suppressive therapy has been demonstrated the increase the risk of SBP [16]. Acid suppressive therapy is associated with increased colonization of the small bowel. Presumably this leads to increased bacterial translocation with an increased risk of SBP.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a significant neuropsychiatric syndrome that most commonly occurs in decompensated cirrhosis [17]. Clinical features range from clinically imperceptible symptoms in minimal HE, which require neuropsychometric testing to identify, to a comatose state in the worst cases. Many factors have been implicated in its pathogenesis, including derangements in neurotransmitter pathways, cerebral blood flow modulation, and systemic inflammatory responses. The ammonia hypothesis states that impaired hepatic breakdown of ammonia results in multiple neurotoxic effects, including altering the transit of amino acids, water, and electrolytes across the neuronal membrane and propagating astrocyte swelling and cerebral edema. Contrary to "classic teaching", Ong and colleagues found a good correlation between the serum ammonia levels and the severity of hepatic encephalopathy [18]. Furthermore, there was no significant difference between venous and arterial ammonia levels. The Working Party for Hepatic Encephalopathy established nomenclature for hepatic encephalopathy in 1998 [19]. Type A HE refers to HE secondary to acute liver failure, type B refers to enteric hyperammonemia (without liver disease), and type C is associated with chronic liver disease. The severity of HE is graded using the West Haven criteria (grades 1–4) [17].

Grades of Hepatic Encephalopathy

- Grade 0
  - No signs or symptoms
- Grade 1
  - Trivial lack of awareness, euphoria or anxiety, shortened attention span impaired performance of addition
- Grade 2
  - Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, impaired performance of subtraction
- Grade 3
  - Somnolence to semi-stupor, but responsive to verbal stimuli, confusion, gross disorientation
- Grade 4 Coma (unresponsive to verbal or noxious stimuli)

Hepatic encephalopathy develops in up to 50 % of patients with cirrhosis and is a feature of decompensated cirrhosis. Hepatic encephalopathy portends a worse survival for patients compared with similar patients without HE. Acute worsening of HE should prompt an evaluation for reversible causes, such as gastrointestinal bleeding, hypovolemia, hypoglycemia, hypokalemic metabolic alkalosis, infection, constipation, hypoxia, or excessive use of sedatives

Colonic bacteria with urease activity produce ammonia in the gut. The disaccharide lactulose (β-galactosidofructose) is the mainstay of induction and maintenance treatment of HE [17]. The microvilli of the small bowel lack disaccharides capable of breaking down lactulose, permitting the entry of this disaccharide into the colon. Lactulose is broken down by bacterial flora to short chain fatty acids lowering colonic pH converting NH^3 to nonabsorbable NH^{4+} which remains in the colon, reducing plasma ammonia. In addition, lactulose shifts the colonic flora from urease to non-urease producing bacterial species and reduces bacterial load by its cathartic effect. The starting dose of lactulose is commonly 30 g twice a day, titrated to two to three soft stools per day. A meta-analysis performed in 2004 found that nonabsorbable disaccharides were superior to placebo but did not improve survival [20]. When only high-quality trials were included in this meta-analysis, nonabsorbable disaccharides had no effect on HE. Despite the lack of high level evidence clinical guidelines recommend lactulose as first-line therapy [21].

Nonabsorbable antibiotics such as rifaximin are frequently added to lactulose to further decrease intestinal ammonia production [22]. Rifaximin is however not FDA approved for the treatment of episodic HE, only for the secondary prevention of HE. Sharma et al. conducted a RCT ($n=120$) comparing rifaximin and lactulose with lactulose and placebo in patients with HE [23]. Patients in the lactulose and rifaximin group had a higher proportion of complete reversal of HE (76 % vs 50.8 %, $P<0.004$), shorter hospital stay, and a striking improvement in 10-day mortality (49.1 % vs 23.8 %, $P<0.05$). Probiotics and prebiotics (Bifidobacterium and fructose-oligosaccharides) which alter the bowel flora favoring non-urease

producing bacterial species have been demonstrated to lower ammonia levels and improve mentation in patients with hepatic encephalopathy [24–26]. Most patients require maintenance medications (lactulose and/or rifaximin) at the time of hospital discharge as secondary prophylaxis for HE [27, 28].

Previously, aggressive protein restriction was recommended; however, this is now believed to worsen the nutritional status of patients and decreases overall survival [29]. Guidelines published by the European Society for Clinical Nutrition and Metabolism (ESPEN) recommended that patients with cirrhosis should have an energy intake of 35–40 kcal/kg body weight per day and a protein intake of 1.2–1.5 g/kg body weight per day [30]. Zinc deficiency impairs the activity of urea cycle enzymes and glutamine synthetase. Zinc deficiency has been implicated in the pathogenesis of hepatic encephalopathy as diminished serum zinc levels and their inverse correlation with blood ammonia levels have been reported [31]. Zinc supplementation in the treatment of hepatic encephalopathy is based on a small number of controlled studies that provided inconsistent results regarding efficacy, types and doses of zinc used, and duration of therapy [32].

Molecular Adsorbent Recirculating System (MARS) was introduced in 1999 and is based on the concept of albumin dialysis. This system was designed to remove protein- and albumin bound toxins, however it also removes non-protein bound molecules such as ammonia [17]. While MARS has been demonstrated to improve HE it has not been demonstrated to improve survival [33].

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a functional form of renal failure that occurs in patients with end-stage liver disease. The pathophysiological hallmark of HRS is vasoconstriction of the renal circulation. The mechanism of the vasoconstriction is incompletely understood; it may be multifactorial, involving disturbances in the circulatory function and activity of the systemic and renal vasoactive mechanisms. Patients with HRS demonstrate arterial vasodilation in the splanchnic circulation with arterial constriction in the cerebral, hepatic and renal vascular beds. Furthermore, patients' who develop HRS appear to have inadequate cardiac output. Non-azotemic cirrhotic patients who develop HRS have lower cardiac output and higher plasma renin activity (PRA) than those who don't progress to HRS [34]. These findings support the hypothesis that a hyperdynamic circulation is essential to maintain renal perfusion. When cardiac output deceases effective hypovolemia occurs, leading to renal hypoperfusion and HRS [35]. In 1996 the International Ascites Club established diagnostic criteria for the diagnosis of HRS [36]. HRS was further classified as type 1 and type 2 according to the rate of decline of renal function. Type 1 was arbitrarily defined as a 100 % increase in serum creatinine reaching a value of greater than 1.5 mg/dL in less than 2 weeks. Patients who had a slower decline in renal function were deemed to have type 2 HRS. The current diagnostic

criteria for HRS (proposed originally by the International Ascites Club in 1996 and revised in 2005) are listed below [35, 36].

Hepatorenal Syndrome: Diagnostic Criteria

- Presence of cirrhosis with ascites
- Serum creatinine >1.5 mg/dL
- Failure of serum creatinine to improve to <1.5 mg/dL after cessation of ALL diuretics + volume expansion with intravenous albumin (see section on SBP)
- HRS can be diagnosed in the presence of infection if shock is absent
- NO current or recent use of nephrotoxic drugs
- No evidence of parenchymal kidney disease; proteinuria <500 mg/d; <50 RBC high power field

Diagnostic Approach

- Urinalysis, including urine Na and fractional Na excretion
- Rule out abdominal compartment syndrome (paracentesis and albumin infusion)
- Rule out SBP (paracentesis and albumin infusion)
- Renal ultrasound to exclude hydronephrosis/obstructive uropathy

In a prospective cohort study of non-azotemic cirrhotic patients with ascites the incidence of HRS was reported as 18 % at 1 year and 39 % at 5 years [37]. Patients with type 1 HRS have a very poor prognosis compared to patients with type 2 HRS. The median survival time for type 1 HRS has been reported to be 14 days. Common precipitating factors for type 1 HRS include bacterial infections, particularly SBP, variceal hemorrhage, major surgery and alcoholic hepatitis. Excessive diuresis and the use of contrast agents have also been implicated in precipitating HRS. Tsai et al. demonstrated that 80 % of patients with HRS precipitated by sepsis had adrenal dysfunction (see hepato-adrenal syndrome) [38]. Replacement therapy with hydrocortisone improves systemic hemodynamics and in-hospital survival [39]. The only effective medical therapy currently available for the management of HRS is the administration of vasoconstrictors together with volume expansion with albumin. Volume expansion with albumin and vasopressin analogues (ornipressin and terlipressin), norepinephrine, midodrine and somatostatin (octreotide) have been used with variable success [40, 41]. Liver transplantation is considered the treatment of choice for patients with cirrhosis and type 1 HRS because it "allows for both the liver disease and associated renal failure to be cured."

HRS is a frequent complication of over overdiuresis (with Lasix), particularly in the setting of a contrast study or a therapeutic paracentesis. Patients who undergo a contrast study and or paracentesis require fluid loading (with albumin).

LASIX is NOT a volume expander; its use may lead to a fatal outcome in patients with cirrhosis.

Treatment of HRS

Renal vasodilators (low dose dopamine, intravenous prostaglandin-E, endothelin antagonists) have no proven role in the treatment of HRS. Reversing splanchnic and peripheral vasodilation with a vasoconstrictor combined with an albumin infusion is currently the cornerstone of treatment of HRS. This strategy is based on a number of small case series and clinical trials [42–46]. Reversal of HRS has been reported in 25–83 % of patients treated with pressor agents plus albumin compared to 8.7–12.5 % of patients treated with albumin alone [47]. However, long term patient survival without liver transplantation is not improved. Albumin alone does not appear to reverse HRS. Furthermore, normal saline should not be used as a volume expander in cirrhotic patients with a decline in renal function. Terlipressin is the most studies vasopressor agent for the treatment of HRS. This synthetic vasopressin derivative is believed to have a much greater effect on vascular receptors (V1) than renal vasopressin receptors (V2). A metaanalysis of ten clinical trials of terlipressin reported that this therapy was well tolerated and reversed HRS in 52 % of cases [48]. Norepinephrine plus albumin appears to be a useful alternative to terlipressin [49].

Combination Therapy for HRS

- Intravenous terlipressin (not yet approved for use in the US) initial dose of 0.5–1 mg every 4–6 h, increased on day 4 to 2 mg 4–6 hourly if serum creatinine has not decreased by >30 % from baseline + intravenous albumin (see section on SBP)
- Intravenous norepinephrine; start at a dose of 0.01 μg/kg/min and titrate to increase the MAP by 10–15 mmHg (even in the absence of hypotension) + intravenous albumin
- Oral midodrine initial dose of 7.5 mg TID titrate up to 15 mg TID to increase MAP by 10–15 mmHg + octreotide 100 μg SQ TID increased to 200 μg TID on day 2 if renal function has not improved + intravenous albumin. The use of octreotide alone without midodrine has not been shown to be effective.

Hepato-adrenal Syndrome

Sepsis and end-stage liver disease have a number of pathophysiologic mechanisms in common (endotoxemia, increased levels of pro-inflammatory mediators, decreased levels of HDL), and it is therefore not surprising that adrenal insufficiency is common in patients with end-stage liver disease [50]. Furthermore, sepsis in the cirrhotic patient likely increases the risk of adrenal insufficiency. Tsai and colleagues performed a corticotrophin stimulation test in 101 patients with cirrhosis and sepsis [38]. In this study 51.4 % of the patients were diagnosed with adrenal insufficiency; survival at 90 days was 15.3 % in these patients compared to 63.2 % in those patients with normal adrenal function. Fernandez and co-authors compared the survival of patients with cirrhosis and sepsis who underwent adrenal function testing in which patients with adrenal insufficiency were treated with hydrocortisone (Group 1) compared to a control group (Group 2) that did not undergo a cosyntropin testing and were not treated with corticosteroids [39]. The incidence of adrenal failure was 68 % in Group 1; the hospital survival was 64 % in Group 1 as compared to 32 % in Group 2 ($p = 0.003$). These data suggest that adrenal dysfunction is common in critically ill patients with end-stage liver disease and that treatment with corticosteroids may improve outcome.

Pulmonary Consequences of Portal Hypertension

Two distinct pulmonary vascular disorders can occur in cirrhosis: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). Both can coexist in the same patient. Portopulmonary hypertension is seen in 0.5–5 % of patients with cirrhosis and/or portal hypertension and presents in similar ways to patients with pulmonary hypertension from other causes. Diagnosis is established by echocardiography and right heart catheterization. Recent case reports and series have demonstrated improvement of pulmonary hypertension with oral sildenafil [51]. HPS is defined as a defect in arterial oxygenation induced by intrapulmonary vascular dilatations. This entity is seen in 8–17 % of patients with cirrhosis, and median survival is 11 months. Liver transplantation resolves HPS in the majority of patients

Infection and Cirrhosis

Cirrhotic patients have several abnormalities which increase the susceptibility to bacterial infection; these include deficiency of bactericidal and opsonic activities, impaired monocyte function, depressed phagocytic activity, defective chemotaxis, and low levels of serum complement. A National Hospital Discharge Survey demonstrated that hospitalized cirrhotics are more likely to develop sepsis (RR 2.6) and to die from sepsis (RR 2.0) than hospitalized non-cirrhotics [52]. Fifteen to 35 % of

cirrhotics develop nosocomial infection, with infection accounting for 30–50 % of deaths in patients with cirrhosis.

- Usual infections
  - SBP
  - Pneumonia
  - Gram-negative bacteremia
  - UTI
- Common pathogens
  - *Escherichia coli*
  - *Staphylococcus aureus*
  - *Enterococcus faecalis*
  - *Streptococcus pneumoniae*
  - *Pseudomonas aeruginosa*
- Diagnosis of infection is difficult in patients with cirrhosis
  - reduced WBC due to hypersplenism
  - tachycardia and hyperdynamic circulation
  - hyperventilation due to hepatic encephalopathy
  - blunted febrile response
  - Cirrhosis itself results in low grade fever

In patients with cirrhosis, infections

- Further impair systemic and splanchnic hemodynamics
- Impair coagulation
- Worsen liver function
- May trigger variceal bleed

Supportive Care of the Hospitalized Cirrhotic

- Do not replace clotting factors or platelets unless bleeding
- Feed with a 1 g/kg protein diet
- SCD's for DVT prophylaxis? heparin 500 sc q 12 or LMWH
- Exclude infection; culture blood, ascitic fluid
- Prophylactic antibiotics in high risk patients
- DO NOT DIURESE… give 25 % albumin
- Paracentesis in patients with tense ascites (replace albumin)
- Avoid nephrotoxic drugs
- AVOID sedatives, particularly benzodiazepines which can precipitate hepatic encephalopathy. Haloperidol and dexmedetomidine are okay.
- Lactulose for regular stool
- Monitor venous ammonia
- ACTH stim test replace with hydrocortisone if adrenal insufficiency
- Ultrasound + Doppler to exclude portal/splenic vein thrombosis and hepatocellular carcinoma
- α feto-protein level

The Coagulopathy of Chronic Liver Disease

Classic teaching suggests that the coagulopathy of liver disease leads to an increased risk of bleeding. However recent data suggests that this dogma is likely incorrect and that chronic liver disease results in a procoagulant state. The concept that patients with liver disease are "auto-anticoagulated" should be abandoned. Patients with cirrhosis have multiple defects in the coagulation pathway including deficiencies in both procoagulant and anticoagulant factors, thrombocytopenia, hypofibrinogenemia and hyperfibrinolysis [53]. These derangements reflected in conventional coagulation indices (low platelet count, increased INR, low fibrinogen) have led cirrhosis to become regarded as a hemorrhagic disorder. Cirrhosis is characterized by a reduction in synthesis of all the procoagulant factors, which worsens as the disease progresses [53]. The exception to this is the powerful procoagulant factor VIII, which is synthesized in extra-hepatic sites (vascular endothelium) and shows the opposite trend. Furthermore, the synthesis of the anti-coagulants Protein S and Protein C is reduced (promoting a pro-thrombotic state). In addition, elevated levels of antiphospholipid antibodies are detected in some patients with cirrhosis [54]. Thrombocytopenia is common owing to a reduction in platelet production sequestration in the spleen and increased turnover. Although platelet numbers are low this may be compensated by platelet hyper-activation owing to increased levels of platelet protein adhesion factor and von Willebrand factor and reduced levels of ADAMTS13 (von Willebrand factor cleaving protease) [53]. A reevaluation of the disturbed coagulation pathways in cirrhosis has now led cirrhosis to be considered a pro-coagulant state. More accurate tests of coagulation including thrombin generation assays have shown that the plasma from patients with cirrhosis appears to be hypercoagulable in comparison with healthy controls [55, 56].

The factors promoting bleeding and/or thrombosis in patients with cirrhosis are listed in Table 34.2. The reader is referred to an excellent review on this topic by Tripodi and Mannucci [57]. Chronic liver disease results in a balanced reduction of both the procoagulant and anticoagulant pathways. However, although rebalanced, the coagulation system in patients with chronic liver disease is not as stable as that in healthy persons, who have an excess of both procoagulants and anticoagulants. Therefore, the relative deficiency of both coagulation-system drivers makes the balance fragile in patients with liver disease and may tip it toward hemorrhage or

Table 34.2 Factor promoting bleeding and/or thrombosis in patients with cirrhosis [53]

Favors bleeding	Favors thrombosis
Decreased procoagulant factors	Deceased anticoagulant factors
Decreased platelet number	Increased von-Willebrand factor
Decreased platelet function	Decreased ADAMTS 13
Decreased fibrinogen	Increased factor VIII
Increased fibrinolysis	Increased procoagulant microvesicles
Decreased red call mass	Lupus anticoagulant

thrombosis, depending on the prevailing circumstantial risk factors [57]. The disturbed coagulation system in patients with cirrhosis may therefore lead to bleeding, thrombosis or even both depending on the trigger (sepsis, renal dysfunction, hypovolemia). Although still common practice, the use of FFP to correct the "coagulopathy" of liver disease should be abandoned, even in patients undergoing invasive procedures. The American Association for the study of Liver Diseases (AASLD) warns against the indiscriminant use of FFP prior to paracentesis, central line placement and liver biopsies (see Chap. 7) [58, 59].

Recent studies have documented an increased risk of venous thrombosis in patients with cirrhosis. Dabbagh et al. reported that 6.3 % of hospitalized patients with chronic liver disease developed venous thromboembolism [60]. In this study the risk of VTE was similar between INR quartiles, with half the cases occurring in patients with an INR > 1.6. VTE prophylaxis was not used in 75 % of patients. In a case-matched study of patients admitted to a tertiary care center Gulley et al. reported a higher incidence of VTE in cirrhotic patients as compared to controls (1.8 % vs. 0.9 %, $P = 0.007$) [61]. Using data from the Nationwide Inpatient Sample in 2005, Ali et al. reported that 1.8 % of hospitalizations in cirrhotic patients were for VTE [62]. The optimal strategy to prevent DVT in hospitalized patients with cirrhosis is unclear. This subject was not addressed in the most recent ninth edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [63]. Since these are high risk patients with a thrombophilia, SCD's together with pharmacologic prophylaxis (heparin or LMWH) may be preferred in non-bleeding patients while SCD's should be used in bleeding patients (esophageal varices). LMWH appears to be safe in patients with cirrhosis and hepatic dysfunction (see below). Patients with cirrhosis are at an increased risk of portal vein thrombosis. This is reviewed below.

Thrombin, the main effector of the coagulation cascade, elicits a number of cellular effects through a family of G-protein coupled receptors known as protease activated receptors [53]. Excessive thrombin generation with activation of these receptors has been implicated in the increased fibrogenesis seen in patients with cirrhosis. Anticoagulants, which decrease thrombin may therefore reduce fibrogenesis in patients with cirrhosis (see below).

Portal Vein Thrombosis

The portal vein originating from the confluence of the superior mesenteric and splenic veins, accounts for 75 % of the blood supply to the liver (see Fig. 34.1) [64]. Portal vein thrombosis (PVT) is an important complication in patients with chronic liver disease. The incidence of PVT varies between 0.6 and 16 % in patients with well-compensated cirrhosis to 35 % in patients with advanced liver disease particularly those with hepatocellular cancer [64, 65]. PVT in the absence of cirrhosis accounts for about 5–10 % of cases of portal hypertension in the Western hemisphere; most of these cases are related to an inherited or acquired thrombophilia.

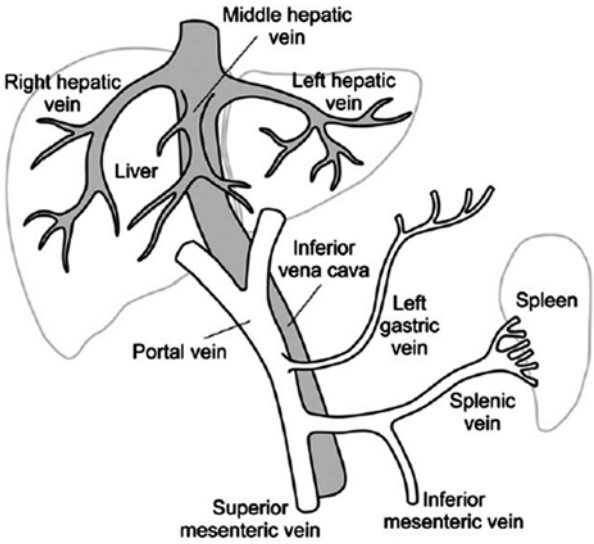

Fig. 34.1 Anatomy of the portal circulation

In developing countries PVT is a common cause of portal hypertension. In candidates for liver transplantation, the patency of the portal vein is crucial. Partial PVT is likely to make anastomoses technically difficult and increases the risk of post-transplant complications including complete PVT. Complete PVT is a contraindication for transplantation [65].

The mechanisms by which cirrhosis leads to PVT is not entirely clear, however decreased portal blood flow and the pro-thrombotic state associated with cirrhosis have been implicated. The role of an inherited thrombophilia is the pathogenesis of PVT associated with liver disease is uncertain. Patients with acute PVT (symptomatic less than 60 days and no evidence of portal hypertension) may complain of abdominal pain, fever and nausea [64]. However, many patients may be asymptomatic or present with non-specific symptoms. In patients with chronic PVT, features of portal hypertension and hepatic dysfunction dominate the clinical picture. Therefore, PVT should be excluded in patients with chronic liver disease who present with hepatic decompensation. Ultrasound with color Doppler imaging is the diagnostic test of choice in diagnosing PVT. Luca and colleagues performed an observational study to determine the natural course of PVT in untreated, non-malignant partial PVT in 42 patients with cirrhosis [66]. After a mean follow-up of 27 months partial PVT worsened in 20 (48 %) patients, improved in 19 (45 %) and remained stable in three (7 %).

The use of anticoagulants in the treatment of cirrhotic patients with PVT is controversial, with some experts in the field recommending against routine anticoagulation [64]. However, others have recommended anticoagulation for PVT to prevent progression and propagation of the clot and the development of complications [67–69]. This recommendation is based on the results of two small studies. Amitrano et al. reported the results of the treatment of 39 patients with PVT treated with

enoxaparin [67]. Overall, a complete recanalization was observed in 75 % of patients. No significant side effects, particularly bleeding complications, were observed during the treatment. Francoz et al. evaluated the effect of anticoagulation in patients with PVT listed for liver transplantation [65]. Anticoagulation was initiated with LMWH followed by a vitamin K antagonist. Partial or complete recanalization was significantly higher in those who received (8/19) than in those who did not receive (0/10, $p=0.002$) anticoagulation. Survival was significantly lower in those who had complete portal vein thrombosis at the time of surgery ($p=0.04$). More recently Villa et al. performed a randomized controlled trial of enoxaparin (40 mg/day) for the prevention of PVT in patients with advanced cirrhosis [70]. At 96 weeks, none of the patients in the enoxaparin group had developed PVT compared 10 of 36 (16.6 %) controls ($p=0.001$). Liver decompensation was less frequent among patients treated with enoxaparin (11.7 %) than controls (59.4 %) ($p<0.0001$). Bacterial infection (SBP or bacteremia) occurred in 8.8 % of treated patients as compared to 33.3 % of controls ($p=0.19$) The probability of survival was greater in the enoxaparin group. No relevant side effects or hemorrhagic effects were reported. In addition, these authors evaluated circulating biomarkers of intestinal integrity and immune activation to bacterial products. Intestinal fatty acid binding protein (I-FABP), a marker of intestinal damage, decreased significantly in the enoxaparin group ($p=0.003$). Similarly IL-6 and circulating levels of bacterial DNA decreased significantly in the enoxaparin group. This suggests that anticoagulation may improve splanchnic microcirculatory flow with functional improvement of the gastro-intestinal tract. While anticoagulation reduces the risk of PVT it is likely that the lower risk of liver decompensation and infection is related to the improved intestinal microcirculation [70]. In summary, these data suggest that LMWH should be considered in both the treatment and prevention of PVT in patients with liver disease. Patients should undergo screening and treatment for esophageal varices prior to anticoagulation.

Vitamin K antagonists are probably not the ideal drugs to use in patients with cirrhosis. Protein C is a vitamin-K dependent protein and treatment with a vitamin K antagonist is likely to further reduce the levels of this naturally occurring anticoagulant, increasing the risk of thrombosis. The newer direct thrombin inhibitors and inhibitors of activated factor X appear to be attractive alternatives to vitamin K antagonists because they do not reduce protein C levels [57]. However, there is currently no data to support the use of these drugs in patients with liver disease.

Acute-on-chronic Liver Failure

Acute on chronic liver disease (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitating event and results in the failure of one or more organs and has a high short term mortality [2]. The precipitating events include alcoholic hepatitis, SBP, bleeding from esophageal varices and sepsis unrelated to the liver.

Alcoholic Hepatitis

Approximately 7.4 % of Americans abuse alcohol or suffer from alcohol dependence [71]. Alcoholic hepatitis is observed in approximately 20 % of heavy drinkers and about 50 % of heavy drinkers who are admitted to an acute-care hospital. Alcoholic hepatitis represents a spectrum of disease ranging from mild injury to severe, life threatening injury, and often presents acutely against a background of chronic liver disease [71]. Alcoholic hepatitis invariably represents an acute deterioration of established chronic liver disease and is consequently categorized as acute-on-chronic liver failure [72]. Alcoholic hepatitis is a clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use (mean intake, approximately 100 g per day) [73]. High risk patients (Maddrey's discriminant function ≥32) have a 28 day mortality of approximately 35 % [74]. Even patients with relatively mild diseases are at a high risk of progressive liver injury with cirrhosis developing in up to 50 %. Not uncommonly, the patient will have ceased alcohol consumption several weeks before the onset of symptoms. The cardinal sign of alcoholic hepatitis is the rapid onset of jaundice. Other common signs and symptoms include fever, ascites, and proximal muscle loss. Patients with severe alcoholic hepatitis may have hepatic encephalopathy. Typically, the liver is enlarged and tender. Severe alcoholic hepatitis is frequently complicated by sepsis, hepatorenal syndrome as well as other organ failures. Histology of the liver reveals hepatocellular injury characterized by ballooned (swollen) hepatocytes that often contain amorphous eosinophilic inclusion bodies called Mallory bodies (also called alcoholic hyaline) surrounded by neutrophils [72]. The presence in hepatocytes of large fat globules, also known as steatosis, is common in alcoholic hepatitis. While the pathophysiology of alcoholic hepatitis is complex and incompletely understood the prevailing theory postulates that ethanol promotes the translocation of lipopolysaccharide (LPS) from the lumen of the small and large intestines to the portal vein, where it travels to the liver. LPS activates Kupffer cells in the liver. TNF-α, produced by Kupffer cells, appears to play a pivotal role in the genesis of alcoholic hepatitis. This inflammatory cascade acts in concert with the direct hepatotoxicity of alcohol to promote hepatocellular injury.

Laboratory studies characteristically reveal:

- Increased AST (but usually <300 IU)
- AST : ALT >2
- Increased WBC with neutrophilia
- Increased bilirubin (usually >5 mg/dL)
- Increased INR
- Increased creatinine

A variety of scoring systems have been developed to assess the severity of alcoholic hepatitis and to guide treatment. Maddrey's discriminant function (mDF) and the Glasgow alcoholic hepatitis score (GAHS) help the clinician decide whether corticosteroids should be initiated (Table 34.3) [75, 76]. These scoring systems share common elements, such as the serum bilirubin level and prothrombin time

Table 34.3 Glasgow alcohol hepatitis score [76]

Score	1	2	3
Age	<50	>50	—
WCC	<15	≥25	—
BUN mg/dL	<14	≥14	—
INR	<1.5	1.5–2.0	>2.0
Bilirubin	<7.3	7.3–14.7	>14.7

(or INR). A more recent model (Lille model) which uses six variables (age, serum creatinine, albumin, prothrombin time, bilirubin and change in bilirubin over a week) has demonstrated improved prognostic ability compared to the mDF [77, 78]. This model is available on the Internet (www.lillemodel.com).

Maddrey's discriminant function is calculated as [4.6 × (patient's prothrombin time − control prothrombin time, in seconds)] + serum bilirubin level (mg/dL).

Differential Diagnosis [72]

- Biliary obstruction
- Decompensated alcoholic cirrhosis including sepsis induced cholestasis
- Alcoholic foamy degeneration
- Zieve's syndrome (hemolysis, hyperlipidemia and jaundice following an alcohol binge)
- Non-alcoholic liver disease
  - Malignant infiltrative disease
  - Drug induced liver injury
  - Viral hepatitis (incl. hepatitis E)
  - Hereditary hemochromatosis
  - Autoimmune liver disease

Alcoholic foamy fatty change is a clinical entity distinct from alcoholic hepatitis characterized by gross elevation of alkaline phosphatase and ϒ-glutamyl transpeptidase in a patient with massive hepatomegaly and jaundice, both of which rapidly improve with abstinence [72]. The need for liver biopsy to confirm the diagnosis of alcoholic hepatitis is controversial and it is not clear that histological confirmation of the diagnosis alters the outcome [72].

Management

- Protein-calorie malnutrition is a common finding in alcoholics, as are deficiencies in a number of vitamins and trace elements including vitamin A, vitamin D, thiamine, folate pyridoxine and zinc [71]. Enteral feeding is rec-

ommended in those patients with poor oral intake and in intubated patients. A daily protein intake of 1–1.5 g/kg of body weight is recommended, even among patients with hepatic encephalopathy [79].

- Patients may develop alcohol withdrawal syndrome. While benzodiazepines are usually recommended dexmedetomidine may be particularly useful in this situation. Benzodiazepines should be used with caution in patients with liver dysfunction.
- Corticosteroid therapy abrogates the inflammatory process. However, the use of these agents has been controversial [71, 80]. An individual patient meta-analysis demonstrated that corticosteroids reduce mortality in patients with a mDF $\geq$ 32 [74]. Forrest et al. demonstrated that in patients with a mDF > 32 only those with a GAHS $\geq$ 9 benefit from corticosteroids [81]. A more recent meta-analysis by the Cochrane Group demonstrated a survival benefit of corticosteroids in patients with a mDF > 32 and/or hepatic encephalopathy [80]. Prednisolone at a dose of 40 mg per/ day for 28 days is usually recommended. A prompt decline in serum bilirubin indicates a favorable response to therapy. Patients who do not exhibit a reduction in serum bilirubin within 1 week are considered non-responders and have a 6-month mortality rate of 50 % or higher [72].
- A small RCT ($n = 101$) published in 2000 showed that pentoxifylline (400 mg q 8 hourly), a phosphodiesterase inhibitor which modulates TNF-α transcription, reduced short-term mortality among patients with alcoholic hepatitis [82]. The survival benefit of pentoxifylline appears to be related to a significant reduction in the development of the hepatorenal syndrome. A more recent study compared pentoxifylline and corticosteroids with corticosteroids alone in patients with alcoholic hepatitis and a MDF score of >32 [78]. At 7 days, response to therapy assessed by the Lille model was not significantly different between the two groups. In this study 6-month survival and risk of hepatorenal syndrome was not improved with combination therapy as compared to steroids alone. Furthermore, pentoxifylline appears to be of no benefit in patients who have failed treatment with corticosteroids [83].
- Direct TNF-α inhibitors have not been demonstrated to improve outcome [71, 84].
- The role of liver transplantation in patients with alcoholic hepatitis who have failed medical therapy is a highly contentious topic; however, transplantation may have a role in selected cases [72].

Fulminant Hepatic Failure

Fulminant hepatic failure (FHF) also known as acute liver failure is defined as the development of impaired hepatic synthetic function with coagulopathy and the development of hepatic encephalopathy in the absence of underlying liver disease within a 2–3 month time period. This condition is uncommon but not rare; affecting approximately 2,000 cases annually in the United States with a mortality ranging 50–90 % despite intensive care therapy [85].

The clinical picture of chronic liver disease is frequently dominated by the complication of portal hypertension. On the other hand the clinical picture of acute/fulminant hepatic failure is dominated by hepatocyte failure. Cerebral edema leading to intracranial hypertension (IH) complicates approximately 50–80 % of patients with severe FHF (grade III or IV coma) in whom it is the leading cause of death [86]. Recovery of functional liver mass in acute liver injury occurs more readily than in the chronic setting because of the lack of long-standing fibrosis and portal hypertension, and the host's overall better nutritional status. Therefore, if the individual can be supported throughout the acute event, and the inciting injury is removed or ameliorated, recovery will follow the rapid regeneration of liver cells. For those in whom spontaneous recovery is not possible, liver transplant may be life-saving.

Causes of Fulminant Hepatic Failure

- Viral Hepatitis
  - Hepatitis B,C and E, and rarely A and D infection
  - CMV infection
  - viral hemorrhagic fevers
- Drugs and toxins
  - acetaminophen
  - alcohol
  - isoniazid
  - valproic acid
  - phenytoin
  - *Amanita phalloides*
  - carbon tetrachloride
  - methylenedioxymethamphetamine ("ecstasy")
- Miscellaneous
  - fatty liver of pregnancy
  - Reye's syndrome
  - Wilson's disease
  - Autoimmune chronic active hepatitis
  - Budd-Chiari syndrome (especially in patients with underlying hepatic disease

Workup of Patients Presenting with FHF

- Blood and Urine testing
  - Complete blood cell count with platelets
  - Electrolytes BUN and creatinine
  - International normalized ratio (INR)
  - Liver panel

  - Blood lactate
  - Ammonia
  - Blood gas with pH
  - Uric acid
  - Pregnancy testing
  - Urine electrolytes and osmolarity
  - Blood cultures
  - Urine cultures
- Diagnostic tests
  - HIV testing
  - Hepatitis A,B,C, E (all markers)
  - Cytomegalovirus (CMV) PCR and Ab
  - Herpes simplex virus (HSV) PCR and Ab
  - Epstein-Barr virus Ab
  - Autoimmune markers
  - Antinuclear antibody
  - Antismooth muscle antibody
  - Anti-liver kidney microsomal antibody
  - Serum copper and urine copper
- Hypercoagulable markers
  - Lupus anticoagulant
  - Factor V Leiden
- Toxicology screen and drug panel
  - Acetaminophen
  - Opiates
  - Barbiturates
  - Cocaine
  - Alcohol
- Imaging and other testing
  - Chest radiograph
  - Abdominal ultrasound with Doppler study of the liver
  - ECG
  - Echocardiogram with estimation of pulmonary artery pressures

Cerebral Edema in FHF

Currently the mechanism(s) which produce cerebral edema and intra-cranial hypertension (IH) in the setting of FHF are multi-factorial in etiology and are only partially understood. Possible contributing mechanisms include cytotoxicity due to the osmotic effects of ammonia, glutamine, other amino acids, and pro-inflammatory cytokines. Cerebral hyperemia and vasogenic edema occur due to disruption of blood brain barrier with rapid accumulation of low molecular substances. Dysfunction of the sodium–potassium ATPase pump with loss of auto-regulation of

cerebral blood flow has been implicated as a cause of hyperemia. As encephalopathy progresses there is gradual cerebral vasodilation due to loss of cerebral autoregulation resulting in increased cerebral blood volume and edema. Finally, in the preterminal phase there is a marked reduction in cerebral blood flow due to cerebral edema with ultimate cerebral herniation.

Clinical signs of IH include systemic hypertension, bradycardia, pupillary abnormalities, decerebrate posturing, epileptiform activity, and brainstem respiratory patterns. These are however late signs and usually indicate impending herniation. An arterial ammonia level higher than 200 μg/dL in stage III and IV encephalopathy is a strong predictor of brain herniation [87]. Though high ICP often results in death in patients with FHF it is not clear how to identify those patients at risk and how to monitor them. Computed tomogram brain scanning often fails to demonstrate cerebral edema in patients with elevated ICP. The use of ICP monitoring in patients with FHF is controversial. There is no evidence that ICP monitoring improves outcome (due to lack of data). In addition, both intraparenchymal and intraventricular monitoring devices are contraindicated as these patients are usually severely coagulopathic. Furthermore, epidural devices are less accurate and many centers no longer use these devices. Consequently, in many centers the ICP is not monitored. Nevertheless, the US Acute Liver Failure Study Group has endorsed the use of ICP monitors in patients with FHF who are at high risk of IH [88].

Trans-cranial Doppler is a valuable non-invasive technique which measures systolic flow velocity of the middle cerebral artery. Cerebral blood flow measured with trans-cranial Doppler appears to correlate fairly well with more direct measures of flow such as xenon, and A-V oxygen content trends [89]. Normal systolic velocity is <120 cm/s. Attenuation of the diastolic flow signal may be a sign of intracranial hypertension and diminished effective cerebral perfusion. In addition, the diastolic waveform may indicate early or late signs of elevated ICP as diastolic flow begin to attenuate. A pulsatility index (Systolic Velocity—Diastolic Velocity/Systolic Velocity) >1.6 is a poor prognostic sign.

Management of Increased ICP

- Optimal management of IH and FHF begins with the recognition that a patient with acute liver disease may die suddenly and are therefore best cared for in an ICU with expertise in the management of liver failure. Since the transportation of patients with advanced levels of coma is hazardous and the disease often worsens rapidly, transfer to a liver transplantation center should be considered at the time of admission of any patient with altered mentation. Increase in ICP often occurs in conjunction with the multiple organ dysfunction syndrome.
- Assisted ventilation must be instituted in all patients with grade III and IV coma. In general sedation of any kind should be avoided in early stages of coma. Patient's head must be positioned at a 30° upright angle to improve

jugular venous outflow and to optimize cerebral perfusion pressure. Coughing, gagging, agitation, fever, seizures, arterial hypertension and frequent head turning and endotracheal suctioning are all associated with surges in ICP and are best avoided. Although neuromuscular blockade may be needed if patients are particularly difficult to ventilate or if severe hypoxia exists, they are best avoided.

- Propofol is the sedative agent of choice in patients with FHF. Propofol permits a faster return to wakefulness and is a useful agent for neurological evaluation in patients with FHF. Liver failure does not influence propofol pharmacokinetics. Propofol has additional properties that may be beneficial in patients with FHF including a decrease in cerebral metabolic rate, decrease ICP, potentiation of GABAminergic inhibition, inhibition of NMDA glutamate receptors and voltage-dependent calcium channels and prevention of lipid peroxidation [90]. Propofol decreases intra-cranial pressure (ICP) in patients with either normal or increased ICP.
- There are no randomized controlled clinical trials which have evaluated lactulose or non-absorbable antibiotics in patients with FHF. However, considering the central role that ammonia is postulated to play in the pathophysiology of FHF, it may be prudent to "detoxify" the gastrointestinal tract with one of these agents.
- Moderate induced hypothermia (32–33 °C) has been shown to delay the onset of encephalopathy, and control cerebral edema in several studies [91]. Several mechanisms have been proposed by which induced hypothermia reduces cerebral edema in patients with FHF. Hypothermia reduces cerebral ammonia levels by decreased brain ammonia uptake, decreased production of ammonia in situ, and improved ammonia clearance in the brain by stimulation of glutamine synthesis [92]. Induced hypothermia should be considered in patients with grade III and IV coma. Mannitol and hypertonic saline have a role in patients with evidence of severely raised ICP.
- The US Acute Liver Failure Study Group conducted a RCT in which patients with FHF not due to acetaminophen were randomized to n-acetylcysteine (NAC) or placebo [93]. Spontaneous survival amongst patients stratified by grade of encephalopathy is shown in Table 34.4. The primary outcome of the trial, overall survival rate (i.e., spontaneous survival + survival after OLT), was 61 of 92 patients (67 %) in the placebo group, and 57 of 81 patients

Table 34.4 Spontaneous Survival of patients with FHF (not due to acetaminophen) randomized to NAC or placebo

Grade at admission	Placebo	NAC	*p* value
1–2	17/56 (30 %)	30/58 (52 %)	0.021
3–4	8/36 (22 %)	2/23 (9 %)	0.177
Total	25/92 (27 %)	32/81 (45 %)	0.09

(70 %) in the NAC group (p = 0.57). Although, the outcome of the trial was considered "negative", considering the safety profile of NAC and greater spontaneous survival in the patients who received NAC, the administration of NAC should become the "standard of care" for FHF patients (at least in those with mild-to moderate hepatic encephalopathy)

Supportive Measures

- Monitor blood glucose; 5–10 % D/W to prevent hypoglycemia
- Monitor neurological status very closely
- Monitor volume status, urine output
- Exclude/treat sepsis
- Routine cultures and infection surveillance
- Prophylactic antibiotics are generally not recommended
- Enteral feeding should be commenced within 24 h of ICU admission and should provide 20–25 kcal/kg/day. 1 g/kg/day protein is recommended. In patients considered to be at high risk of IH or in whom circulating ammonia is approaching or above 150 mmol/L, this protein load may be reduced (to 0.5 g/kg/day)
- Vitamin K 10 mg intravenously given as a single dose
- Prophylactic transfusions to normalize coagulation profile are not recommended. FFP/fibrinogen for active bleeding only. Unnecessary correction of coagulopathy will remove one of the most important parameters for determining patient prognosis and further complicate the already difficult decision-making process around transplantation listing
- Monitor INR and lactate closely; at least every 8 h
- N-acetyl cysteine should be considered
- Extracorporeal liver assist devices (ELAD) hold promise for temporary hepatic support.

Indications for Liver Transplantation

The decision as to whether a patient will recover with conservative management or require transplantation has been the subject of many different reports and case series; however, the Kings College Criteria remain the current standard for clinicians [94]. These criteria are used to predict death in patients presenting with ALF in the setting of acetaminophen and other causes of ALF. Despite these criteria the decision as to when to "list" a patient with FHF is extremely difficult. In the authors' experience, the trend in both the INR and serum lactate is very useful in assisting with this decision.

Kings Criteria

- Acetaminophen-induced acute liver failure (ALF)
  - Hepatic encephalopathy coma grades 3–4
  - Arterial pH <7.3
  - Prothrombin time (PT) greater than 100 s
  - Serum creatinine greater than 3.4 mg/dL
- Non-acetaminophen-induced ALF
  - PT of greater than 100 s or
  - Three of the following five criteria:
    - Age less than 10 years or greater than 40 years
    - ALF caused by non-A, non-B, non-C, hepatitis, halothane hepatitis, or idiosyncratic drug reactions
    - Jaundice present more than 1 week before onset of encephalopathy
    - PT greater than 50 s
    - Serum bilirubin greater than 17.5 mg/dL

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Chapter 35
GI Bleeding

Initial Assessment

- The urgency with which GI bleeding is managed is dictated by the rate of bleeding
  - the patient with trace heme-positive stools and without severe anemia can be managed as an outpatient
  - visible blood requires hospitalization and inpatient evaluation
  - persistent bleeding or re-bleed with hemodynamic instability necessitates ICU admission
  - massive bleeding is defined as loss of 30 % or more of estimated blood volume or bleeding requiring blood transfusion of 6 or more units/24 h.
- Hemodynamic assessment (see Table 35.1)
  - blood pressure, pulse, postural changes and assessment of peripheral perfusion.
- The presence of co-morbid disease must be determined, especially CAD and cardiac failure
- Estimating blood loss. This can be estimated by measuring the return from a NG tube.
- An approximate estimate of blood loss can also be made by the hemodynamic response to a 2-L crystalloid fluid challenge:
  - If BP returns to normal and stabilizes, blood loss of 15–30 % has occurred
  - If BP rises but falls again, blood volume loses of 30–40 % has occurred
  - If BP continues to fall, blood volume loss of >40 % has probably occurred
- History and examination: Attempt to localize most likely source of bleeding
  - Use of NSAID, alcohol, antiplatelet drugs and anticoagulants

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Table 35.1 Correlation between physical signs and severity of UGIB

Physical sign	Mild	Moderate	Severe
Blood Loss	<1 L	1–2 L	≥2 L
Blood pressure	Normal	N-borderline low	Hypotensive
Orthostasis	No	Possible	Likely
Tachycardia	None-mild	Moderate	Severe
Skin	Warm, perfused	Diaphoretic	Cool, clammy
Urine output	Normal	Diminished	Poor
Sensorium	Alert/anxious	Anxious	Confused/drowsy

  - History of GERD, chronic epigastric pain, renal failure, weight loss, vomiting before bleeding, etc.
  - Previous history of bleeding
  - The presence for melena indicates upper GI bleeding
  - Hematemesis indicates upper GI bleeding
  - When small amounts of bright red blood are passed per rectum; the lower GI tract can be assumed to be the source
  - In patients with large-volume maroon stools, NG tube aspiration should be performed to exclude upper GI hemorrhage. It should be noted that in about 15 % of patients with upper gastrointestinal bleeding NG aspirate will fail to obtain blood or "coffee ground" material.
- Nasogastric aspiration with saline lavage is beneficial to detect the presence of intragastric blood, to determine the type of gross bleeding, to clear the gastric field for endoscopic visualization, and to prevent aspiration of gastric contents. NG tube placement is essential to monitor ongoing bleeding and to decompress the stomach.
  - Concerns that placement of a nasogastric tube may induce bleeding in patients with coagulopathies are outweighed by the benefits of the information obtained.
- Laboratory tests:
  - serum chemistries (incl. BUN and creatinine), CBC, coagulation profile PT, PTT, INR), liver function tests
  - Cardiac enzymes (troponins) and ECG
- Patients should be risk stratified on admission based on the patient's age (over 65 years), hemodynamics, hemoglobin, renal function and comorbidities into a high and low risk group. The Blatchford risk score can be used for this purpose (see Table 35.2) [1]. A score ≥6 indicates an increased risk for an intervention to control bleeding. Such patients should be admitted to the ICU.

Table 35.2 Blatchford risk severity score

Admission risk marker	Score
BUN (mg/dL)	
<17.1	0
>17 < 22.5	2
>22.5 < 28	3
>28 < 70	4
>70	6
Hemoglobin (g/dL)—men	
≥13	0
≥12 < 13	1
≥10 < 12	3
<10	6
Hemoglobin (g/dL)—women	
≥12	0
≥10 < 12	1
<10	6
Systolic blood pressure	
>109	0
100–109	1
90–99	2
<90	3
Other markers	
Pulse >100	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

Initial Resuscitation

- Establish 2 large bore IV lines or a large bore central line.
- Insert NG tube and aspiration (by hand).
- Volume expansion with crystalloids (LR preferred, see Chap. 9).
- Monitor BP, pulse and urine output.
- Cross match blood. Blood products are the most efficient volume expanders and should be infused as soon as possible in patients with significant bleeds. Transfusion requirements are determined by multiple factors, including patient age, presence of comorbidities, cardiovascular status, baseline hematocrit, and tempo of the bleeding, along with the current hematocrit level. RBCs are transfused in patients who have significant blood loss, continuing active bleeding, and those who manifest cardiac, renal, or cerebral ischemia. The rate of blood transfusion is determined by the severity of the hypovolemia, by the tempo of the bleeding, and by the presence of comorbidities. Patients should be resuscitated to a target hemoglobin of 7 g/dL; targeting a higher hemoglobin is associated with an increased risk of rebleeding, infec-

tions and death (see Chap. 38). Villanueva et al. randomized patients with an UGIB to a transfusion trigger of 7 g/dL or 9 g/dL [2]. In this study, the restrictive transfusion strategy was associated with a lower risk of rebleeding (10 % vs. 16 %, $P=0.01$) and adverse events (40 % vs. 48 %, $P=0.02$) with a greater probability of survival in the subgroup of patients with cirrhosis and Child–Pugh class A or B disease (hazard ratio, 0.30; 95 % CI, 0.11–0.85).

- It is important to note that it takes up to 72 h for the hematocrit to reach its nadir after a single episode of bleeding (assuming no other intervention). Therefore a normal hemoglobin (on admission or soon thereafter) does not exclude significant bleeding. Blood transfusion should not be withheld from actively bleeding patients, based on their hemoglobin/hematocrit. Conversely a falling hematocrit does not imply continued bleeding; but rather may represent equilibration of fluid between the intravascular and extra-cellular extravascular compartment.
- In patients with active bleeding fresh frozen plasma should be given if the INR > 1.6. However, as there is limited data that correcting the INR improves outcome endoscopy should NOT be delayed pending attempts at correcting the INR [3].
- Platelet transfusion is indicated if the platelet count is <50,000/mm3. In general FFP and platelets should be given after 4–6 units of RBC's (see Chap. 38). While a ratio of 1:1:2 (1 unit FFP, one unit platelets for each unit 2 units of blood) has shown a benefit in trauma patients, there is a lack of data for the use of these blood products in non-traumatic patients requiring massive transfusion.

- Airway protection. The risk of aspiration is especially high in patients with massive bleeding or those who have an altered mental status. Endotracheal intubation is recommended in these patients. In addition, endotracheal intubation facilitates endoscopy. It may be advisable to place a NG tube prior to intubation in an attempt to empty the stomach and reduce the risk of aspiration during endotracheal intubation.
- In patients with severe upper GI bleeding and clinical evidence or a history of advanced liver disease or a history of previous variceal bleeding an octreotide infusion should be commenced prior to endoscopy (see treatment of variceal hemorrhage below).
- In patients with presumed UGIB proton pump inhibitor (PPI) therapy is recommended before EGD. The rationale for PPI therapy is that the most common causes of UGIB, including ulcers, gastritis, duodenitis and hemorrhagic reflux esophagitis, are medically treated with acid-suppressive therapy. PPI therapy is also useful, however, for hemostasis of lesions that are not caused by acid and are not usually treated by PPI therapy, probably because neutralization of intraluminal gastric acid promotes hemostasis by stabilizing blood clots. Experimental data have shown that gastric acid impairs clot formation, promotes platelet disaggregation, and favors fibrinolysis.
- Intravenous erythromycin (70–100 mg), through its effect as a motilin receptor agonist, has been shown to promote gastric motility and substantially improve visualization of the gastric mucosa on initial endoscopy. A meta-analysis by

Barkun et al. demonstrated that a prokinetic agent significantly reduced the need for repeat EGD (OR 0.55; 95 % CI, 0.32–0.94) [4]. Prokinetic agents may therefore be useful in patients who are suspected to have substantial amounts of blood or clot in their upper GI tract or those who have recently eaten [3].

- All patients who have acute GIB require gastroenterology consultation.
- Surgical consultation is recommended for patients who have ongoing active bleeding, massive bleeding, recurrent bleeding, bleeding associated with significant abdominal pain, acute lower gastrointestinal bleeding, and abdominal findings suggestive of an acute abdomen.

Triage of Patients. Who to Admit to the ICU?

At the time of triage the following criteria can stratify patients into a high risk group (high risk of re-bleeding, requiring surgery, and dying).

- a systolic blood pressure of <100 mmHg on admission
- severe comorbid disease
- evidence of active, ongoing GI hemorrhage at the time of triage
- INR > 1.6

The rate of rebleeding is approximately 3 % in the low risk group as compared to 25 % in the high risk group. Patients in the low risk group do not require admission to an ICU and can be adequately managed on a general medical floor. The Blatchford Risk Severity Score can also used to risk stratify patients (see Table 35.2). A score ≥6 indicates an increased risk for an intervention to control bleeding. Such patients should be admitted to the ICU.

Upper GI Bleeding

Upper gastrointestinal bleeding (UGIB) is a common, potentially life threatening condition responsible for more than 300,000 hospital admissions and about 30,000 deaths per annum in America. Accurate patient evaluation and appropriate early management before esophagogastroduodenoscopy (EGD) is critical to decrease the morbidity and mortality [5].

UGIB is defined as bleeding proximal to the ligament of Treitz, to differentiate it from lower gastrointestinal bleeding involving the colon, and middle gastrointestinal bleeding involving the small intestine distal to the ligament of Treitz. It has a mortality of 7–10 % [5]. The mortality has decreased only minimally during the last 30 years, despite the introduction of endoscopic therapy that reduces the rate of rebleeding. This observation has been attributed to the increasing percentage of UGIB occurring in the elderly, who have a much worse prognosis than other patients because of their frequent use of antiplatelet medications or anticoagulants, and their frequent comorbid conditions. Peptic ulcer disease causes more than 60 % of cases of UGIB whereas esophageal varices cause approximately 6 % [6].

The Major Causes of UGIB Include

- Peptic ulcer disease
- Esophageal and gastric varices
- Hemorrhagic gastritis
- Esophagitis
- Mallory-Weiss tear
- Upper GI malignancy
- Dieulafoy lesion

Helicobacter pylori and the use of NSAIDs are the predominant cause of PUD in the US accounting for approximately 50 and 25 % of cases respectively [7]. *H. pylori* adheres to the gastric epithelium and renders the underlying mucosa more vulnerable to damage by producing enzymes and toxins, affecting gastrin levels and acid output. Dieulafoy lesions are large, tortuous, histologically normal vessels located in the submucosa. These vessels often protrude through mucosal defects, rendering them at risk for rupture because necrosis of the arterial wall from exposure to acid.

Further Management of Upper GI Bleeding (See Fig. 35.1)

Early upper gastrointestinal endoscopy is the cornerstone of management of upper gastrointestinal bleeding. Endoscopy within 12–24 h of presentation is generally recommended. EGD is the prime diagnostic and therapeutic tool for UGIB [8].

Early endoscopy serves three vital roles:

- Diagnosis.
  - It accurately delineates the bleeding site and determines the specific cause. EGD is 90–95 % diagnostic for acute UGIB
- Treatment
  - Non-variceal bleeding. Endoscopic therapy has been shown to improve outcomes in patients with non-variceal bleeding. The endoscopic methods of controlling bleeding include, thermal coagulation of a bleeding vessel, injection of a bleeding site with epinephrine or a sclerosing agent and laser therapy to produce tissue coagulation. Endoscopic therapy has been shown to be of benefit to patients with actively bleeding lesions or lesions that have a protuberance in the ulcer crater (i.e. a visible vessel) seen on endoscopy. The rate of re-bleeding in patients with active bleeding or non-bleeding visible vessel is reduced by about 50 % with endoscopic therapy [9]. However, in about 20 % of such patients, bleeding recurs.
  - Variceal bleeding. Endoscopic band ligation is the method of choice in controlling active variceal hemorrhage.

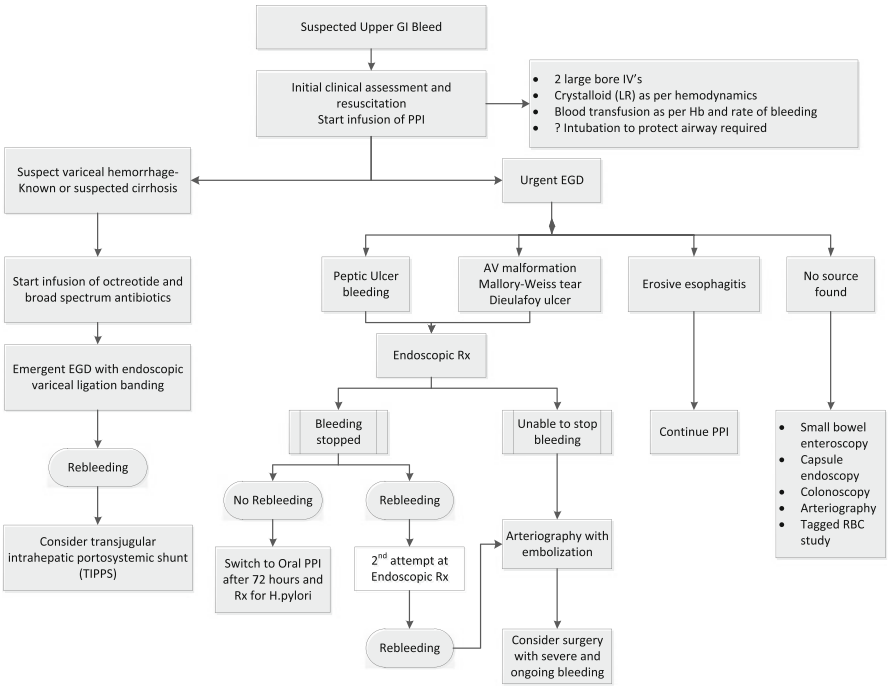

Fig. 35.1 Approach to upper GI bleeding

- Risk stratification.
  - Establishing an endoscopic diagnosis of the lesion and associated stigmata greatly enhances the ability to predict outcomes (i.e. the risk of rebleeding).
  - The endoscopic appearance of a bleeding ulcer can be used to predict the likelihood of recurrent bleeding on the basis of the Forrest classification, which ranges from IA to III. High risk lesions include those characterized by active spurting of blood (grade IA) or oozing blood (grade IB), a non-bleeding visible vessel described as a pigmented protuberance (grade IIA), and an adherent clot (grade IIB). Low-risk lesions include flat, pigmented spots (grade IIC) and clean-base ulcers (grade III) [9]. The Rockall risk score can also be to risk stratify patients after endoscopy and has been validated in multiple countries [10–13] (see Tables 35.3 and 35.4).

Further Management of Bleeding Peptic Ulcers

- A meta-analyses demonstrated that the use of PPI's significantly decreased the risk of ulcer rebleeding (odds ratio, 0.40; 95 % CI, 0.24–0.67), the need for urgent surgery (odds ratio, 0.50; 95 % CI, 0.33–0.76), and the risk of death (odds ratio, 0.53; 95 % CI, 0.31–0.91) [14].

Table 35.3 Post Endoscopy risk stratification based on the Rockall risk score

Variable/score	0	1	2	3
Age	<60	60–79	>79	–
Hemodynamics	SBP > 100 HR < 100	SBP > 100 HR > 100	SBP < 100	–
Comorbidities	No major comorbidities	–	Heart failure, CAD any major comorbidity	Renal failure, liver failure, metastatic malignancy
Endoscopic diagnosis	M-W tear or no lesion identified, and no stigmata of recent hemorrhage	All other diagnoses	Malignancy of upper GI tract	–
Stigmata of recent hemorrhage	None or dark spot only	–	Blood in upper GI tract, adherent clot, visible or spurting vessel	–

Table 35.4 Risk of rebleeding and mortality based on the Rockall risk score

Risk/score	0	1	2	3	4	5	6	7	≥8
Rebleeding (%)	4.9	3.4	5.3	11.2	14.1	24.1	32.9	43.8	41.8
Mortality (%)	0	0	0.2	2.9	5.3	10.8	17.3	27.0	41.1

- A pooled analysis of 16 RCT's that enrolled more than 3,800 patients suggested that an intravenous bolus loading followed by a continuous infusion of a PPI is more effective than bolus dosing alone in decreasing the rates of rebleeding and the need for surgery [15]. However, a more recent meta-analysis demonstrated that the risk of rebleeding with intermittent PPI therapy is comparable to that of a continuous infusion of PPIs in patients with endoscopically treated high-risk bleeding ulcers [16]. This suggests that intermittent dosing with PPI's may be preferable to a continuous infusion in patients with PUD.
- Planned, second-look endoscopy that is performed within 24 h after initial endoscopic therapy is not recommended in low to moderate risk patients [9].
- For most patients with evidence of persistent ulcer bleeding or rebleeding, a second attempt at endoscopic hemostasis is often effective, may result in fewer complications than surgery, and is the recommended management approach [8, 17].
- Angiography with transcatheter embolization provides a nonoperative option for patients in whom a site of acute bleeding has not been identified or controlled by endoscopy. Transcatheter embolization has been shown to significantly reduce mortality in patients with UGIB, although uncommon complications include bowel ischemia, secondary duodenal stenosis, and gastric, hepatic, and splenic infarction. In most institutions, radiologic intervention is reserved for patients in whom endoscopic therapy has failed, especially if such patients are high-risk surgical candidates.

- Patients should be tested and treated for *H. pylori* infection
- Evaluation for any ongoing need for a nonsteroidal antiinflammatory or antiplatelet agent and, if such treatment is indicated, appropriate coadministration of a gastroprotective agent are important.

Recurrent Hemorrhage

Rebleeding after successful endoscopic therapy occurs in 10–20 % of patients. The risk of rebleeding and mortality can be calculated with a clinical decision rule such as the Rockall risk score [10]. If rebleeding occurs, a second attempt at endoscopic therapy is recommended. In patients at high risk of rebleeding, scheduled repeat endoscopy may reduce the rebleeding rate and be cost effective [3].

Further Management of Esophageal Varices

- Gastroesophageal varices develop in up to 50 % of cases of cirrhosis with life threatening acute variceal bleeding occurring at a rate of 5–15 % a year. Bleeding form esophageal varices is mainly a result of portal hypertension and local vessel wall abnormalities. Deranged hemostasis due to the coagulopathy of liver disease probably plays a minor role (see Chap. 34, Liver disease) [18].
- In patients with variceal hemorrhage there remains a 40 % chance of recurrent variceal bleeding within 72 h and a 60 % chance within 10 days if no additional treatment is pursued.
- Octreotide 50 μg bolus followed by an infusion of at a rate of 50 μg/h has been recommended to reduce the risk of early rebleeding. Endoscopic banding in combination with an octreotide infusion has been considered more effective than endoscopic therapy alone for controlling bleeding and reducing the incidence of rebleeding. However the role of octreotide in variceal bleeding is controversial. A meta-analysis performed by the Cochrane group demonstrated that somatostatin analogues did not reduce mortality (RR 0.97, 95 % CI 0.75–1.25) nor the risk of rebleeding (RR 0.84, 95 % CI 0.52–1.37) however, fewer units of blood were transfused 0.7 (0.2–1.1) and the number of patients failing initial hemostasis were reduced (RR 0.68; 95 % CI 0.54–0.87) [19]. Considering octreotide's favorable safety profile and "marginal" benefit the use of this drug is not unreasonable in the initial management of patients with variceal hemorrhage.
- There is a close association between infection and variceal bleeding. A complete microbiological work-up, including blood cultures and diagnostic paracentesis when appropriate should be performed. Furthermore, antibiotic prophylaxis has been demonstrated to reduce the risk of infections in patients

with variceal bleeding and to improve short term survival [20]. A review of 12 trials involving 1,241 patients with variceal hemorrhage found that broad-spectrum antibiotics reduced overall mortality (RR-0.79) and risk of rebleeding (RR-0.53) [21]. Prophylaxis with a third generation cephalosporin, quinolone or amoxicillin-clavulanic acid is recommended.

- Paracentesis significantly decreases variceal pressure and tension [22]. This suggests that ascites removal can be useful in the treatment of variceal bleeding in cirrhotic patients
- There is a small chance that placement of a feeding tube/NG tube after variceal banding may dislodge the bands and or cause bleeding. This should therefore be delayed for 48–72 h.
- Balloon tamponade with a Minnesota or Sengstaken-Blackmore tube can be lifesaving in the presence of severe ongoing bleeding when carried out by experienced staff. However, placement by inexperienced staff is associated with an increased risk of death, due largely to esophageal perforation and pulmonary aspiration.
- TIPPS (transjugular intrahepatic portosystemic shunt) is a radiological intervention that creates a portosystemic tract through the liver parenchyma, through which an 8–12 mm expandable metal stent is inserted. TIPPS has become the treatment of choice as rescue therapy for the 10–20 % of patients with variceal hemorrhage unresponsive to endoscopic management. TIPPS has largely replaced emergency surgical shunting. The main limitations of TIPPS are the development of encephalopathy in about 20 % of patients and progressive development of shunt insufficiency (thrombosis).
- Garcia-Pagan et al. randomized patients with cirrhosis and acute variceal bleeding to early TIPPS or conventional therapy with insertion of a TIPPS if needed for rescue therapy [23]. During a mean follow-up of 16 months rebleeding occurred in 3 % of the early TIPPS group compared to 45 % in the conventional group ($p = 0.001$). One year actuarial survival was 86 % in the TPPS group compared to 61 % in the conventional group ($p < 0.001$).
- Gastric varices are the source of bleeding in 10–36 % of patients with variceal hemorrhage. Unless the gastric varices are located on the proximal lesser curve they are not amenable to endoscopic ligation and for this reason early TIPPS is generally recommended.
- Non-selective β blocker's (nadolol or propranolol) reduce the risk of rebleeding. A combination of endoscopic treatment together with β blocker's reduces overall and variceal rebleeding more than either therapy alone [24].

Management of Patients with Lower GI Bleeding

Hemorrhage from the lower gastrointestinal tract accounts for about 20 % of all cases of acute gastro intestinal bleeding [25]. Compared with acute UGIB patients with acute lower GI bleeding are significantly less likely to experience shock,

Table 35.5 Causes of hematochezia

Source	Frequency
Diverticulum	17–40
Angiodysplasia	9–21
Colitis (ischemic, IBD, infectious)	2–30
Neoplasia	11–14
Anorectal disease, including varices	4–10
Upper GI bleeding	0–11
Small bowel bleeding	2–9

require fewer blood transfusions) and have a significantly higher hemoglobin level [25]. The common sources of hematochezia (passage of fresh blood through the anus) are listed in Table 35.5 [26]. The spontaneous remission rate, even with massive bleeding is approximately 80 %. Colonoscopy is considered the initial diagnostic modality of choice and can identify the origin of severe lower bleeding in 74–82 % of patients [27]. It is important to exclude an upper GI bleed as a source of lower GI bleeding. Up to 11 % of patients with hematochezia have massive upper gastrointestinal bleeding [26, 28]. Nasogastric tube placement with irrigation and aspiration is therefore required. Should there be bloody NGT aspirate then an EGD is warranted. However, it is important to appreciate that 10–15 % of patients will have an upper GI bleeding despite a "negative" NGT aspirate, leading some to recommend an EGD in all patients with hematochezia [29].

In patients with ongoing lower GI bleeding a radionuclide bleeding scan is indicated. The favored approach is to use technetium-labeled red blood cell (Tc-RBC) scanning [29]. This is performed by ex vivo labeling of an aliquot of the patient's own RBCs, followed by injecting them back into the patient. Nuclear scintigraphy can detect bleeding rates between 0.1 and 0.5 cm^3/min and is considered 10 times more sensitive than mesenteric angiography for detecting bleeding [27]. Nuclear scintigraphy has a reported diapnotic sensitivity of 86 % for ongoing bleeding.

CT angiography has emerged as a useful diagnostic aid in patients with lower GIB. Multidetector CT scanners with special angiographic protocols have been used to help localize GI bleeds. These scans are performed without the use of oral contrast, and a positive study is predicated on visualization of intraluminal extravasation of intravenous contrast [29]. CT angiography has a reported diagnostic sensitivity of approximately 90 % in the presence of active bleeding [30, 31].

Selective mesenteric angiography detects arterial bleeding that occurs at a rate of 0.5 mL/min or faster. It can be both diagnostic and therapeutic. Transcatheter embolization is an effective method of controlling gastrointestinal hemorrhage. Embolization proximal to the mesenteric border of the colon was initially carried out via large catheters (5 Fr), which led to a significant rate of bowel infarction. However, the availability of microcatheters (2.7 Fr) and embolization methods such as micro-coils, gelfoam, and polyvinyl alcohol particles has resulted in success rates ranging from 70 to 90 % without major ischemic complications and recurrent bleeding in less than 15 % of cases [25]. The location and etiology of bleeding has

important therapeutic implication. Bleeding from the right colon and cecum is less amenable to embolization than bleeding in the left colon. Furthermore angiodysplasias are more difficult to treat using embolization compared to diverticular bleeding, and have a greater tendency to rebleed [25]. If bleeding continues and no source has been found, surgical intervention is warranted. Emergency surgery may be needed to control bleeding in about 10–25 % of patients in whom nonoperative management is unsuccessful or unavailable. Surgical intervention is also recommended in patients with recurrent diverticular bleeding.

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Chapter 36
Pancreatitis

Acute pancreatitis is a common disease that causes significant morbidity and mortality. Pancreatitis is the most common principle gastrointestinal discharge diagnosis in the United States [1]. More than 250,000 patients are admitted per year for pancreatitis and about 3,000 die from this disease per year in the US [1, 2]. Furthermore, the hospitalization rate for acute pancreatitis in the US is rising [2]. About 15 % of all patients with acute pancreatitis develop necrotizing pancreatitis. Mortality ranges from 3 % for patients with interstitial edematous pancreatitis to 15 % for patients who develop necrosis [3, 4]. In developed countries, obstruction of the common bile duct by stones (38 %) and alcohol abuse (36 %) are the most frequent causes of acute pancreatitis. Gallstone-induced pancreatitis is caused by duct obstruction of gallstone migration. Obstruction is localized in the bile duct, the pancreatic duct, or both. Other well established causes of acute pancreatitis include:

- Hypertriglyceridemia
- Post–ERCP
- Drug induced
- Autoimmune
- Genetic
- Abdominal trauma
- Postoperative
- Ischemia
- Infections
- Hypercalcemia and hyperparathyroidism
- Posterior penetrating ulcer
- Scorpion venom

Abdominal pain is the cardinal symptom. It occurs in about 95 % of cases. Typically it is generalized to the upper abdomen, but it may be more localized to the right upper quadrant, epigastric area, or, occasionally, left upper quadrant. The pain typically occurs acutely, without a prodrome, and rapidly reaches maximum intensity. It tends to be moderate to severe in intensity and tends to last for several days.

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The pain typically is boring and deep because of the retroperitoneal location of the pancreas. About 90 % of patients have nausea and vomiting, which can be severe and unremitting. The severity of the physical findings depends on the severity of the attack. Mild disease presents with only mild abdominal tenderness. Severe disease presents with severe abdominal tenderness and guarding, generally localized to the upper abdomen. Rebound tenderness is unusual.

Diagnosis

- Leukocytosis is common because of a systemic inflammatory response.
- Mild hyperglycemia is common because of decreased insulin secretion and increased glucagon levels.
- The serum lipase level is the primary diagnostic marker for acute pancreatitis because of its high sensitivity and specificity. Serum lipase is more than 90 % sensitive for acute pancreatitis [5]. The serum lipase level rises early in pancreatitis and remains elevated for several days.
- Serum amylase concentrations exceeding three times the normal upper limit supports the diagnosis of acute pancreatitis. However, the serum amylase is within the normal range on admission in up to 20 % of the patients.
- In a meta-analysis, a serum ALT level higher than 150 IU/L had a positive predictive value of 95 % in diagnosing acute gallstone pancreatitis [6].
- Any patient who has unexplained, severe abdominal pain should undergo supine and upright chest and abdominal radiographs. Abdominal radiographs are performed mainly to exclude alternative abdominal diseases, such as gastrointestinal perforation.
- Abdominal ultrasonography is the primary imaging study for abdominal pain associated with jaundice and for excluding gallstones as the cause of acute pancreatitis. It has the advantages of low cost, ready availability, and easy portability for bedside application in very sick patients. It is ubiquitous in the evaluation of pancreatitis. When adequately visualized, an inflamed pancreas is recognized as hypoechoic and enlarged because of parenchymal edema. The pancreas is visualized inadequately in 30 % of cases.
- Patients who present with severe pancreatitis or who present initially with mild to moderate pancreatitis that does not improve after 5–7 days of supportive therapy should undergo abdominal CT imaging [7]. CT scan *with contrast* is the standard approach for the diagnosis and work-up of severe pancreatitis. Except in cases of initial diagnostic uncertainty, it is advisable to wait 5–7 days to obtain the initial scan. A contrast enhanced CT scan obtained within the first few days cannot be used to determine whether a patient has necrotizing or severe interstitial pancreatitis. Patients should receive both intravenous and oral contrast. Areas of necrosis with diminished or no enhancement upon contrast bolus are detected with an accuracy of 87 % (see

CT Grading system below). Renal insufficiency is a relative contraindication to the use of intravenous contrast agent.

- Magnetic resonance cholangiopancreatography (MRCP) has become a useful procedure for identifying retained common bile duct stones [7]. Selective use of MRCP can reduce the need for endoscopic retrograde cholangiopancreatography (ERCP) for patients with suspected gallstone pancreatitis.

Risk Stratification

Most episodes of acute pancreatitis are mild and self-limiting, needing only brief hospitalization. However, 20 % of patients develop severe disease with local and extrapancreatic complications characterized by early development and persistence of hypovolemia and multiple organ dysfunction. Risk stratification plays a key role in the management of patients with acute pancreatitis. Although amylase and lipase remain the standard for diagnosis, they are poor predictors of severity. A number of scoring systems have been developed to assess the severity of pancreatitis. The Ranson Criteria was the first scoring system to be developed and remains commonly employed today [8]. More recently, the APACHE II Scoring System and the Imrie Score have been used to predict severity. The Balthazar computed tomography grading system is widely used in patients who have undergone CT scanning. Severe Acute Pancreatitis as defined by the Atlanta Symposium include a Ranson Score ≥ 3, APACHE-II score ≥ 8, organ failure and/or local complications (necrosis, abscess or pseudocyst) [9]. The Bedside Index of Severity in Acute Pancreatitis is a 5-factor scoring system that can be performed during the first 24 h of admission [10]. The Bedside Index of Severity in Acute Pancreatitis score >2 within 24 h is associated with a sevenfold increase in the risk of organ failure and a tenfold increase in the risk of mortality [11, 12].

(a) *Ranson's Criteria*

- At presentation
  - Age older than 55 years
  - Blood glucose level greater than 200 mg/dL
  - White blood cell count greater than 16,000/mm^3
  - Lactate dehydrogenase level greater than 350 IU/L
  - Alanine aminotransferase level greater than 250 IU/L
- 48 h after presentation
  - Hematocritd 10 % decrease
  - Serum calcium less than 8 mg/dL
  - Base deficit greater than 4 mEq/L
  - Blood urea nitrogen increase greater than 5 mg/dL
  - Fluid sequestration greater than 6 L
  - PaO_2 less than 60 mmHg

(b) *Glasgow (Imrie) Severity Scoring System*
- Age >55 years
- White cell count $>15 \times 10^9$/L
- $PaO_2 < 60$ mmHg Serum lactate dehydrogenase >600 units/L
- Serum aspartate aminotransferase >200 units/L*
- Serum albumin <3.2 g/dL
- Serum calcium <2 mmol/L (8 mg/dL)
- Serum glucose >10 mmol/L (180 mg/dL)
- Serum urea >16 mmol/L (44.8 mg/dL)

(c) *Balthazar CT Grading System*
- A: Normal
- B: Gland enlargement, small intrapancreatic fluid collections
- C: Peripancreatic inflammation, >30 % pancreatic necrosis
- D: Single extrahepatic fluid collection, 30–50 % pancreatic necrosis
- E: Extensive extrapancreatic fluid collections, >50 % pancreatic necrosis

(d) *The Bedside Index of Severity in Acute Pancreatitis* (one point each)
- Bun > 25 mg/dL
- Altered mental state
- Systemic inflammatory response syndrome (SIRS)
- Age ≥ 60 years
- Pleural effusion

(e) *The Revised Atlanta Classification recognizes 3° of severity* [13].
- Mild disease is defined as acute pancreatitis not associated with organ failure, local complications or systemic complications.
- Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications or systemic complications. Transient organ failure is define by organ failure that is present for <48 h.
- Severe acute pancreatitis is defined by the presence of persistent organ failure (>48 h). Most patients with severe pancreatitis have pancreatic necrosis and a reported mortality of about 30 % [14].

Complications

- Local complications
  - Interstitial pancreatitis involves acute collection of peripancreatic fluid formation
  - Pancreatic necrosis is the most severe local complication because it is frequently associated with pancreatic infection. Infection of pancreatic necrosis develops during the second or third week in 40–70 % of patients.
  - Pancreatic abscess consists of a circumscribed collection of pus that arises around a restricted area of pancreatic necrosis.

  - Pseudocyst is a collection of pancreatic fluid enclosed by a wall of granulation tissue that results from pancreatic duct leakage.
  - intraperitoneal hemorrhage
  - splenic vein thrombosis (causing left sided portal hypertension)
  - obstructive jaundice
- Renal dysfunction/failure
- Pulmonary complications
  - ARDS
  - Pleural effusion
  - Atelectasis
  - Pneumonia
- other
  - DIC/coagulopathy
  - upper GI bleeding
  - hypocalcemia
  - hyperglycemia
  - hypertriglyceridemia

Management

Significant advancements in the management of patients with pancreatis have occurred in the last decade. These include three major area of focus:

- Less “aggressive” fluid resuscitation
- Early enteral nutrition
- A conservative and minimally invasive approach to necrotizing pancreatitis
- In mild forms of disease, besides the etiological treatment (mostly for gallstone-induced pancreatitis), therapy is supportive and includes fluid resuscitation, analgesia, oxygen administration, and antiemetics.
- Fluid resuscitation to correct fluid losses and maintain an adequate intravascular volume is an important component of the management of patients with severe pancreatitis (see Chap. 9). However, aggressive fluid therapy during the first days of hospitalization as recommended by most guidelines and reviews on this topic is not supported by clinical evidence. Aggressive fluid resuscitation based on non-physiologic end-points is associated with an increased risk of organ dysfunction. de-Madaria et al. demonstrated that administration of > 4.1 L of fluid (more than the third quartile) during the initial 24 h was significantly and independently associated with persistent organ failure, fluid collections, respiratory insufficiency, and renal insufficiency [15]. Fluid resuscitation should be guided by an assessment of the patient’s fluid responsiveness. Lactate Ringers solution (LR) is the fluid of choice; this fluid has been shown to have anti-inflammatory properties in patients with

pancreatitis [16]. An albumin infusion should be considered in patients with an albumin <3.0 g/dL.

- Respiratory, cardiovascular, and renal function must be closely monitored.
- Morphine traditionally has been disfavored for acute pancreatitis because it increases the sphincter of Oddi pressure. Meperidine, 50–100 mg every 4–6 h, has been the traditional opiate regimen of choice because it does not raise the sphincter pressure. Caution should be used with this agent as it active metabolite normeperidine accumulates with renal dysfunction and can cause seizures. Fentanyl is a useful alternative in this situation.
- Nasogastric tube aspiration traditionally was used to prevent pancreatic stimulation induced by gastric distention and acid secretion. Multiple clinical trials, however, have demonstrated no benefit from nasogastric aspiration (see feeding below) [17].
- Prophylactic antibiotics have previously been recommended to reduce the risk of pancreatic infection [18]. However, meta-analyses have failed to demonstrate a benefit from prophylactic antibiotics [19–21]. Guidelines issued by the American College of Gastroenterology do not recommend antibiotic prophylaxis to prevent pancreatic infection [22, 23]. In most patients, infection of pancreatic or extrapancreatic necrosis does not occur until week 3 or 4. Antimicrobial agents with favorable pancreatic tissue penetration such as carbapenems and quinolones are recommended at this time [24].
- Peritoneal lavage to remove toxic necrotic compounds is no longer recommended for severe pancreatitis. In a meta-analysis of eight RCTs involving a total of 333 patients, peritoneal lavage did not reduce morbidity or mortality [25].
- Adrenal insufficiency (CIRCI) has been reported to occur in up to 35 % of patients with severe pancreatitis [26]. A cosyntropin stimulation test and treatment with hydrocortisones is recommended in those patients with adrenal insufficiency (see Chap. 39).
- Most patients with gallstone-induced pancreatitis present with mild disease and quickly recover after early resuscitation. ERCP is indicated for clearance of bile duct stones in patients with severe pancreatitis, in those with cholangitis, in those who are poor candidates for cholecystectomy, in those who are postcholecystectomy, and in those with strong evidence of persistent biliary obstruction [22].
- Probiotics should be avoided in patients with pancreatitis [27]. The role of prebiotic fiber supplementation is controversial [28].
- Patients with acute pancreatitis have traditionally been treated with "bowel rest"; this included NG suction and NPO. Patients with mild pancreatitis were started on oral feeds once the pain had subsided while patients with severe pancreatitis were treated with parenteral nutrition until the disease process resolved. There is, however, no scientific data to support this approach to the management of patients with acute pancreatitis. "Bowel" rest is a meaningless term and it is impossible to rest the bowel (see Chap. 32). Trying to rest the bowel by not feeding is akin to inducing asystole to rest the heart. Both experimental and clinical data strongly support the concept that enteral nutri-

tion started within 24 h of admission to hospital reduces complications (primarily pancreatic infection), length of hospital stay and mortality in patients with acute pancreatitis [29, 30]. Enteral nutrition should begin within 24 h after admission and following the initial period of volume resuscitation and control of nausea and pain. Patients with mild pancreatitis can take a low fatty diet by mouth while patients with severe pancreatitis should receive enteral tube feeds. Clinical trials suggest that both gastric and jejunal tube feeding are well tolerated in patients with severe pancreatitis. However, post-pyloric feeding is generally recommended. While there is limited data as to the optimal type of tube feed, a semi-elemental formula with structured lipids is recommended (see Chap. 32). An elemental formula may be appropriate in patients with very severe pancreatitis or in those demonstrating gastro-intestinal intolerance. Parenteral nutrition is associated with increased complications and mortality and should be avoided in patients with acute pancreatitis.

- There has been a shift away from urgent surgical debridement of infected necrosis toward more conservative, less invasive approaches. This approach is recommended by the most recent international consensus for the management of necrotizing pancreatitis [31]. In a multicenter, randomized, controlled trial from the Netherlands, a step-up approach to management of infected necrosis was compared with open necrosectomy [32]. The step up approach involved placement of percutaneous drainage catheters in addition to treatment with antibiotics. Among patients whose clinical condition failed to improve within 72 h, minimally invasive debridement was performed via a retroperitoneal approach. The step up approach reduced major complications or death by 29 % compared with traditional open necrosectomy. Van Santvoort et al collected data from 639 patients with necrotizing pancreatitis treated at 21 Dutch hospitals [4]. Treatment was conservative in 62 % of patients; the mortality in these patients was 7 % as compared to 38 % in those treated by an invasive approach. Furthermore, patients with longer times between admission and intervention had a lower mortality. Fine needle aspiration culture of pancreatic or extrapancreatic necrosis to diagnose “infected necrosis” does not lead to a significant change in management and is therefore not routinely recommended [24].

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Chapter 37
Diarrhea & Constipation

Diarrhea

Diarrhea is a common problem in the ICU [1]. Diarrhea is best defined as ≥3 loose stools per day [2, 3]. The incidence of diarrhea in the ICU varies widely according to the definition used [1]. However, approximately 20–30 % of ICU patients will develop clinically relevant diarrhea [4, 5]. In the ICU diarrhea is best classified as infectious or non-infectious, due to different therapeutic approaches. Multiple risk factors contribute to the causation of both infections and non-infectious diarrhea.

The risk factors for "non-infectious" diarrhoea include previous/concurrent antibiotic use, hypoalbuminemia, change in tube feed formula, high volume tube feeds, high osmolarity tube feeds, ICU/hospital LOS, previous starvation (NPO) and medications (containing sorbitol) [4–8]. The use of third generation cephalosporins has been strongly associated with both "non-infectious" diarrhea as well as *C. difficile* colitis [4, 9–11].

Infectious Diarrhea

Clostridium difficile is the primary cause of infectious nosocomial diarrhea in developed countries (see Chap. 16). Risk factors include broad spectrum antibiotics, acid suppressive therapy and direct/indirect contact with infected/colonized patients. *C. difficile* must be excluded in all ICU patients who develop diarrhea. In addition, *Pseudomonas aeruginosa* has been reported to be a cause outbreaks of diarrhea associated with the use of antibiotics in ICU patients [4]. Other enteric pathogens that can cause diarrhea include salmonella, *C. Perfringens* type A and *Staphylococcus aureus* [9]. Although Candida species have been considered culprit pathogens associated with infectious diarrhea, there is no convincing data to support this association [12].

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"Non-Infectious" Diarrhea

Antibiotic Associated Diarrhea (AAD)

Bartlett defines AAD as diarrhea of unknown etiology that occurs in patients who are using antibiotics; in 10–20 % of these cases, *Clostridium difficile* infection is found [9, 10]. The pathophysiological explanation for AAD is that antibiotics reduce the concentration of anaerobic bacteria normally present in the intestine; this decreases carbohydrate (dietary fiber) fermentation and causes an osmotic diarrhea (see below) [9].

Enteral Feeding-Associated Diarrhoea

Enteral feeding is frequently "blamed" as the cause of diarrhea resulting in the interruption of tube feeds. However, many studies have found no association between the risk of nosocomial diarrhea and enteral tube feeds [4, 7]. Interestingly, in a recent meta-analysis comparing the complications of parenteral and enteral nutrition, enteral feeding was not found to increase the risk of diarrhea [13]. Furthermore, many experimental and clinical studies have demonstrated that, in comparison with parenteral nutrition, enteral nutrition can actually reduce the incidence of diarrhea via a better preservation of the gastrointestinal mucosal structure and function [1].

Energy-dense formulae have a high osmolality result in significant fluid shifts into the stomach and proximal small bowel. The resulting excessive intraluminal volume may accelerate small intestinal transit resulting in a greater fluid load in the large bowel and subsequent diarrhea. In addition, high enteral feed volumes increase the risk of diarrhoea [5].

Management of "Non-Infectious" Diarrhoea

- Bolus feeding of a low osmolarity enteral formula is preferred. If patients' develop diarrhoea DO NOT STOP the feed, rather reduce the rate.
- Dietary fiber are carbohydrates that cannot be digested by endogenous digestive enzymes and undergo fermentation by the colonic bacteria. Short-chain fatty acids, products of carbohydrate fermentation in the colon, play an important role in salt and water absorption in the colon. Furthermore, short-chain fatty acids, such as butyrate, are an important fuel for colonocytes. Consequently, dietary fibers have been added to enteral nutrition formulas to normalize bowel function. Experimental studies have shown that enteral feeding with fiber results in better colonic mucosal trophicity and in a lower rate of bacterial translocation than does enteral feeding without fiber [14]. The clini-

cal use of dietary fibre in patients receiving tube feed is controversial, with contradictory findings [15–18]. However, a recent meta-analysis which included hospitalized patients receiving enteral nutrition demonstrated that the incidence of diarrhoea was reduced with fibre administration (OR 0.68, 95 % CI: 0.48–0.96) [19]. This effect was attenuated when ICU patients were analyzed as a distinct group. Meta-regression showed a more pronounced effect when the baseline incidence of diarrhoea was high.

  - Soluble fibers are a better substrate for colonic bacterial fermentation than insoluble fiber. However, until recently, water-soluble fiber supplements were used rarely in enteral formulas because of their high viscosity.
  - Recently, new fiber processing techniques have been used to produce highly water-soluble and low-viscosity dietary fibers for use in enteral formulas. A multi-fibre-enriched enteral formula and/or the enteral administration of a fiber mixture should be considered in patients with diarrhoea [19, 20].

- The use of opioids including loperamide can induce a paralytic ileus. These drugs are best avoided. However, they can be considered as a "last resort" in patients in whom an infectious diarrhea has been excluded.

The Use of Probiotics and Prebiotics

The gut flora is profoundly disturbed during critical illness and this can profoundly alter gut function. Ingestion of specific fibre-fermenting lactic acid bacteria (probiotics) and fermentable fibre (prebiotics) is known reduce intestinal colonization with potentially pathogenic gram negative bacteria, to reduce bacterial translocation, to reduce pro-inflammatory cytokine induction and upregulate immune function The use of probiotics and prebiotics is however controversial [21, 22].

- Four meta-analyses have demonstrated that probiotics significantly reduce the risk of AAD including *C. difficile* associated diarrhoea and were beneficial in patients with *C. difficile* colitis [23–26]. The most recent meta-analysis demonstrated that probiotics reduced the incidence of *C. difficile* associated diarrhoea by 66 % [25]. A recent Cochrane review reported similar findings and concluded that "based on this systematic review and meta-analysis moderate quality evidence suggests that probiotics are both safe and effective for preventing *Clostridium difficile*-associated diarrhea" [26].
- Selinger et al. performed a small RCT which demonstrated that the use of the probiotic VSL#3 significantly reduced the incidence of AAD (0 % vs 11.4 %, $p = 0.006$) [27]. VSL#3 contains *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii subsp. Bulgaricus and Streptococcus thermophilus*.

- Hickson et al. randomized 135 patients over the age of 65 to receive a drink containing *Lactobacillus casei*, *L. bulgaricus*, *and Streptococcus thermophilus* twice a day during a course of antibiotics and for 1 week after the course finished [28]. The placebo group received a sterile milkshake. Twelve percent of the probiotic group developed AAD compared with 34 % in the placebo group ($p=0.007$).
- A more recent large ($n=2{,}941$) multicentre, randomized, double-blind, placebo-controlled trial of inpatients aged 65 years and older who were exposed to one or more antibiotics did not confirm these findings [29]. In this study patients were randomized to either a multi-strain preparation of lactobacilli and bifidobacteria for 21 days or placebo. AAD (including CDD) occurred in 10.8 % of patients receiving probiotics vs 10.4 % in the placebo group (RR 1.04; 95 % CI 0.94–1.28; $p=0.71$).
- Petrov et al. performed a meta-analysis evaluating the impact of the use of probiotics in ICU patients [30]. Twenty-three randomized controlled trials were included in this analysis. Probiotics were associated with reduced infectious complications (RR 0.82; 95 % CI 0.69–0.99; $p=0.03$) and VAP (RR 0.75; 95 % CI 0.59–0.97; $p=0.03$). When only high quality studies were included, probiotics had no effect on the risk of infections. Probiotics had no effect on hospital mortality, intensive care unit or hospital length of stay.
- Gu et al. performed a meta-analysis evaluating the role of probiotics in preventing ventilator associated pneumonia (VAP) [31]. In this study probiotics did reduce the incidence of VAP (OR, 0.82; 95 % CI, 0.55–1.24; $p=0.35$). However, in trauma patients these authors demonstrated that probiotics were associated with a reduction in the incidence of nosocomial infections (RR, 0.65; 95 % CI, 0.45–0.94, $P=0.02$) and VAP (RR, 0.59; 95 % CI, 0.42–0.81, $P=0.001$) [32].
- The Dutch Acute Pancreatitis Study randomized 298 patients with severe pancreatitis to receive a probiotic preparation (containing multiple species of Lactobacilli and Bifidobacterium) or placebo administered enterally twice daily for 28 days [33]. There was no difference in the rate of infections complications between groups, however the group of patients receiving the probiotic had a significantly higher incidence of multi-system organ failure and a higher mortality (16 % vs 6 %, $p=0.01$). Nine patients in the probiotic group developed non-occlusive mesenteric ischemia while none of the patients in the placebo group developed this complication. The cause of the increased occurrence of bowel ischemia in the probiotic group is unclear. It should be noted that the formulation containing high concentrations of multiple probiotic species and prebiotics was infused directly into the jejunum; this unusual trial design may have affected the outcome of the study.
- *Saccharomyces boulardii* (a live fungus) is frequently used in critically ill patients to treat diarrhoea, and is the only yeast probiotic that has been proved to be effective. However, *Saccharomyces fungemia* has been described in ICU patients being treated with this agent [34].

- *L. plantarum* has properties that may be beneficial in the critically ill. *L. plantarum* inhibits nuclear factor-κB, its cell wall components possess anti-inflammatory properties, it produces bacteriocins and lantibiotics with antimicrobial properties and it up-regulates mucous production in intestinal epithelial cells, rendering adherence of pathogens more difficult [30].

Analysis of current data is complicated by the fact that the effects of probiotics are not only dose-related but are also strain and species-specific and dependent on the specific combinations of probiotics used in any study. This issue questions the validity of combining studies using different probiotics and doses into a meta-analysis.

Due to the uncertainty regarding the benefits and risk associated with probiotics in critically ill patients it is difficult to recommend the widespread use of these agents until more definitive data becomes available. However, probiotics appear to have a beneficial role in the management of patients with hepatic encephalopathy (see Chap. 34) and AAD.

Constipation

Constipation has been defined as the lack of a bowel movement for 3 consecutive days. The reported incidence of constipation in ICU patients varies between 20 and 80 % [35, 36]. Risk of constipation is increased in critically ill patients due to immobility and inability to act or respond to the urge to defecate, which can result in abdominal distension, vomiting, restlessness, gut obstruction, and perforation. Activation of opioid receptors, particularly μ-receptors within the gastrointestinal tract, contributes to the pathophysiology of ileus with opioid use.

The ideal pharmacologic regimen for the prophylaxis and treatment of constipation has yet to be determined for critically ill patients. Stool softeners are unlikely to be effective in the critically ill patient. Bulk laxatives such as psyllium, methylcellulose, and polycarbophil may not be an appropriate choice for critically ill patients who need immediate relief from constipation. Moreover, these laxatives must be administered with adequate amounts of fluid, which may not be possible in these patients. Bulk laxatives should be avoided in patients who require fluid restriction, are confined to bed, or have strictures or partial obstructions. The use of fiber-based laxatives may result in fecal impaction without adequate fluid intake and may further complicate existing fecal impaction. Two commonly used stimulant laxatives in the United States are senna and bisacodyl, which work by increasing intestinal motility and secretions. Onset of action is within hours, and the major adverse effect is abdominal cramps. Patanwala et al. reported that the use of a stimulant (senna, bisacodyl) or osmotic laxatives (lactulose) were effective in treating constipation in ICU patients [35].

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Part V
Miscellaneous

Chapter 38
Transfusion of Blood and Blood Products

In transfusion medicine, several blood products can be prepared and used as replacement therapy; however, four of these products are more commonly used in general practice: RBCs, fresh frozen plasma (FFP), platelets and cryoprecipitate. RBC transfusions are mainly administered to improve tissue oxygenation in cases of anaemia or acute blood loss due to trauma or surgery. FFP, platelets and cryoprecipitate are used for the prevention and treatment of bleeding.

Red Blood Cell Transfusions

Red blood cell transfusions have been the standard of care for treating anemia for more than 100 years. Approximately 15 million units of red blood cells (RBCs) are transfused annually in the United States, and about 85 million units are transfused annually worldwide [1–3]. Historically, patients have been transfused when the hemoglobin level fell below 10 g/dL [4]. The 10/30 transfusion trigger has been ascribed to a paper by Adams and Lundy published in 1941 [5]. In this paper the authors made the following recommendation "*when concentration of hemoglobin is less than 8–10 g/100 cm³ of whole blood, it is wise to give a blood transfusion before operation*" [5]. The 10/30 transfusion trigger was widely accepted without supporting evidence from clinical trials. Over the last two decades the transfusion trigger has drifted down as RCTs have failed to demonstrate a benefit from the 10/30 trigger.

Anemia is common in critically ill patients. More than 90 % of patients have a "subnormal" hemoglobin concentration by the third day of ICU admission. The etiology of anemia of critical illness is multi-factorial and complex. Decreased production of erythropoietin (EPO), impaired bone marrow response to erythropoietin, reduced red cell survival as well as blood loss from repeated phlebotomies and surgical procedures have been implicated in the anemia of critical illness. Despite the fact that blood transfusions have not been shown to improve the outcome of ICU

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Table 38.1 Effect on oxygen delivery (DO_2) by increasing cardiac output, PaO_2 or hemoglobin by 20 %

Hemodynamic variable	20 % increase	% increase in DO_2
Cardiac output	5–6 L/min	18 %
PaO_2	60–72 mmHg	6 %
Hemoglobin	10–12 g/dL	18 %

patients (discussed in detail below) and that the current guidelines only recommend blood transfusion when the hemoglobin falls below 7.0 g/dL, almost half of all patients admitted to an ICU receive a blood transfusion [6, 7].

Why Transfuse?

$$DO_2 = CO \times \left[\left(Hb \times Sat \times 1.34 \right) + 0.031 \times PaO_2 \right]$$

As is evident from the oxygen delivery equation (DO_2) one of the most efficient means of increasing oxygen delivery to is increase the hemoglobin concentration (see Table 38.1). Therefore, the obvious indication to transfuse blood would be too increase oxygen delivery which should then theoretically increase tissue oxygen tension and tissue oxygen utilization. Unfortunately there is little data to support this concept and it is likely that blood transfusion increases oxygen utilization only in patients with a hemoglobin of less than 4 g/dL…. Yes that is right, less than 4 g/dL [8, 9]. A number of studies in critically ill patients have measured oxygen consumption before and for up to 6 h following a blood transfusion. All of these studies have failed to demonstrate an increase in tissue oxygen tension and oxygen utilization following blood transfusion [10–12]. Indeed, paradoxically (dependent on the age of the transfused cells), red blood transfusions may compromise tissue oxygenation.

Risks Associated with Blood Transfusion (See Fig. 38.1)

For much of the last century RBC transfusion has been viewed as having obvious clinical benefits and blood transfusion was considered as a lifesaving strategy [5]. However over the last 20 years RBC transfusion practice has come under increased scrutiny. Initially this was driven by concerns over transfusion related infections, HIV in particular. While the risk of transfusion transmitted infections has received considerable attention, the risks of this complication with modern blood banking techniques is now exceedingly remote [13]. On the other hand, it is now becoming clear that there are other important, less recognized risks of RBC transfusion related to RBC storage effects and to immunomodulating effects of RBC transfusions which occur in almost all recipients [14, 15]. The risks of blood transfusion include

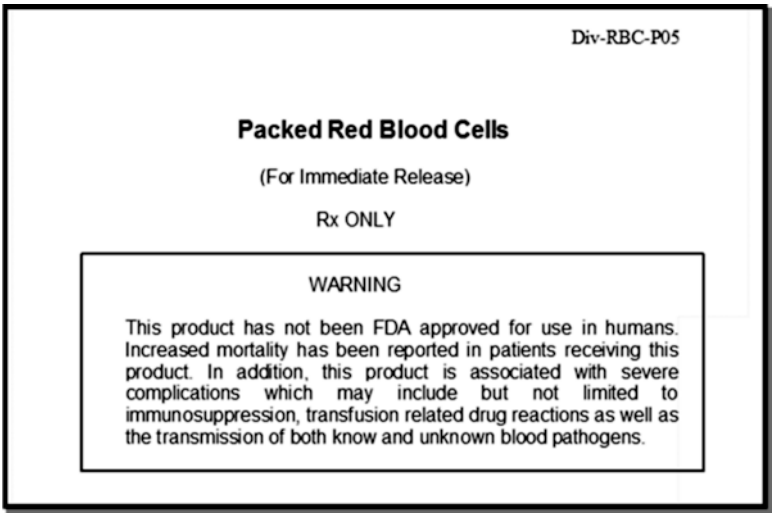

Fig. 38.1 Blood products do not have a package insert. If a package insert did existed for packed red blood cells it would probably be accompanied by a black box warning as suggested in this figure [15–17]

both infectious and non-infections complications; these are listed below [16]. Several strategies such as leukoreduction and shorter storage times (still under investigation) have been employed to reduce transfusion complications. However, the most obvious approach to reduce transfusion-related complications is to reduce the number of transfusions administered.

Risks Associated with Blood Transfusion

Infectious

- Human immunodeficiency virus (HIV)
- Hepatitis B, C, D
- Cytomegalovirus
- Parvovirus B19
- Epstein–Barr virus
- Human T cell leukemia/lymphoma virus
- Human herpes virus 6, 7 and 8
- Toxoplasmosis
- Malaria
- West Nile virus
- TT virus
- Prion disease?

Noninfectious

- Immune activation
  - Non-hemolytic febrile reactions
  - Anaphylactoid allergic reactions
  - Acute hemolytic reaction
  - Delayed hemolytic reactions
  - Transfusion related acute lung injury (TRALI)
  - Delayed TRALI syndrome
  - Transfusion associated graft versus host disease
- Immune tolerance
  - Nosocomial/postoperative infections
  - Multi-organ failure
  - Transplant tolerance
  - Cancer recurrence?
  - Auto-immune disease
- Activation of clotting
  - Increased risk of acute coronory syndrome
  - Increased risk of thromboembolic disease
  - Increased risk of arterial thrombosis
- Proinflammatory
- Increased oxidative injury

Complications associated with massive blood transfusion (>10 units in 24 h)

- Citrate toxicity
- Hypocalcaemia and hypomagnesaemia
- Hyperkalemia
- Hypothermia
- Coagulopathy

Transfusion-Associated Immunomodulation

Transfusion related immunomodulation (TRIM) occurs to some degree in almost all recipients of blood and blood products and are the cause of most of the complications associated with blood transfusion [14]. Clinical evidence for the existence of TRIM was first reported in 1973. Opelz and colleagues provided evidence that allogenic blood recipients had improved renal allograft survival [18]. This observation was subsequently confirmed in prospective clinical trials [19]. TRIM may result in either immune activation or immune suppression, this being dependent on the interaction between host and donor factors. Clinical syndromes associated with immune activation in the recipient include a variety of transfusion reactions including febrile non-hemolytic transfusion reactions (FNHTR), transfusion associated graft-versus-host disease (TA-GvHD), transfusion related acute

lung injury (TRALI), alloimmunization and possible development of various autoimmune diseases. Syndromes associated with tolerance induction and immunosuppression include increased predisposition to nosocomial and postoperative infections, cancer recurrence, microchimerism and enhanced survival of various allografts in recipients.

While TRIM appears to be a ubiquitous phenomenon the mechanisms leading to immunomodulation remains poorly understood. A number of mechanisms have been proposed relating to the transfusion of donor antigen presenting cells (APC), donor stem cells (leading to microchimerism), donor white blood cells, donor immunoglobulins, donor cytokines from activated WBC's and iron and free hemoglobin from hemolyzed red blood cells. It is likely that these mechanism act in concert to alter the immune status of the host. Allogenic blood transfusions introduce a multitude of foreign antigens including HLA-class II bearing donor dendritic antigen presenting cells (APC) in recipients. Blood transfusions induce TRIM in two opposite ways causing either i) allo-immunization or ii) tolerance induction. Immunization is reflected by the induction of HLA alloantibodies and T cell activation, while the induction of tolerance is suggested by enhanced renal, hepatic, cardiac, pancreatic and skin allograft survival in transfused versus non-transfused recipients. Presence or absence of "autologous" HLA-DR Ag on the leucocytes of the transfusion donor plays a decisive role whether immunization or immune suppression will ensue following allogenic blood transfusion [20]. Transfusions sharing at least one HLA-DR antigen with the recipient will induce tolerance while fully HLA-DR mismatched transfusions lead to immunization. Accumulation of various soluble bioactive substances occurs during storage and includes histamine, lipids, cytokines, fragments of cellular membranes, soluble HLA class I antigens, many of which are WBC derived and play an important role in TRIM. TRIM associated immunosuppression has been associated with a decrease in the helper:suppressor T-lymphocyte ratio, a decrease in natural killer cell function, defective antigen presentation and suppression of lymphocyte blastogenesis. Since WBC's are assumed to play a pivotal role in TRIM, it has been suggested that leukodepleted blood may have less immunomodulating properties and hence reduce the complications associated with the transfusion of non-leukodepleted blood. Hebert and colleagues reported a retrospective before-and-after cohort study conducted from August 1998 to August 2000 in 23 hospitals in Canada, enrolling 14,786 patients who received RBC transfusion following cardiac surgery or repair of hip fracture [21]. A total of 6,982 patients were enrolled during the control period and 7,804 patients were enrolled following prestorage leukoreduction. In this study the adjusted odds of death following leukoreduction were reduced (OR 0.87; CI 0.75–0.99) but serious nosocomial infections did not decrease (OR 0.97; CI 0.87–1.09). Furthermore, the frequency of febrile non-hemolytic transfusion reactions (FNHTR) decreased significantly (OR 0.86; CI 0.79–0.94) as did antibiotic use (OR 0.90; CI 0.82–0.99). While the risk of nosocomial infections were not reduced in the study by Hebert et al., a meta-analysis investigating the use of leukodepleted RBC transfusions in surgical patients demonstrated a significant reduction of postoperative infections (OR 0.522; CI 0.33–0.82, $p = 0.005$) [22].

"Age" of Transfused Red Blood Cells

Transfused RBC's are stored refrigerated in a preservative solution. Saline-adenine-glucose-mannitol (SAG-M) is the most commonly used preservative solution and enables refrigerated storage of RBCs for up to 42 days following collection. This "shelf-life" is based on criteria set by the Food and Drug Administration (FDA), which requires that 75 % of transfused RBCs must be recoverable in the peripheral blood circulation 24 h after transfusion [23]. The reported mean storage duration of blood in the US is 18 days [2]. However this varies widely, with larger tertiary/quaternary hospitals generally transfusing older blood than smaller community hospitals. The mean age of blood transfused in ICU patients varies from about 16 to 24 days with "younger" blood being transfused in European as compared to US ICUs [6, 7]. Differences in blood banking protocols may explain this finding.

During refrigerated storage of RBC units, the RBCs undergo numerous physicochemical changes, collectively referred to as the RBC storage lesion, which affects the quality, function and *in vivo* survival of the transfused RBCs [24, 25]. Many of these changes are the consequence of oxidative stress, leading to the generation of reactive oxygen species, altered proteins and lipids, loss of cell membrane and cell constituents forming microparticles and changes to the RBC cytoskeleton resulting in alterations in the shape and deformability of the RBC. With storage the RBC loses its biconcave shape, become more spherical and spiculated. The physical changes that occur to stored RBCs appear to be similar to those that occur to diseased RBCs (such as in malaria, sickle cell disease, thalassemia). Loss of RBC membrane results in the formation of microparticles which float in the supernatant. As a result of ongoing glycolytic metabolism, lactic acid and protons accumulate in the storage solution. Furthermore, stored white cells become activated resulting in the release of cytokine and other inflammatory mediators.

RBC Storage Lesion [25]

RBC changes

- Acidosis, decreased pH
- Slowed metabolism, decreased ATP
- Decreased 2,3 DPG, decreased O2 off-loading
- Shape change, cytoskeletal damage, band 3 denaturation
- Loss of cation pumping
- Oxidative damage, increased lipid peroxidation
- Loss of cell membrane (shedding of microparticles)
- Cell shrinkage, decreased deformability
- Loss of cell membrane phospholipid, cell asymmetry
- RBC lysis

Accumulation in the supernatant

- Acidotic, decreased pH, increased lactate
- Increased K+
- Increased free hemoglobin
- Oxidized protein and lipids
- Increased RBC microparticles
- Cell debris
- Bioactive mediators

Storage of RBC's under standard blood banking conditions results in the accumulation of cell-free and microparticle-encapsulated hemoglobin. The concentration of cell-free hemoglobin increases linearly with increasing storage time [26]. Cell-free hemoglobin is cytotoxic. The cytotoxic effect of free heme is related to its pro-oxidant activity driven by the divalent Fe atom contained within its protoporphyrin IX ring, which promotes the production of free radicals [27]. Free heme has been demonstrated to play a critical role in the pathogenesis of sepsis [28]. The pro-inflammatory cytokines released following exposure to a pathogen act synergistically with free heme to promote oxidative injury [28]. In addition, free hemoglobin binds with nitric oxide (NO) leading to endothelial dysfunction and contributing to the intravascular thrombosis, vasoconstriction, and leukocyte adhesion which occurs in the septic patient [26]. The pathogenetic importance of free heme in patients sepsis is supported by an observational study reported by Janz and colleagues who demonstrated a significant increase in the mortality of septic patients with increasing concentration of cell-free hemoglobin [29]. Heme oxygenase-1 (HO-1) is the rate-limiting enzyme in the breakdown of heme into equimolar amounts of biliverdin, iron and carbon monoxide. HO-1 has a protective effect in severe sepsis and it is likely that genetic polymorphisms of this enzyme play a role in determining the severity of the septic response [27, 28].

Oxidation of cell-free hemoglobin releases free iron. The most recent theory to explain the increased risk of infectious complications following blood transfusion and the interaction with the duration of storage relates to an increased concentration of circulating non-transferrin-bound iron, which promotes proliferation of pathogenic bacteria [30, 31]. In mouse models, transfusion of RBCs stored for longer durations was followed by brisk extravascular clearance of cells damaged during storage by macrophages in the spleen and liver [31]. The iron liberated by phagocytic digestion of these RBCs rapidly entered the systemic circulation in amounts that exceeded the transport capacity of plasma transferrin, increasing the concentration of circulating non-transferrin-bound iron. A study conducted in healthy volunteers reported the presence of higher extravascular hemolysis after older RBC transfusion (storage of 40–42 days) compared with fresh blood (storage of 3–7 days) [32]. In this study transferrin saturation and non-transferrin-bound iron increased significantly after transfusion of the old blood. The increased concentrations of non-transferrin-bound iron correlated with enhanced proliferation in vitro of a pathogenic strain of *Escherichia coli*.

A large range of adverse effects related to RBC storage have been reported in patients when RBC's stored for 2–4 weeks are transfused. These include increased

mortality, nosocomial infections, multiple organ failure, renal failure, deep vein thrombosis, and an increase in ICU and hospital length of stay and duration of mechanical ventilation [33]. However, the clinical importance of the storage lesions is controversial as all of the studies demonstrating an association between storage time and adverse outcomes are observational studies many of which are small studies [33]. Furthermore, a number of studies have been unable to find an association between adverse clinical outcomes and the duration of storage [25, 33]. Those studies that have shown an increased risk of complication with "old" blood suggest that the increased risk of complications occurs with blood stored for longer than 14 days [10, 33, 34]. To complicate this issue further, Phelan et al. demonstrated that the deleterious effects of aging on banked blood are ameliorated by pre-storage leukoreduction [35, 36].

Currently a number of RCT's are being conducted which should help resolve this controversial issue. The Canadian ABLE study (Age of Blood Evaluation trial) is planned to enroll a total of 2,510 ICU patients in Canada, France, and the United Kingdom who will be randomized to standard transfusion practice or receive fresh blood (7 days or less) [37]. TRANSFUSE (clintrial.gov NCT01638416) is a large (5,000 patients) pivotal, multicenter, randomized, controlled trial in critically ill patients to determine whether, compared with standard care, transfusion of the freshest available RBC decreases patient mortality. The Red Cell Storage Duration Study (RECESS) is a similar study in patients undergoing cardiac surgery (clintrial.govNCT00991341), while the *Age of Blood in Children in Pediatric Intensive Care Units* (ABC PICU) study (clintrial.gov NCT01977547) is investigating the effect of fresh versus aged blood in pediatric ICU patients.

The most important complications associated with the transfusion of packed red cells are reviewed below (briefly).

Increased Risk of Postoperative and Nosocomial Infections

Starting in the mid-1980s, a dose–response relationship has been reported between the quantity of RBC's transfused and infections in various settings. Multiple observational studies have demonstrated that blood transfusion is associated with an increased risk of postoperative and nosocomial infections, increased length of hospital stay and increased mortality. While sicker patients receive more blood transfusions, multivariate analysis has consistently demonstrated that blood transfusions are independent predictors of infectious complications, morbidity and mortality. We performed a meta-analysis of 45 cohort studies that assessed the effect of RBC transfusion on patient outcomes [15]. These studies included postoperative, cardiac and ICU patients. Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in all these studies blood transfusion was an independent risk factor for infection. The pooled odds ratio for developing an infectious complication was 1.8 (95 % CI; 1.5–2.2). Hill and colleagues performed a meta-analysis of studies investigating the risk of postoperative infections in patients receiving a blood transfusion [38]. In this study, the odds ratio ranged from 1.43 to

15.15, with a common odds ratio of 3.45. A more recent meta-analysis by Rohde et al. demonstrated that in hospitalized patients a liberal transfusion strategy (as compared to a restrictive strategy) was associated with an increased risk of health care associated infections [39]. It is important to note that leukodepletion has reduced but not eliminated the risk of infections complications following a blood transfusion. A metaanalysis by Blumberg et al. reported that leukoreduced transfusions reduced the odds of a postoperative infection by approximately 50 % (OR 0.522; CI 0.332–0.821; p = 0.005) [22]. In a large prospective study which included 5,158 adult patients undergoing cardiac surgery at 10 centers in the United States and Canada, Horvath and colleagues demonstrated **a** dose-related association between the quantity of RBCs transfused (all leukocyte-reduced) and risk of infection, with the risk increasing by an average of 29 % with each RBC unit transfused [40]. Similarly in ICU patients, Juffermans and colleagues have demonstrated that transfusion of leukodepleted blood increases the risk of secondary infections [41, 42]. In this study patients who received older blood had an increased risk of infections [42]. These studies provide overwhelming evidence that RBC transfusions increase the risk of postoperative and nosocomial infections; this risk is reduced but not eliminated by the transfusion of leukodepleted blood.

Febrile Non-hemolytic Transfusion Reactions (FNHTR)

A FNHTR is defined, arbitrarily, as a temperature increase of 1 °C (1.8 °F) or more associated with a RBC transfusion in the absence of any other likely causes for fever [43]. This reaction may occur either during or up to 1–2 h following the transfusion. Additional features include increases in respiratory rate, changes in blood pressure, anxiety and, more unusually, nausea or vomiting. FNHTRs are the most commonly encountered transfusion reaction occurring in approximately 0.5–2.0 % of units transfused and are more likely to occur following transfusion of platelets than RBCs. FNHTRs and believed to be due to leucocyte activation, either donor or receipt with the release of cytokines (similar mechanism to acute TRALI). Leucocyte reduction decreases the incidence of FNHTRs with prestorage leucocyte reduction being more effective than post-storage leucocyte reduction. Fever following a transfusion is attributed to FNHTR when other potential life-threatening transfusion reactions, such as acute homolytic transfusion reaction, bacterial contamination or TRALI are excluded. In patients with suspected FNHTR the transfusion should be immediately discontinued. The remainder of the transfused unit and a post-transfusion blood sample from the patient should be sent to the laboratory for further investigation. FNHTRs are typically benign, and usually resolve completely within 1–2 h after the transfusion is discontinued. Antipyretics may be administered to shorten the duration of the fever and provide analgesia. About 10–15 % of patients who experience an FNHTR may have a similar reaction in the future transfusion [43]. Administration of antipyretics (acetaminophen) 30–60 min before starting transfusion is often recommended for a patient who has had two or more FNHTRs, although there is little data to support this approach.

Transfusion Related Acute Lung Injury (TRALI)

TRALI is a serious transfusion adverse reaction characterized by the acute onset of non-cardiogenic pulmonary edema following transfusion of blood products. Although all blood components have been implicated, TRALI is more commonly associated with plasma-containing products (e.g., FFP and aphaeresis platelets), which account for the majority (50–63 %) of TRALI fatalities. TRALI is characterized by the abrupt onset of respiratory failure within 6 h following the transfusion of a blood product. While TRALLI is usually mild and resolves within hours it is the commonest cause of death following the transfusion of a blood product. It is likely that TRALI is underdiagnosed with the features of respiratory compromise frequently being ascribed to circulatory overload (TACO). TRALI is usually caused by donor anti-leukocyte antibodies. A single unit of packed cells or blood component product (FFP and platelets) is usually implicated in initiating this syndrome. It has, however, recently been recognized that the transfusion of blood products in critically ill or injured patients increases the risk for the development of acute lung injury (ALI) 6–72 h after the transfusion. This "Delayed TRALI Syndrome" is common, occurring in up to 25 % of critically ill patients receiving a blood transfusion, and is associated with a mortality of up to 40 % [44]. While the delayed TRALI syndrome can develop after the transfusion of a single unit, the risk increases as the number of transfused blood products increase. The management of both the classic and delayed TRALI syndromes is supportive.

Transfusion Associated Circulatory Overload (TACO)

TACO is defined as cardiogenic pulmonary edema that occurs during or immediately following a blood transfusion. It is believed to occur due to rapid intravascular volume expansion in the setting of diminished cardiac reserve (systolic or diastolic heart failure). It may be quite difficult to distinguish TACO from TRALI; however patients with TACO are likely to have abnormal LV function on echocardiography.

Transfusion-Associated Thrombosis

The transfusion of stored RBC increases the risk of thrombotic complications. A number of mechanisms have been postulated to explain this finding [45]. The microparticles shed from the RBC membrane contain high concentrations of phosphatidyl-l-serine, a potent promoter of factor VIIa activation and thrombin generation [46]. Plasminogen activator inhibitor 1 (PAI-1) accumulates in stored blood. The transfusion of blood products has been associated with the release of CD40 ligand from platelets. CD40L binding to vascular endothelial cells stimulates the expression of metalloproteinases, matrix-degrading enzymes implicated in plaque rupture and thrombosis. RBC transfusions in patients with cancer, traumatic injuries and subarachnoid hemorrhage have been reported to have an increased risk of

venous thromboembolism and arterial thromboses [47–49]. Increasing storage time (presumably with an increased released of bioactive lipids) appears to increase the pro-thrombotic properties of transfused blood [48].

Decreased Survival and Tumor Recurrence Following Surgery

As blood transfusions may result in immune tolerance and interfere with immune surveillance it has been suggested that perioperative blood transfusions may increase the likelihood of tumor recurrence. Evidence for a possible deleterious effect of allogenic blood transfusion has been reported in the context of tumors of the colon, rectum, breast, head and neck, lung, prostrate, stomach, kidney, cervix and vulva [50]. In a prospective study by Nosotti and colleagues in patients with stage I lung cancer undergoing lobectomy, blood transfusion resulted in decreased disease-free and overall survival [51]. A meta-analysis of randomized controlled studies of patients undergoing curative resection of colorectal cancer by the Cochrane group reported a pooled odds ratio of cancer recurrence of 1.42 (95 % CI, 1.20–1.67) associated with blood transfusion [52]. More recently Ng and colleagues demonstrated that transfusion of leukodepleted blood (as compared to no transfusion) was associated with a worse disease-free and overall survival in patients with resected stage I non-small cell lung cancer [53].

Blood transfusion should be considered as an organ transplant. The need for transfusion should be carefully evaluated, avoided when possible and considered only as a last-resort life-saving measure.

Tolerance to Anemia

In health, the amount of oxygen delivered to the whole body exceeds resting oxygen requirements almost fourfold. An isolated decrease in hemoglobin concentration to 10 g/dL with all other parameters remaining constant will result in an oxygen delivery that remains approximately twice that of the resting oxygen consumption. Humans have a remarkable ability to adapt to anemia by increasing cardiac output (in the absence of volume depletion), increasing microcirculatory density, as well as by increasing red cell synthesis of 2,3-DPG with a resultant rightward shift of the oxyhemoglobin dissociation curve (aids oxygen unloading) and by increasing oxygen extraction. Healthy volunteers can tolerate isovolemic hemodilution down to hemoglobin concentration of 4.5 g/dL without apparent harmful effects [54]. However, due to the high extraction ratio of oxygen in the coronary circulation, coronary blood flow appears to be the major factor which limits the tolerance of low hemoglobin concentrations. In experimental animal models of coronary stenosis, depressed cardiac function occurs at hemoglobin concentrations between 7 and 10 g/L [55, 56].

Extensive experience in patients who decline blood for religious reason, as well as in patients with chronic renal disease, myelodysplastic syndromes and severe autoimmune hemolytic anemias have confirmed that humans tolerate extreme anemia quite well [57, 58]. The best data comes from the Jehovah Witness literature [57]. Carson and colleagues performed a retrospective cohort study in 1,958 patients who underwent surgery and declined blood transfusions for religious reasons [59, 60]. In those patients without cardiovascular disease and with a blood loss of less than 2.0 g/dL there was no significant increase in perioperative mortality (for a baseline hemoglobin of 6–6.9 g/dL and a decline in hemoglobin of less than 2 g/dL the odds ratio (OR) for death was 1.4; 95 % CI, 0.5–4.2). However, in patients with cardiovascular disease, pre-operative anemia was associated with a significant increase in peri-operative mortality. This data confirms that humans can adapt to very low hemoglobin levels with cardiovascular disease being the major limiting factor.

Weighing the Risks and Benefits of Blood Transfusion

The benefit/harm of blood transfusion are related to a number of factors including:

- Leukodepleted versus non leukodepleted blood
- The length of storage (age of the blood)
- The number of units transfused
- The immune status of the recipient
- The baseline hemoglobin
- Presence of coronary artery disease
- Presence of ongoing bleeding
- Presence of comorbidities

So, When Should Patients' Be Transfused?

No randomized clinical trial comparing transfusion with no transfusion has been performed. However, a number of randomized clinical trials have been conducted that compared a more or less restrictive transfusion strategy using different transfusion triggers. Three randomized controlled trials which enrolled 2,364 patients evaluated a restrictive hemoglobin transfusion trigger of <7 g/dL as compared with a more liberal trigger. These studies include:

- The Canadian Critical Care Trials Group Study (TRICC) which randomized 838 adult ICU patients to a transfusion trigger of <7 or 10 g/dL [61].
- The TRIPICU study randomized 889 pediatric ICU patients to a transfusion trigger of <7 or <9.5 g/dL [62].
- Villanueva et al. randomized 921 patients with severe acute upper gastrointestinal bleeding to a transfusion trigger of <7 or <9 g/dL [63].

The pooled results from these three studies showed that a restrictive hemoglobin transfusion trigger of <7 g/dL resulted in reduced in-hospital mortality (RR 0.74; CI 0.60–0.92), total mortality (RR, 0.80; CI, 0.65–0.98), rebleeding (RR, 0.64; CI, 0.45–0.90), acute coronary syndrome (RR, 0.44; CI, 0.22–0.89), pulmonary edema (RR, 0.48; CI, 0.33–0.72), and bacterial infections (RR, 0.86; CI, 0.73–1.00), compared with a more liberal strategy [17].

Carson et al. randomized 2,016 patients >50 years of age who had undergone hip surgery and had risk factors for cardiovascular disease to a liberal transfusion strategy (trigger of 10 g/dL) or a restrictive transfusion strategy (trigger of 8 g/dL) [64]. There is no difference in morbidly or mortality between the two groups. In a pilot study, Walsh et al. randomized "older" (>55 years of age) patients requiring mechanical ventilation to a restrictive (transfusion trigger < 7 g/dL) or liberal transfusion strategy (transfusion trigger < 9 g/dL) [65]. Mortality at 180 days postrandomization trended toward higher rates in the liberal group (55 %) than in the restrictive group (37 %); relative risk was 0.68 (95 % CI, 0.44–1.05; $p = 0.073$).

Anemia is a well-recognized to be a poor prognostic factor in patients with congestive cardiac failure as well as acute coronary syndromes (ACS) [66, 67]. However, this does not mean that blood transfusion improves outcome. Kansagara et al. performed a meta-analysis which included 6 RCT's and 26 observational studies investing the role of blood transfusion in patients with heart disease [68]. These authors concluded that "*evidence from suggests that liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols* (RR 0.94; CI 0.61–1.42)." Chatterjee et al. performed a meta-analysis investigating the association between blood transfusion and outcomes in patients with acute myocardial infarction [69]. In this meta-analysis blood transfusion increased all-cause mortality (OR 2.91; CI, 2.46–3.44, $p < 0.001$). Multivariate meta-regression revealed that blood transfusion was associated with a higher risk for mortality independent of baseline hemoglobin level, nadir hemoglobin level, and change in hemoglobin level during the hospital stay. Blood transfusion was also significantly associated

with a higher risk for subsequent myocardial infarction (OR 2.04; CI 1.06–3.93, p = 0.03). Rao and colleagues examined the potential impact of red blood cell transfusion in 24,111 patients with ACS [70]. Blood transfusion was an independent predictor of myocardial infarction and 30-day all-cause mortality (adjusted hazard ratio 3.94). Furthermore, the 30-day mortality was significantly increased when transfusions were given to patients with hematocrits of 25 % or above (compared to those with a hematocrit below 25 %). Similarly Aronson and colleagues demonstrated an increase in mortality and the composite end-point of death/recurrent MI/heart failure in patients with acute myocardial infarction who had a hemoglobin > 8 g/dL and received a blood transfusion [71].

The 2012 guidelines from the *American Association of Blood Banks* (AABB) recommend adhering to a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence) [72]. Furthermore these guidelines state that "*transfusion decisions should be influenced by symptoms as well as hemoglobin concentration*" (Grade: weak recommendation; low-quality evidence). The 2013 guidelines from the *American College of Physicians* recommend recommends using a restrictive blood cell transfusion strategy (trigger hemoglobin threshold of 7–8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease (Grade: weak recommendation; low-quality evidence) [73].

Based on current evidence in patients who are not actively bleeding, RBC transfusions should be restricted to those patients with a Hb < 7 g/dL. However, it is likely that many patients can tolerate a hemoglobin concentration lower 7 g/dL, suggesting that the patients' physiologic reserve, presence of coronary artery disease and other comorbidities should be taken into account when making blood transfusion decisions. Furthermore, in most instances patients should be given one unit of RBC at a time. One unit of packed RBCs should increase levels of hemoglobin by 1 g/dL and the hematocrit by 3 %.

Coagulation Disorders in the ICU

Coagulation disorders are commonly encountered in the ICU. Many conditions including sepsis, malignancy, trauma, vasculitic disorders and obstetrical accidents may give rise a coagulopathy. In addition patients may have medical conditions which predispose them to developing a coagulopathy; e.g. patients with liver disease, renal failure, lupus, leukemia, etc. Sepsis, however, is the single most common factor leading to a coagulopathy and DIC. DIC has been reported in about 10–20 % of patients with gram-negative bacteremia and 70 % of patients with septic shock. In patients with sepsis, DIC appears to be an important independent predictor of ARDS, multiple organ dysfunction syndrome and death.

A coagulopathy is best defined as the presence of an abnormal coagulation test(s). The Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH) has sug-

gested that DIC be considered "*an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, produce organ dysfunction*' [74]. DIC is characterized by the generation of *fibrin related products* (soluble fibrin monomer, fibrin degradation products, D-dimer, etc.) and is indicative of an acquired (inflammatory) or non-inflammatory disorder of the *microvasculature*.

DIC results from the systemic activation of both the clotting and fibrinolytic systems leading to the consumption of many coagulation factors and platelets. The initial activation of coagulation in sepsis is primarily dependant on activation of the extrinsic (tissue-factor dependant) pathway. DIC is generally considered to be a systemic hemorrhagic syndrome. However, this is only because hemorrhage is obvious and often impressive. Less commonly appreciated is the formidable microvascular thrombosis that occurs. Fibrin deposition in the microcirculation is a frequent, if not invariable finding in patients with DIC. This microvascular thrombosis is closely related to the development of multiple organ dysfunction syndrome and is therefore closely linked to the prognosis of patients with DIC. This microvascular damage is especially pronounced in the lungs and kidneys. In septic patients with DIC, the thrombotic (anti-fibrinolytic) pathways tend to dominate. The DIC that characterizes the early stage of traumatic shock is characteristically hemorrhagic (fibrinolytic) which then becomes thrombotic by day 2–4; this pattern has important implications with regards to resuscitation with blood and blood products [75]. A dilutional coagulopathy and DIC frequently occur in cases of massive hemorrhage regardless of their cause. Coagulation tests can be used to assess the severity of the dilutional coagulopathy and DIC as well as their evolution under the influence of therapeutic interventions. However, coagulation tests fail to predict the risk of bleeding (see below).

The "common" causes of coagulopathy/DIC in the ICU include:

- Sepsis with DIC
- Trauma
- Massive hemorrhage
- Liver disease
- Malignancy
- Obstetrical calamities
- Excessive anticoagulation

Diagnosis of DIC

- Laboratory features
  - peripheral blood smear will show fragmented red blood cells
  - prolonged PT and PTT
  - thrombocytopenia
  - decreased levels of fibrinogen
  - decreased levels of Protein C
  - decreased levels of anti-thrombin III
  - increased levels of fibrin split products and D-dimer

- Clinical features associated with bleeding
  - bleeding from venipuncture sites, mucous membranes, hematuria, GI bleeds, intra-cerebral bleeds
  - petechia, purpura, and subcutaneous hematomas
- Clinical features of end organ damage due to thrombosis
  - acute lung injury
  - proteinuria and renal insufficiency
  - hepatocellular dysfunction
  - mental state changes and neurological deficits

The treatment of DIC remains controversial. This is primarily because there are very few studies which have objectively examined various therapeutic strategies in patients with DIC. The essential therapeutic modality is to treat the triggering disease process. Patients with DIC should NOT be given FFP in order to correct abnormal coagulation tests. The administration of FFP should however be considered in patients with DIC who are actively bleeding.

Fresh Frozen Plasma

Fresh frozen plasma (FFP) contains normal levels of the stable clotting factors, albumin and immunoglobulins [76]. It contains at least 70 % of the original coagulant factor VIII and at least similar quantities of the other labile clotting factors and natural inhibitors of coagulation.

- Derived from whole blood usually, sometimes apheresis
- Frozen within 8 h of collection
- Volume: 200–250 mL
- Storage: frozen up to 1 year
- Content: “normal” levels of all coagulation factors
- Expiration: 24 h after thawing
- The recommended therapeutic dose of FFP is 10–15 mL/kg of body weight
- ABO compatibility required, crossmatching not required
- Of all the individual blood components FFP is one of the most hazardous, the major risks include:
  - TRALI
  - Allergic reactions
  - Transmission of infections
  - Fluid overload
  - Increased risk of infections
  - Hemolysis due to anti-A and anti-B

FFP is an important cause of TRALI. Khan et al. demonstrated that TRALI was more likely to develop in patients who received FFP transfusions (OR, 2.48; 95 % CI, 1.29–4.74) and platelet transfusions (OR, 3.89; 95 % CI, 1.36–11.52) than in

those who received only RBC transfusions (OR, 1.39; 95 % CI, 0.79–2.43) [77]. Watson demonstrated that FFP was an independent predictor of MODS and ALI in trauma patients [78]. In addition, similar to blood transfusion, transfusion of FFP has been associated with an increased risk of infections in ICU patients [79].

***Indications for FFP* [76]**

- Ongoing bleeding in patients with liver disease
- Together with vitamin K and 3-factor prothrombin complex concentrate (used for severe bleeding) for reversal of prolonged INR in patients with Coumadin related bleeding
- Patients with acute disseminated intravascular coagulation (DIC) and active bleeding
- Prevention of bleeding in patients undergoing surgery or invasive procedures in whom the INR > 1.8
- Apheretic treatment of thrombotic microangiopathies (TTP)
- Hereditary angioedema due to deficiency of the inactivator of C1 esterase, in the absence of the specific plasma derivative
- Damage control resuscitation together with RBCs

Hemorrhage accounts for 40 % of deaths from trauma and is the most common cause of preventable mortality. Trauma-induced coagulopathy is multifactorial in origin and includes dilution, acidosis, hypothermia and a process known as acute traumatic coagulopathy characterized by global anticoagulation and fibrinolysis [80]. Damage control resuscitation targets acute traumatic coagulopathy with the early administration of FFP. Evidence from both civilian and military practice suggests improved outcomes with damage control resuscitation [80, 81]. While varying ratios of FFP to RBC have been proposed the optimal ratio appears to be between 1:1 and 1:2 [80, 81]. An additional theoretical benefit of FFP relates to its effect on the endothelial glycocalyx (see Chap. 9). Experimental models have demonstrated marked degradation of the endothelial glycocalyx following hemorrhagic shock [82, 83], which was restored following an infusion of FFP [83]. Resuscitation with FFP may therefore improve both coagulation as well as endothelial integrity with improved microvascular blood flow following traumatic injuries [83].

FFP Prior to Invasive Bedside Procedures or Surgery

Over four million units of FFP are transfused annually in the United States. Approximately 1/3 of all FFP is used to prepare patients with an elevated INR or PTT for a procedure [84]. Transfusion of FFP prior to an invasive procedure in patients with abnormal coagulation test results rests upon two assumptions: [85]

- that abnormal coagulation test results identify patients at increased risk of procedure-related bleeding and
- that transfusion of FFP will reduce that risk

For patients with mild to moderate abnormalities of coagulation test results, evidence to support these two assumptions is scant to non-existent. A growing body of literature documents that the INR and PTT do not predict which patients will have procedure-related bleeding and should not be used to make decisions about prophylactic preprocedure transfusions [86]. Several factors account for this lack of predictive value for bleeding. Coagulation tests such as the PT and PTT were developed primarily to identify specific coagulation deficiencies such as hemophilia. In addition, they are carried out *in vitro* (in a test tube), at room temperature, and may fail to reflect the efficacy of coagulation pathways *in vivo*, which are affected by both core temperature and the interaction with circulating cells and substances. Clinical data suggests that there is no increased risk of bleeding in patients with PT or INR values within 1.5–1.8 times the normal range. In a review of 25 studies of patients undergoing invasive procedures, Segal et al. determined that "*that there was insufficient evidence to conclude that abnormal test results predict bleeding*". Matevosyan et al. measured factors II, VII and VIII in neurosurgical patients with a prolonged INR (1.3–1.7) [87]. In this study all patients with a mildly prolonged INR had levels of coagulation facts within the hemostatic normal range. Based on this data the authors recommended that plasma not be transfused to simply correct this abnormal laboratory value.

The second assumption of preprocedure FFP transfusion is that the infused product will correct the coagulopathy. For the great majority of patients who are given such transfusions—namely, those with mild to moderate prolongation of the INR—there is very little evidence to support this assumption [85]. In fact, the evidence speaks to the contrary. Holland and Brooks reported the effect of FFP on the INR in 179 patients with a prolonged INR who were given FFP for a variety of indications [88]. For patients with INR's of 1.7 or less, infusion of FFP in typical doses used had no effect on the patient's INR. For patients with INR values greater than 2, the correction of INR was modest and incomplete. For example, even for patients with an INR = 4.0, the average correction with FFP transfusion was partial resulting in an INR = 3.0. Similar findings were reported by Abdel-Wahab et al. who noted that among 121 adult patients with a pretransfusion INR of 1.6 or less who were given 1–4 units of FFP, the posttransfusion INR corrected to within the normal range in only two patients [89]. In a population of stable trauma patients McCully demonstrated that the use of FFP did not affect coagulation factor function and that the INR did not predict bleeding [90].

The exponential shape of the INR curve implies that increasing the concentration of clotting factors by FFP transfusion will have a substantial correcting effort on the INR when the pretransfusion INR level is markedly prolonged but will have an ever-diminishing impact as the pretransfusion INR approaches the normal physiologic range [85]. This data suggests that as a general rule FFP should not be transfused prophylactically in patients with an INR < 1.8 undergoing an invasive procedure. In patients' with an INR ≥ 1.8 the risk/benefits of pre-procedure FFP should be weighed in each patient; should FFP be infused, normalization of the INR should not be attempted. FFP should not be administered prophylactically to patients with normal

coagulation tests undergoing high risk surgery or invasive diagnostic tests in an "attempt to limit bleeding".

Coagulopathy and Central Venous Catheterization

In many instances central venous catheterization is required in patients with a coagulopathy in whom correction of the coagulopathy prior to line placement is not possible. However, the risk of bleeding appears to be increased only in patients with an INR > 2.0 and a platelet count $< 20 \times 10^9$ L^{-1}. Doerfler described their experience with placement of 104 central lines in 76 coagulopathic medical patients. All insertions were performed by experienced operators; none of the patients received "prophylactic" transfusions of platelets or FFP [91]. There were no serious bleeding complications, with only minor bleeding (skin) in 7 (6.5 %) patients (who had a mean platelet count of 22,000 μL^{-1}). Similarly, Mumtaz et al. reviewed their experience in 330 surgical patients with disorders of hemostasis [92]. In 88 of the 330 patients, the underlying coagulopathy was not corrected before catheter placement. In these patients, there were three bleeding complications requiring placement of a purse string suture at the catheter entry site. These authors concluded that "*central venous access procedures can be safely performed in patients with underlying disorders of hemostasis. Even patients with low platelet counts have infrequent (3 of 88) bleeding complications and these problems are easily managed.*" Fisher and colleagues reported their experience with 658 central venous cannulations in patients with liver disease and a coagulopathy (mean INR 2.4, platelet count 81,000 μL^{-1}), none who received prophylactic transfusions of either FFP or platelets [93]. These authors reported only one major bleeding complication (a hemothorax after accidental subclavian artery cannulation) with minor oozing or local hematoma in 6 % of patients. Goldfarb et al. reported their experience with 1,000 cannulations of the internal jugular vein to facilitate obtaining a transvenous liver biopsy [94]. All the patients had coagulopathies (prothrombin time activity less than 50 % and/or a platelet count less than 50,000 μL^{-1}). In 74 patients, the common carotid artery was inadvertently punctured. A clinically detectable hematoma occurred in ten patients; in one patient, the hematoma compressed the airway; this patient recovered completely after a surgical drainage. In this patient, puncture of the internal jugular vein was difficult because of a goiter, but the carotid artery apparently was not punctured. Similarly, Foster and colleagues reported on their experience with 200 cannulations in patients undergoing liver transplantation who had coagulopathies (that remained uncorrected) [95]. These authors reported no cases of bleeding complications.

This data indicates that the risk of bleeding is related to the skill of the operator and not the ability of the blood to clot. In the hands of an experienced operator the risk of bleeding may be higher in patients with a platelet count less than 20,000 μL^{-1}; in these patients a platelet transfusion should be considered (if existing venous access allows). In the hands of the inexperienced operator, the femoral site (which

is compressible) is recommended (in the coagulopathic patient). However, even in this circumstance the risks of blood product transfusion likely exceed the benefit.

Thoracentesis and Chest Tube Placement

Hemothorax and pulmonary hemorrhage are very rare complications of thoracentesis; these complications have occurred in patients with normal hemostasis. McVay et al. reported no bleeding complications in patients with a mild to moderate coagulopathy (defined as PT or PTT twice normal or a platelet count of 50,000–99,000 μL^{-1}) who underwent a thoracentesis [96].

Hibbert et al. evaluated the risk of bleeding following 1,009 ultrasound guided thoracentesis in patients with an INR > 1.5 and/or a platelet count < 50,000 μL^{-1} [97]. In this study the mean INR was 1.9, the mean platelet count was 190,000 μL^{-1} with 25 % of patients having a platelet count of <50,000 μL^{-1} and 81 % of patients having an INR > 1.6. A hemorrhagic complications occurred in 0.4 % of patients in who did not receive pre-procedure coagulation factors as compared to 1.32 % in those patients in whom attempts were made to correct the INR and/or platelet count. This data would suggest that replacement with coagulation factors may only be required when the platelet count < 20,000 μL^{-1} and/or the INR > 2.0. As chest tube placement is more "invasive" than thoracentesis a platelet count > 50,000 μL^{-1} and INR > 2 is suggested.

Paracentesis

According to the position state of the American Association for the Study of Liver Disease (AASLD) "*the practice of giving blood products (fresh frozen plasma and/or platelets) routinely before paracentesis in cirrhotic patients with coagulopathy is not data-supported. The risks and costs of prophylactic transfusions exceed the benefit*" [98]. The guideline states that "*since bleeding is sufficiently uncommon, the prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended*".

Management of Non-therapeutic INRs With or Without Bleeding (Due to Coumadin Therapy)

For most indications, an INR range of 2.0–3.0 is targeted; INR values less than 2.0 are associated with an increased risk for thromboembolism, and INR values greater than 4.0 are associated with an increase in bleeding complications. The risk for bleeding, particularly intracranial bleeding, increases markedly as the INR exceeds 4.5.

The management of patients whose INR is outside the therapeutic range is controversial because many of the various options have not been compared. The

interventions include administering vitamin K and/or infusing fresh frozen plasma, prothrombin concentrates or recombinant factor VIIa. The preferred approach is based largely on the potential risk of bleeding, the presence of active bleeding, and the level of the INR [99]. Phytonadione (vitamin K1, a form of vitamin K derived from plants) has been used in the treatment of warfarin-associated coagulopathy [100]. When oral phytonadione is administered in conjunction with temporary interruption of warfarin therapy, approximately 1.4 days are required for an INR between 6 and 10 to decline to <4.0 [100]. When administered intravenously, low doses of phytonadione produce similar reductions as oral phytonadione in the INR value at 24 h, whereas subcutaneous phytonadione appears to be less effective than low-dose oral phytonadione. The response to vitamin K administered subcutaneously is less predictable than that of oral or IV vitamin K. Dezee performed a meta-analysis of trials that used vitamin K to treat patients without major hemorrhage with an INR greater than 4.0 [101]. The primary outcome was achievement of the target INR (1.8–4.0) at 24 h after vitamin K administration. This study demonstrated equal efficacy of oral and IV vitamin K (1.0–2.5 mg) in normalizing the INR, whereas subcutaneous vitamin K was no better than placebo.

When administered at higher doses for the management of the bleeding patient, intravenously administered phytonadione works more rapidly than either oral or subcutaneous vitamin K1 [100]. Reduction of the INR begins within 2 h, and a correction to within the normal range is generally achieved within 24 h if hepatic function is normal and if a sufficiently large dose is given. To minimize the risk of anaphylactoid reactions, vitamin K1 should be mixed in a minimum of 50 mL of intravenous fluid and administered, using an infusion pump, over a minimum of 20 min [100]. High doses of vitamin K, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for 1 week or more. Low doses of vitamin K are therefore recommended. A dose of 1.25 is recommended when the INR is between 4.0 and 9.0, but larger doses (i.e., 2.5–5 mg) are required to correct INRs of >9.0.

For life-threatening bleeding, immediate correction of the INR is mandatory. Although fresh frozen plasma can be given in this situation, immediate and full correction can only be achieved by the use of factor concentrates because the amount of FFP required to fully correct the INR is considerable and may take hours to infuse. Prothrombin Complex Concentrates (PCC) are recommended in these patients. PCCs do not require a cross-match, are virally inactivated, do not pose a risk of volume overload, and can be infused in 15–30 min. PCC may be classified as Three-Factor products (with adequate levels of factors II, IX, X, and low factor VII levels) and Four-Factor products (4-factor PCC), which contain adequate levels of factors II, VII, IX, and X as well as protein C and S. Hickey et al. compared the use of FFP with a 4-factor PCC in patients who required emergent reversal of Coumadin [102]. In this study the 4-factor PCC resulted in faster reversal and lower red cell transfusion requirement with fewer adverse events than FFP.

Kcentra is first non-activated 4-factor PCC available in the USA. Pabinger et al. demonstrated that Kcentra reduced the INR to less than 1.3 at 30 min in 93 % of patients who required emergent reversal [103]. Kcentra is dosed in units of factor IX (500 units factor IX per vial) as follow:

- For a pretreatment INR of 2–4, administer 25 units/kg IV, with a maximum dose of 2,500 units.
- For a pretreatment INR of 4–6, administer 35 units/kg IV, with a maximum dose of 3,500 units.
- For a pretreatment INR greater than 6, administer 50 units/kg IV, with a maximum dose 5,000 units.

OR

- Patients INR (max 8.00) × Weight in kg (max 100) × 6.25 = Number units.

ACCP Guidelines for managing elevated INR's (due to Coumadin) [99]

- INR more than therapeutic range but <5.0; no significant bleeding
  - Lower dose or omit dose; monitor INR
- INR ≥ 5.0, but <9.0; no significant bleeding
  - Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1.25 mg po), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (2.5–5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h.
- INR ≥ 9.0; no significant bleeding
  - Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h. (Grade 1B). Monitor more frequently and use additional vitamin
- Serious bleeding at any elevation of INR
  - Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion) and FFP; vitamin K can be repeated q12h
- Life-threatening bleeding
  - Hold warfarin therapy and give 4-factor PCC with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR

Platelet Transfusion

Thrombocytopenia (defined as a platelet count < 100,000 μL^{-1}) is a common problem in ICU patients and is associated with adverse outcomes. A platelet count of less than 100,000 μL^{-1} is seen in 20–50 % of ICU patients, whereas 12–15 % of patients will have a platelet count of <50,000 μL^{-1} at some point during their ICU admission [104–106]. Typically the ICU patient's platelet count decreases during the first 4 days in the ICU [107]. Regardless of the cause, thrombocytopenia is an independent predictor of ICU mortality in multivariate analysis with a relative risk of 1.9–4.2 in various studies [105]. In an observational study of 820 patients with severe community acquired pneumonia admitted to the ICU, Brogly et al. found that thrombocytopenia on admission was an independent predictor of mortality [108]. Moreau

reported that a 30 % or more decline in platelet count by the fifth ICU day was an independent predictor of death [106].

The causation of thrombocytopenia in ICU patients is often multifactorial, with sepsis being the most important cause. Thrombocytopenia is an early sign of sepsis and may occur in the absence of other features of DIC. Dilutional thrombocytopenia due to blood and fluid replacement is the second most common cause of thrombocytopenia in the ICU. Other causes include:

- Consumptive coagulopathy (DIC) due to liver failure, HELP syndrome, abruption placentae
- Microangiopathic hemolytic anemia; i.e. Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS)
- Immune thrombocytopenias
  - idiopathic (ITP)
  - heparin (see below)
  - allo-antibodies
  - collagen vascular diseases
  - malignancy
  - viral
  - drug induced
- Myelosuppressive chemotherapeutic agents
- Drugs are commonly implicated in the etiology of thrombocytopenia. Almost any drug can cause a thrombocytopenia. The commonly implicated drugs include:

  Antimicrobials

  - linezolid
  - vancomycin
  - fluoroquinolones
  - amphotericin
  - tetracyclines
  - sulfonamides
  - penicillins
  - chloramphenicol
  - cephalosporins

  Anticonvulsants

  - phenytoin (Dilantin)
  - carbamazepine

  Diuretics

  - furosemide
  - thiazides
  - ethacrynic acid

Others

- alcohol
- phenylbutazone
- aspirin
- gold salts
- colchicine
- chlorpromazine
- chlordiazepoxide
- H2 blockers

Up to 25 % of acutely ill patients develop drug-induced thrombocytopenia (DIT) [109]. The mechanism of DIT is decreased platelet production from bone marrow suppression, increased platelet destruction, or platelet sequestration. DIT can develop from either nonimmune or immune causes. Nonimmune-mediated DIT is the result of bone marrow suppression from agents including antineoplastics, antivirals, ethanol, thiazide diuretics, and tolbutamide, and it develops slowly over a period of several weeks. Heparin is the medication most commonly associated with DIT. A nonimmune-mediated and an immune-mediated form of thrombocytopenia occur from heparin (see HIT below). Nonimmune-mediated thrombocytopenia occurs in 10–20 % of patients receiving unfractionated heparin 1–4 days after initiation. Platelets typically do not decrease to 100×10^9 L^{-1}. Linezolid is the antimicrobial most likely to cause thrombocytopenia. The mechanism of thrombocytopenia is not fully understood, although potential mechanisms include direct myelosuppression and immune mediated platelet destruction. Vancomycin and fluoroquinolones may be under-recognized as a cause of thrombocytopenia [109].

A large percentage of thrombocytopenic patients in the ICU receive a platelet transfusion. Many of these transfusions are administered outside of published guidelines [110]. This is important as platelet transfusions are not benign, being associated with many of the same complications as FFP, including TRALI, immune sensitization, etc. Platelets are obtained by two different methods; i.e., preparing platelet concentrates from donated units of whole blood, and by platelet apheresis procedures. The "composition" of pheresed (SDP) as well as single and pooled whole blood derived platelets (WBDP) as listed in Table 38.2.

Platelet transfusion may be indicated to prevent hemorrhage in patients with thrombocytopenia or platelet function defects (see Table 38.3). Contraindications to platelet transfusion include thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia. Transfusion of platelets in these conditions can result in further thrombosis [76, 111]. One unit of apheresis platelets should increase the platelet count in adults by 30,000–60,000 μL^{-1}. The platelet count should be measured within an hour of transfusion. Both hemorrhage and the underlying conditions that cause bleeding may increase platelet consumption and appreciably shorten platelet survival. Most ICU patients respond poorly to platelet transfusion.

Table 38.2 Platelet product contents

	Pheresis (SDP)	WBDPs (single unit)	WBDP pool (5 units)
Platelets Av	~4.2×10^{11}	~$7–9 \times 10^{10}$	~4×10^{11}
Leukocytes	10^5–10^7	~8×10^7	~4×10^8
RBC	Rare	<1 mL	<5 mL
Volume (mL)	200–300	45–60	~300
Matching potential	Yes	Yes	No
Shelf life	5 days	5 days	5 days

Table 38.3 Indications of platelet transfusion

Prophylactic transfusion indication	Platelet count $x \times 10^9$ L^{-1}
Major surgery or invasive procedure, no bleeding	≤50
Epidural anesthesia, gastroscopy and biopsy, transbronchial biopsy, liver biopsy	≤50
Ocular surgery or neurosurgery, no bleeding	≤100
Lumbar puncture	<20
Surgery active bleeding	<50
Stable, non-bleeding	<10
Stable non-bleeding and minor procedure	<20

Salman et al. studied 90 ICU patients who received a platelet transfusion; the mean increase in platelet count was 22,600 μL^{-1} with 64 % having a poor response (defined as an increase of <30,000 μL^{-1} after 6 units WBDP [104].

Spontaneous bleeding through intact endothelium does not occur unless the platelet count is less than 5,000 μL^{-1} [76, 111]. Previously, a platelet count of 20,000 μL^{-1} was considered to be an indication for a prophylactic platelet transfusion. However, four randomized prospective transfusion trials comparing prophylactic platelet transfusion triggers of 10,000 μL^{-1} versus 20,000 μL^{-1} showed no differences in hemorrhagic risks [111].

Elderly patients are frequently prescribed anti-platelet drugs; intracerebral hemorrhage is not an uncommon complication in these patients. Platelet transfusion has therefore been considered in patients taking an anti-platelet drug who suffer an intracerebral bleed. While no RCT has been performed data from observational studies suggest the platelet transfusions do not improve outcome [112]. There is currently an ongoing study known as the Platelet Transfusion in Cerebral Hemorrhage trial, which aims to answer this question in the setting of spontaneous intracerebral hemorrhage [113]. This is a prospective, randomized, multicenter study, which will examine the effect of platelet transfusion within 6 h compared with standard care.

Heparin Associated Thrombocytopenia

Recognition of heparin-induced thrombocytopenia (HIT) and HIT with thrombosis (HITT) is of particular importance given its paradoxical association with thrombosis. HIT/HITT is an immune-mediated disorder that is triggered by exposure to any form of heparin; it is also known as type II HIT, to distinguish it from the non-immune-mediated, mild thrombocytopenia associated with heparin termed type I HIT. Type II HIT is caused by the generation of heparin-induced, platelet activating immunoglobulin G (IgG) antibodies that recognize heparin-platelet factor 4 complexes [114]. The resulting platelet activation and thrombin generation lead to a significant risk of both arterial and venous thrombosis. Depending on the patient population studied, the risk of thrombosis has ranged from 29 to 89 %. Even after cessation of heparin therapy, the threat of thrombosis persists. In one study, the 30-day risk of thrombosis after the diagnosis of HIT was 53 % [115]. However, only a small proportion of patients who form HIT antibodies (seroconversion) will develop thrombocytopenia, and a smaller proportion will develop HIT-associated thrombosis.

The incidence of HIT varies depending on the patient population studied and the type of heparin preparation used. Patients undergoing cardiac or orthopedic surgery are among those at highest risk of developing HIT. HIT is less common in medical patients, with studies suggesting a frequency of 1 % or less [114]. Women have approximately twice the risk of developing HIT as men. Patients receiving unfractionated heparin (UFH) are at increased risk of HIT compared with those given the low molecular weight heparin (LMWH) preparations. Diagnosis of HIT requires consideration of both clinical and serologic findings. Because nonpathogenic heparin-platelet factor 4 antibodies occur commonly in patients treated with heparin, a positive test for HIT antibodies is not sufficient to make the diagnosis. Diagnostic specificity can be increased by use of a sensitive washed platelet activation assay; a positive platelet activation assay is much more specific for clinical HIT than a positive platelet factor 4-dependent immunoassay. However, given the risk of thrombosis in patients with HIT, appropriate therapy should not be withheld while awaiting the results of serologic testing. HIT should be suspected in patients who develop thrombocytopenia or experience a relative drop in platelet count of >50 %, typically occurring 4–10 days after initiation of heparin therapy. Thrombocytopenia may occur much more rapidly after exposure to heparin, however, in patients who have received heparin within the previous 100 days. New or recurrent venous or arterial thromboses in patients who are receiving, or have recently received, a heparin product should also raise suspicion for HIT. It should be appreciated that in about 25 % of HIT patients, a thrombotic event during heparin treatment precedes the subsequent HIT-associated platelet count fall [114].

Only a subset of anti-PF4/heparin antibodies activate platelets. There is a correlation between the degree of reactivity in the EIA, expressed in optical density (OD) units, and the presence of PF4/heparin antibodies. Thus, the greater the magnitude

Table 38.4 4T score to determine the likelihood of HIT

	Score = 2	Score = 1	Score = 0
Thrombocytopenia	>50 % fall and nadir > 20 AND no surgery within 3 days	>50 % fall BUT surgery within 3 days or 30–50 % platelet fall or nadir 10–19	<30 % platelet fall or nadir < 10
Timing	5–10 days after start of heparin or fall within 1 day of start heparin and exposure to heparin within past 5–13 days	Platelet fall within 1 day of heparin AND exposure to heparin in past 31–100 days or platelet fall after day 10	Platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis	Confirmed new thrombosis, skin necrosis at injection site, adrenal hemorrhage	Recurrent venous thrombosis in patient receiving therapeutic anticoagulation or suspected thrombosis (awaiting confirmation)	Thrombosis not suspected
O**T**her causes	No alternative cause for platelet fall evident	Possible other cause	Probable other cause

Score 0–3 low risk, 4–5 intermediate risk, score 6–8 high risk

of a positive EIA test result, the greater the likelihood that the patient has HIT. Functional assays, such as the serotonin release assay (SRA) and heparin induced platelet activation (HIPA) are sensitive and specific for HIT because they only detect antibodies that are capable of activating platelets. HIT is recognized as a clinicopathologic syndrome because diagnosis is based on the combination of a compatible clinical picture and the presence of platelet-activating anti-PF4 antibodies [116]. The 4Ts clinical prediction rule has been developed as an aid in the diagnosis of HIT (see Table 38.4) [116]. Patients with a low 4Ts score have a very low probability of HIT (0–3 %), however, many patients (24–61 %) with a high 4Ts score prove not to have HIT [116, 117]. This suggests that clinical assessment plays an essential role in the diagnosis of HIT.

If HIT is suspected, all heparin products must immediately be discontinued. Given the high risk of thrombosis with HIT it is currently recommended that an alternate, non-heparin anticoagulant replace heparin in patients strongly suspected of having HIT [114]. The ACCP guidelines recommend that following agents for the treatment of HIT [116]:

- argatroban or lepirudin in patients who have normal renal function
- argatroban in patients with renal insufficiency
- bivalirudin in patients who require urgent cardiac surgery

For patients receiving lepirudin, the initial lepirudin infusion rate should be no higher than 0.10 mg/kg/h. The usual starting dose of argatroban is 2.0 μg/kg/min with dosage adjustment according to the PTT. In patients with heart failure, multiple organ system failure, or severe anasarca or who are postcardiac surgery, an initial infusion at a rate between 0.5 and 1.2 μg/kg/min is recommended [114]. In patients

with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, the ACCP guidelines suggest the use of heparin (short-term use only) over non-heparin anticoagulants. In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, the ACCP guidelines suggest the use of non-heparin anticoagulants over heparin or LMWH [116]. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, the ACCP guidelines recommend the use of fondaparinux at full therapeutic doses until transition to Coumadin can be achieved. In patients with HIT and severe thrombocytopenia, platelet transfusions should only be given for bleeding or during the performance of an invasive procedure with a high risk of bleeding [116].

Coumadin should not be started before the platelet count has increased above 150,000 μL^{-1}. Low dose Coumadin is recommended (5 mg/day) with the non-heparin anticoagulant being continued until the platelet count has reached a stable plateau, the INR has reached the intended target range, and after a minimum overlap of at least 5 days between the non-heparin anticoagulant and Coumadin. Because thrombocytopenia is common in ICU patients and because these patients are invariably receiving heparin the possibility of HIT is frequently entertained. It is important to consider HIT in thrombocytopenia patients as the consequences (to the patient and physician) are devastating should the diagnosis be missed. Consequently, these patients usually undergo an expensive and often frustrating diagnostic workup. This scenario is best avoided by minimizing the use of unfractionated heparin (UH), particularly in high risk patient groups. As the risk of HIT is lower with LMWH and essentially zero with fondaparinux, these agents are useful alternatives to UH (in patients with normal renal function).

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) usually refers to the disorder of thrombocytopenia, hemolysis with schistocytes on blood smears, renal dysfunction and neurologic abnormalities, such as headache, confusion, focal deficits, seizures, or coma [118–120]. These manifestations are due to widespread microvascular thrombosis involving the capillaries and arterioles of the brain and other organs. Thrombocytopenia results from consumption of platelets, whereas erythrocyte fragmentation and hemolysis may be due to mechanical injury as the red cells encounter the intravascular thrombi or abnormally high levels of shear stress. Typically, TTP affects previously healthy adolescents or adults and almost invariably follows a rapid course of deterioration and death unless plasma infusion or exchange therapy is instituted immediately. A similar disorder occurs in children, the hemolytic-uremic syndrome (HUS). Childhood HUS, typically preceded by abdominal pain and diarrhea is recognized as a complication of infection caused by bacteria that produce Shiga toxins, such as Escherichia coli O157:H7. Currently, about 90 % of children with typical HUS survive with supportive care, without plasma exchange treatment.

Common clinical and laboratory features of TTP

- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Neurologic abnormality or complaint
- Renal abnormalities
- Proteinuria and microscopic hematuria
- Increased BUN and creatinine
- Temperature > 38.3 °C
- Microthrombi on tissue biopsy

Exclusion

- Evidence of intravascular coagulation
- Evidence of underlying condition associated with or producing microangiopathic syndrome
- Positive antinuclear antibody or anti-DNA antibody
- Oliguria or anuria

The pathophysiological hallmarks of acute TTP are von Willebrand factor (VWF)—platelet-rich thrombi occluding the microvasculature. The VWF-platelet thrombi are thought to be the consequence of insufficient processing of newly secreted, extremely adhesive and ultra large VWF multimers. In the majority of patients, this insufficient processing of ultra large VWF multimers is the result of a severe deficiency of the VWF-cleaving protease, now denoted as ADAMTS13 [118–120]. ADAMTS13 activity levels are less than 10 % of normal control in patients who have acute TTP. TTP is considered an autoimmune disease, with ADAMTS13-binding IgG is detectable in 97–100 % of cases.

Platelet transfusion should be avoided because bleeding complications are uncommon in TTP, and marked deterioration in neurologic status has been reported in association with platelet transfusions. In acute bouts of acquired TTP, the treatment of choice is daily plasma exchange with replacement of plasma. Plasma exchange should be initiated immediately once a diagnosis of acute TTP is seriously considered or has been established, as deferral in starting treatment is associated with increased numbers of treatment failure and adverse outcome [121]. In case plasma exchange is not available, patients should be treated with plasma infusions until their referral to a center where plasma exchange can be performed. The efficacy of plasma exchange therapy is believed to result from replenishment of the missing ADAMTS13. Although it also may remove the inhibitors, this process is not very effective and by itself is insufficient for therapeutic responses.

Plasma exchange treatment is frequently supplemented with immunosuppressive drugs. Although controlled trials are lacking, the finding that in the majority of patients, idiopathic acquired TTP is an autoimmune disorder with circulating inhibitory anti-ADAMTS13 autoantibodies leading to severe ADAMTS13 deficiency supports the potential efficacy of these drugs. Methylprednisolone is the most commonly used drug. However, the combination of plasma exchange and cyclosporine is an alternative with apparent success [122]. Rituximab, a chimeric monoclonal anti-CD20, has been used with presumed benefits in patients with protracted TTP.

Cryprecipitate

Cryoprecipitate is prepared by thawing fresh frozen plasma and collecting the precipitate. Cryoprecipitate contains high concentrations of factor VIII and fibrinogen [123]. Cryoprecipitate is used in cases of hypofibrinogenemia, which most often occurs in the setting of massive hemorrhage or consumptive coagulopathy. Each unit will raise the fibrinogen level by 5–10 mg/dL, with the goal of maintaining a fibrinogen level of at least 100 mg/dL [123]. The usual dose in adults is 10 units of pooled cryoprecipitate.

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Chapter 39
Adrenal Insufficiency

The stress system receives and integrates a diversity of cognitive, emotional, neurosensory and peripheral somatic signals that are directed to the central nervous system through distinct pathways. The stress response is normally adaptive and time limited and improves the chances of the individual for survival. The stress response is mediated largely by activation of the hypothalamic-pituitary-adrenal (HPA) axis with the release of cortisol. In general, there is a graded cortisol response to the degree of stress, such as the type of surgery. Cortisol levels also correlate with the severity of injury, the Glasgow Coma Scale and the APACHE score. Cortisol effects the transcription of thousands of genes in every cell of the body. In addition, the cortisol-glucocorticoid receptor complex effects cellular function by non-transcriptional mechanisms. Cortisol has several important physiologic actions on metabolism, cardiovascular function and the immune system. Cortisol increase the synthesis of catecholamines and catecholamine receptors which is partially responsible for its positive inotropic effects. In addition, cortisol has potent anti-inflammatory actions including the reduction in number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils and eosinophils at sites of inflammation. Cortisol is the most important inhibitor of the transcription of pro-inflammatory mediators (inhibits NF-kB and AP-1 by multiple mechanisms) [1].

There is increasing evidence that in many critically ill patients activation of the HPA axis and the release of cortisol is impaired. The reported incidence varies widely (0–77 %) depending upon the population of patients studied and the diagnostic criteria used to diagnose adrenal insufficiency (AI) [2]. However, the overall incidence of adrenal insufficiency in critically ill medical patients approximates 10–20 %, with an incidence as high as 60 % in patients with septic shock [2]. The major sequela of adrenal insufficiency in the critically ill is on the systemic inflammatory response (excessive inflammation) and cardiovascular function (hypotension).

Until recently the exaggerated pro-inflammatory response that characterizes patients with systemic inflammation has focused on suppression of the HPA axis and "adrenal failure." However, experimental and clinical data suggest that

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corticosteroid tissue resistance may also play an important role. This complex syndrome is referred to as "*Critical Illness Related Corticosteroid Insufficiency* (CIRCI)" [1, 3]. CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patients illness; i.e. CIRCI may be due to acute adrenal insufficiency, corticosteroid tissue resistance or both. The mechanisms leading to dysfunction of the HPA axis and tissue glucocorticoid resistance during critical illness are complex and poorly understood [1]. CIRCI manifests with insufficient corticosteroid mediated downregulation of inflammatory transcription factors.

CIRCI is most common in patients with severe sepsis (septic shock) and patients with ARDS. In addition, patients with liver disease have a high incidence of AI (Hepato-adrenal syndrome). CIRCI should also be considered in patients with pancreatitis. A subset of patients may suffer structural damage to the adrenal gland from either hemorrhage or infarction and this may result in long term adrenal dysfunction. Furthermore, a number of drugs are associated with adrenal failure. However, most patients with AI (and CIRCI) develop reversible dysfunction of the HPA system; this is probably initiated by inflammatory mediators, may be self-perpetuating and follows the same time course of the immune deregulation in patients with sepsis and SIRS [1].

Causes of Adrenal Insufficient/Circi

Reversible Dysfunction of HPA Axis

- Sepsis/SIRS
- Pancreatitis
- Drugs
  - ***Etomidate*** (primary AI)
  - Corticosteroids (secondary AI)
  - Ketoconazole (primary AI)
  - Megesterol acetate (Secondary AI)
  - Rifampin (increased cortisol metabolism)
  - Phenytoin (increased cortisol metabolism)
  - Metyrapone (primary AI)
  - Mitotane (primary AI)
  - Hypothermia

Primary Adrenal Insufficiency

- Autoimmune adrenalitis
- HIV infection
  - HART therapy
  - HIV virus
  - CMV

- Metastatic carcinoma
  - Lung
  - Breast
  - Kidney
- Systemic fungal infection
  - Histoplasmosis
  - Cryptococcus
  - Blastomycosis
- Tuberculosis
- Adrenal hemorrhage/infarction
  - DIC
  - Meningococcemia
  - Anticoagulation
  - Anti-phospholipid syndrome
  - HIT
  - Trauma

Glucocorticoid Tissue Resistance

- Sepsis
- SIRS
  - ARDS
  - Trauma
  - Burns
  - Pancreatitis
  - Liver failure
  - Post cardiac surgery
  - HELLP syndrome

Clinical Features of Adrenal Insufficiency/Circi

Patients with chronic adrenal insufficiency (Addison's disease) usually present with:

- weakness
- weight loss
- anorexia and lethargy
- nausea, vomiting and abdominal pain

Clinical signs include:

- orthostatic hypotension
- hyperpigmentation (primary adrenal insufficiency)

Laboratory testing may demonstrate:

- hyponatremia
- hyperkalemia
- hypoglycemia
- normocytic anemia

This presentation contrasts with the features of CIRCI. The clinical manifestations of CIRCI are consequent upon an exaggerated pro-inflammatory immune response and include:

- Hypotension refractory to fluids and requiring vasopressors is a common manifestation of CIRCI. CIRCI should therefore be considered in all ICU patients requiring vasopressor support
- An excessive systemic inflammatory response
  - ALI/ARDS
  - Trauma
  - Burns
  - Pancreatitis
  - Liver failure
  - Post cardiac surgery
  - HELLP syndrome

Laboratory assessment may demonstrate:

- eosinophilia
- hypoglycemia
- hyponatremia and hyperkalemia are uncommon

Diagnosis of Adrenal Insufficiency/Circi

At the current time there are no clinically useful tests to assess the cellular actions of cortisol; the accurate clinical diagnosis of CIRCI therefore remains somewhat elusive. Furthermore, while the diagnosis of AI in the critically ill is fraught with difficulties, at this time this diagnosis is best made by [1]:

- a random (stress) cortisol of less than 10 μg/dL or
- a delta cortisol of less than 9 μg/dL after a 250 μg ACTH stimulation test.

From a mechanistic and practical standpoint it may be useful to divide CIRCI into two subgroups, namely [4]:

Type I: Characterized by a random (stress) cortisol < 10 μg/dL.

Type II. Characterized by a random cortisol ≥ 10 μg/dL AND a delta cortisol less than 9 μg/dL.

Type II CIRCI is associated with high levels of pro-inflammatory mediators (notably IL-6 and IL-10), high CRP levels and high ACTH levels. These patients may have both ACTH and tissue glucocorticoid resistance [4].

Type I CIRCI is associated with low levels of pro-inflammatory mediators and "normal" stress ACTH levels; these patients may have impaired cortisol production (adrenal insufficiency). Future studies should distinguish between these two subtypes, as this may have prognostic and therapeutic implications.

Factors Affecting the Response to Corticosteroid Treatment

The Immune Status of the Host

The immune status of the host is critical in determining the risk/benefit associated with corticosteroids therapy. Corticosteroids are likely to compound the immunoparesis in immune-paresed patients increasing the risk of acquired infections. Classic teaching suggests that tissue injury from trauma and surgery results in a systemic inflammatory response syndrome (SIRS) with "unbridled inflammation" which after a few days/weeks evolves into an immuno-paretic phase known as the compensated anti-inflammatory response syndrome (CARS) [5–9]. However, multiple reports over the last two decades have indicated that the proliferative response to T cell mitogens is significantly impaired in patients and experimental animals immediately after traumatic or thermal injury [10–14]. The T-cell dysfunction after traumatic stress is characterized by a decrease in T-cell proliferation, an aberrant cytokine profile, decreased T-cell monocyte interactions and attenuated expression of the T-cell Receptor Complex (TCR). Furthermore, surgical stress induces a shift in the T-helper (Th)1/Th2 balance resulting in impaired cell mediated immunity [15–17]. While the Th1 cytokines may be increased following trauma and surgery, these cytokines do not reach the levels seen in patients with sepsis and unlike patients with sepsis, the Th2 response predominates. As corticosteroids are likely to compound the immuno-paresis following trauma and stress these agents are probably best avoided in the surgical patient who becomes septic. This hypothesis is supported by the failure of corticosteroids to improve outcome in the *Corticosteroid Therapy of Septic Shock Study* (CORTICUS) study where the majority of patients were surgical patients [18]. It would therefore appear illogical to give septic post-surgical patient corticosteroids as this is only likely to compound the immunosuppressive state and increase the risk of secondary infections (which is exactly what the CORTISUS study demonstrated). Furthermore, it should be noted that the incidence of CIRCI is very low in surgical/trauma patients. In a 5 year retrospective study of 2,100 trauma patients admitted to an ICU the incidence of CIRCI was only 3.3 % [19]. Similarly, in an analysis of 1,795 intubated trauma patients, 82 (4.5 %) were diagnosed with adrenal insufficiency [20]. Fann and colleagues performed statistical modeling to predict adrenal insufficiency in trauma patients [21]. In this study 3.3 % of patients admitted to the ICU were diagnosed with adrenal insufficiency.

Boomer and colleagues performed cytokine secretion assays and immunophenotyping of cell surface receptor-ligand expression profiles from postmortem spleen and lung tissue samples from 40 patients who died from sepsis and 29 brain-dead

controls [22]. In this study, patients who died in the ICU following sepsis compared with patients who died of non-sepsis etiologies had biochemical, flow cytometric, and immunohistochemical findings consistent with severe immunosuppression. In patients with sepsis, the initial pro-inflammatory response is followed by three distinct clinical pathways, namely i) homeostasis is restored with return to a "normal immune status" ii) patients may develop a prolonged a pro-inflammatory response with ongoing tissue injury iii) while other patients may progress to a state of immuno-suppression (CARS). It is important for clinicians to be able to accurately determine the patients' immune status before instituting immunomodulating interventions. It is likely that patients who receive corticosteroids late in the course of their disease and have progressed to CARS will suffer adverse sequela from such therapy (see timing below). Future research in sepsis will need to focus on developing tools that can dynamically and in real-time characterize the patient's immune response to allow targeted immune therapy.

Timing of Corticosteroids

Since steroids enhance local immune defences but reduce global NF-kappa B expression and cause a predominant TH2 immunosuppressive state, steroids are likely to be beneficial early in the course of the disease but likely to compound the immunosuppression when given later in the course of sepsis. The time dependent initiation of the use of corticosteroids has not been taken into consideration in those studies (and meta-analyses) which have analyzed the benefits/risk of steroids in sepsis. In the study by Annane et al., the window for enrollment into the study was initially 3 h and then it was increased to 8 h [23]. In the CORTICUS study, the initial time frame of 24 h, increased to 72 h [18]. This time dependent effect was demonstrated by Park et al. who in a retrospective analysis of 178 patients with septic shock found that corticosteroids were only of benefit if given within 6 h after the onset of septic shock-related hypotension [24]. Similarly, Katsenos et al. demonstrated that in patients receiving hydrocortisone for septic shock initiation of therapy within 9 h was associated with improved survival [25]. Furthermore, ex-vivo mononuclear stimulation studies demonstrated attenuated TNF-α release only in those patients who received early corticosteroid therapy.

Dose and Dosing Strategy

The effect of glucocorticoids on immune suppression is critically dose dependent. It is well know from the organ transplant experience that high-dose corticosteroids effectively abolish T-cell mediated immune responsiveness and are very effective in preventing/treating graft rejection. However, while stress-doses of corticosteroids inhibit systemic inflammation with decreased transcription of pro-inflammatory

mediators, they maintain innate and acquired immune responsiveness and do not increase the risk of secondary infections [26–28]. Lim et al. demonstrated that the effect of corticosteroids on macrophage function was dose dependent [29]. Low doses enhanced macrophage function whereas high doses strongly depressed macrophage function.

It is important to recognize that patients with ARDS and many with sepsis have prolonged immune dysregulation requiring a more prolonged course of therapy [30]. Two longitudinal studies in patients with severe community acquired pneumonia found high levels of circulating inflammatory cytokines 3 weeks after clinical resolution of sepsis [31, 32]. Trials from the 1980s which investigated short-term (24–48 h) massive glucocorticoid doses (up to 40,000 mg/hydrocortisone eq./day) were associated with an increased risk of side effects, and no clear outcomes benefit [33, 34]. Recent studies, which investigated the use of low dose (stress dose) corticosteroids given over a more prolonged period have shown clinical benefit in terms of reduction in mortality with an increase in pressor free, ventilator free and ICU free days [33, 34].

Acute Rebound After Discontinuation of Corticosteroids

Corticosteroids should never be stopped abruptly; this will lead to a "rebound" of inflammatory mediators with an increased likelihood of hypotension and/or rebound inflammation (lung injury). There is ample evidence that early removal of glucocorticoid treatment may lead to rebound inflammation and an exaggerated cytokine response to endotoxin [26, 35–42]. Experimental work has shown that short-term exposure of alveolar macrophages or animals to dexamethasone is followed by enhanced inflammatory cytokine response to endotoxin [43, 44]. Similarly, normal human subjects pretreated with hydrocortisone had significantly higher TNF-α and IL-6 response after endotoxin challenge compared to controls [45]. Two potential mechanisms may explain rebound inflammation: homologous down-regulation and GC-induced adrenal insufficiency. Glucocorticoid treatment down-regulates the GR levels in most cell types, thereby decreasing the efficacy of the treatment [46]. Down-regulation takes place at both the transcriptional and translational level, and hormone treatment decreases receptor half-life by approximately 50 % [46]. In experimental animals, overexpression of GRs improves resistance to endotoxin-mediated septic shock while GR blockade increases mortality [47].

Genetic Polymorphisms

Not all patients with sepsis/ARDS treated with corticosteroids respond to this treatment. Genetic polymorphisms of a number of genes may explain this finding. Gessner demonstrated that hydrocortisone failed to abolish NF-κB protein nuclear

translocation in deletion allele carriers of the NFKB promoter polymorphism (-94ins/delATTG) [48]. In addition, these authors demonstrated that patients with this polymorphism receiving hydrocortisone had a much greater 30-day-mortality (57.6 %) than the other genotypes (24.4 %; HR: 3.18, 95 % CI: 1.61–6.28; p = 0.001). It is likely that other polymorphisms including those of the glucocorticoid receptor (GR) may influence the clinical response to glucocorticoids [49].

Abnormalities of the Glucocorticoid Receptor

Deceased concentration or abnormal function of the GR may underlie the observation of variability of cortisol sensitivity amongst patients. Cortisol diffuses rapidly across cell membranes binding to the GR. Two isoforms of the GR have been isolated, namely GR-α and GR-β. The GR-β isoform fails to bind cortisol and activate gene expression and thus functions as a negative inhibitor of GR-α [50]. Through the association and disassociation of chaperone molecules the glucocorticoid-GR-α complex moves into the nucleus where it binds as a homodimer to DNA sequences called glucocorticoid-responsive elements (GRE's) located in the promoter regions of target genes which then activate or repress transcription of the associated genes.

Guerrero et al. demonstrated increased expression of the GR-β isoform in patients with sepsis [51]. In a sheep model of ALI induced by *Escherichia coli* endotoxin, Liu et al. demonstrated decreased nuclear GRα binding capacity [52]. In an *ex vivo* model Meduri and colleagues compared the cytoplasmic to nuclear density of the GR-complex in patients with ARDS who were improvers with those of non-improvers [53]. These authors demonstrated a markedly reduced nuclear density of the GR-complex in non-improvers while the cytoplasmic density was similar between improvers and non-improvers. This study suggests glucocorticoid resistance due to diminished nuclear translocation of the GR-complex. Siebig et al. demonstrated deceased cytosolic receptor levels in critically ill patients as compared to control subjects [54]. Similarly, van den Akker noted that children with sepsis or septic shock had depressed levels of glucocorticoid receptor mRNA in their neutrophils.

Treatment of Adrenal Insufficiency/CIRCI

Who to Treat with Steroids?

Over the last three decades approximately 20 randomized controlled trials (RCTs) have been conducted evaluating the role of glucocorticoids in patients with sepsis, severe sepsis, septic shock and ARDS. Varying doses (37.5–40,000 mg/hydrocortisone

eq./day), dosing strategies (single bolus/repeat boluses/continuous infusion/dose taper) and duration of therapy (1–32 days) were used in these studies [33, 55]. Despite multiple guidelines and over 20 meta-analyses, the use of glucocorticoids in patients with sepsis remains extremely controversial with conflicting recommendations. Furthermore, while there are large geographic variations in the prescription of glucocorticoids for sepsis up to 50 % of ICU patients receive such therapy [56]. Currently a number of large multicenter RCT's are being conducted, which should hopefully resolve this issue. While it is difficult to make strong evidence based recommendations at this time, an evidence based review of the literature allows one to make the following conclusions [57, 58]:

i. Short-course high-dose glucocorticoids are not beneficial in the treatment of severe sepsis/septic shock and ARDS [34, 59, 60].
ii. Treatment of septic shock with moderate-dose glucocorticoids for 7 days significantly reduces vasopressor dependency (ACTH responders and non-responders) and ICU length of stay [34, 59, 60].
iii. Glucocorticoids may reduce mortality in sub-groups of patients with septic shock [34, 59, 60].
iv. In patients' with progressive early (<72 h) ARDS glucocorticoids significantly increase the number of ventilator, ICU and hospital free days with a reduction in the risk of death [58].
v. Glucocorticoids appear to be of no benefit in patients with sepsis who are at a low risk of dying and in patients with mild and rapidly resolving ARDS [61].
vi. Glucocorticoids do not increase the risk of super-infections [34, 59, 60].
vii. The addition of fludrocortisone does not appear to have additional benefits when treating patients with hydrocortisone [62].
viii. Treatment with glucocorticoids may reduce the risk of post-traumatic stress disorder [63].
ix. Etomidate causes suppression of cortisol synthesis for up to 24 h [64]. Replacement with glucocorticoids is only recommended in vasopressor dependent septic shock patients [65–67].

Low-dose corticosteroids should be considered in the treatment of patients with septic shock who have responded poorly to fluids and vasopressors (requiring > 0.05–0.1 μg/kg/min of norepinephrine or eq.) and patients with ARDS who show progressive disease after 48 h of supportive care. Adrenal testing is not required in these patients. Additional ICU patients who meet the diagnostic criteria for adrenal insufficiency (as defined above) *and* who have hemodynamic instability or evidence of an excessive inflammatory response should also be treated with corticosteroids (liver failure, pancreatitis, etc.).

Traditionally, patients with sepsis have been treated with hydrocortisone while patients with ARDS have received methylprednisolone. This appears to be rather arbitrary with no scientific data to support this distinction. However, it is likely that different corticosteroids have different binding capacities for the GR isoforms and

hence may have different biological actions. Furthermore, research is underway to develop GR agonists that have more selective biological properties.

The suggested treatment approach is outlined below. In patients' with sepsis and/or ARDS corticosteroids should never be stopped abruptly; this will lead to a "rebound" of inflammatory mediators with an increased likelihood of hypotension and/or rebound inflammation (lung injury). A continuous infusion of glucocorticoid may be associated with better (smoother) glycemic control [68]. Since blood glucose variability has been demonstrated to have prognostic implications [69, 70], this may be the preferable method of dosing.

- Hydrocortisone 50 mg IV q 6 hourly or 100 mg bolus then 10 mg/h continuous infusion for at least 7 days, and ideally for 10–14 days. Patients should be vasopressor and ventilator "free" before taper
- Hydrocortisone taper
  - Hydrocortisone 50 mg IV q 8 hourly for 2–3
  - Hydrocortisone 50 mg IV/PO q 12 hourly for 2–3 days
  - Hydrocortisone 50 mg IV/PO daily for 2–3 days
  - Re-institution of full dose hydrocortisone with recurrence of shock or worsening oxygenation
- Hydrocortisone and methylprednisolone are considered interchangeable
- Dexamethasone should be avoided; it lacks mineralocorticoid activity. Dexamethasone has a long half-life and suppresses the HPA axis; it should therefore NOT be used pending an ACTH stimulation test.

Adverse Effects of Corticosteroids

The complications associated with the use of corticosteroids are dependent upon the dose, the dosing strategy and the duration of therapy. In the ICU setting the most important complications include immune suppression, hyperglycemia and HPA axis and GR suppression. Both glucocorticoids and TNF-α stimulate muscle catabolism (reviewed in Chap. 32). Since glucocorticoids are potent inhibitors of TNF-α it is likely that corticosteroids may limit muscle breakdown during acute illness. This postulate is supported by the fact that patients with ARDS treated with glucocorticoids have significantly increased ventilator free days. In the CORTICUS study neuromuscular weakness was very rarely reported [18]. While myopathy is common in patients treated with high-dose corticosteroids this complication is uncommon with stress dose corticosteroids [33, 55]. Similarly, while high dose corticosteroids may impair wound healing this complication does not occur with stress dose corticosteroids. Schreiber et al. reported that the use of corticosteroids in ICU patients was associated with an increased risk of delirium [71]. In this study the authors were unable to establish a relationship between the dose of corticosteroid and the risk of delirium.

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Chapter 40
Electrolyte Disturbances

Sodium and Water

Rules of the Game

Sodium balance determines volume status.

Water balance determines tonicity i.e. Na^+ concentration.

- Volume Overload = increased total body sodium (regardless of serum Na concentration)
- Euvolemia = normal total body sodium (regardless of serum Na concentration)
- Volume Depletion = decreased total body sodium (regardless of serum Na concentration)
- Hyponatremia = relative water excess
- Hypernatremia = relative water deficit
- In volume depleted patients, volume should be corrected prior to correction of tonicity; i.e. patients should initially be volume resuscitated with Ringers Lactate regardless of serum sodium concentration (see Chap. 9).
- Hyponatremic dehydration; volume replacement with 0.9 % NaCl
- Hypertonic dehydration: volume replacement with Ringers Lactate then change to 0.45 % NaCl.

Hyponatremia

Hyponatremia defined as a serum sodium <135 mEq/L, is the most common electrolyte abnormality encountered worldwide and is an independent risk factor for higher morbidity and mortality rates [1, 2]. The meta-analysis by Corona et al. demonstrated that the hyponatremia-related risk of overall mortality was inversely

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correlated with serum sodium concentration [2]. Symptoms related to hyponatremia have been traditionally associated with severe hyponatremia and acute reductions in serum sodium, but there is growing awareness that even mild hyponatremia is associated with mental dysfunction, unsteady gait and osteoporosis [2–4].

The traditional diagnostic approach and management of hyponatremia is based on an assessment of the patient's volume status; i.e. fluid overloaded, euvolemia or dehydration (see Fig. 40.1). This diagnostic workup includes measurement of urine and serum electrolytes and osmolarity, thyroid function tests, lipid profile and serum

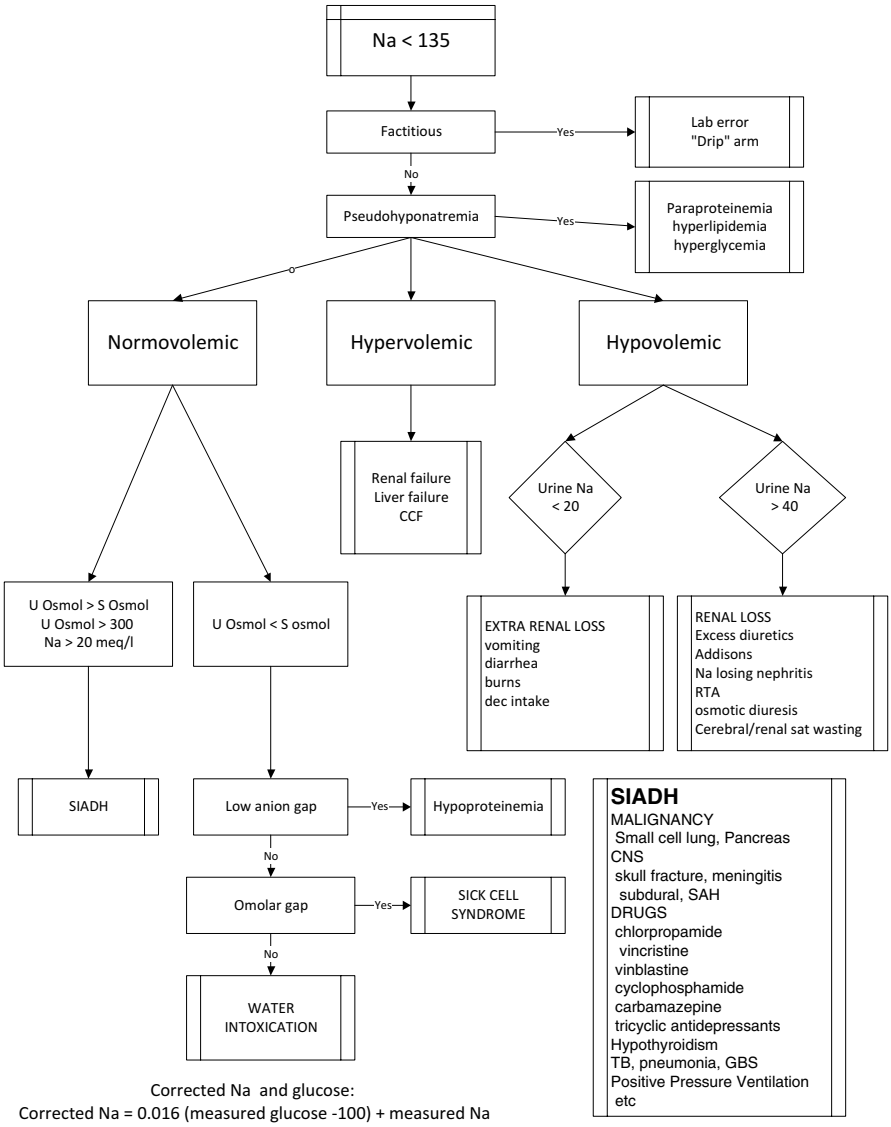

Fig. 40.1 Traditional approach to hyponatremia based on the patient's volume status

cortisol (and possibly ACTH stimulation test). The problem with this approach is that the clinical assessment of volume status is notoriously unreliable and that in many patients it is difficult to determine their volume status with any degree of accuracy (see Chap. 9). This distinction is of utmost importance in distinguishing SIADH from cerebral/renal salt wasting syndrome [3]. The only accurate method to determine volume status is by direct measurement using radiolabelled albumin or RBC. When the true circulating blood volume is measured many patients with SIADH are shown to be volume depleted and likely to have renal salt wasting [3].

Maesaka et al. have proposed a new approach to hyponatremia based on the fractional excretion of urate (FEurate) (see Fig. 40.2) [3]. FEurate is normally 4–11 %. FEurate is decreased in volume depleted states and increased in SIADH and RSW. In SIADH, correction of hyponatremia will normalize FEurate while it remains persistently increased in RSW. The value of determining FEurate in hyponatremic conditions has been further amplified by a normal FEurate in patients with Reset Osmostat [5].

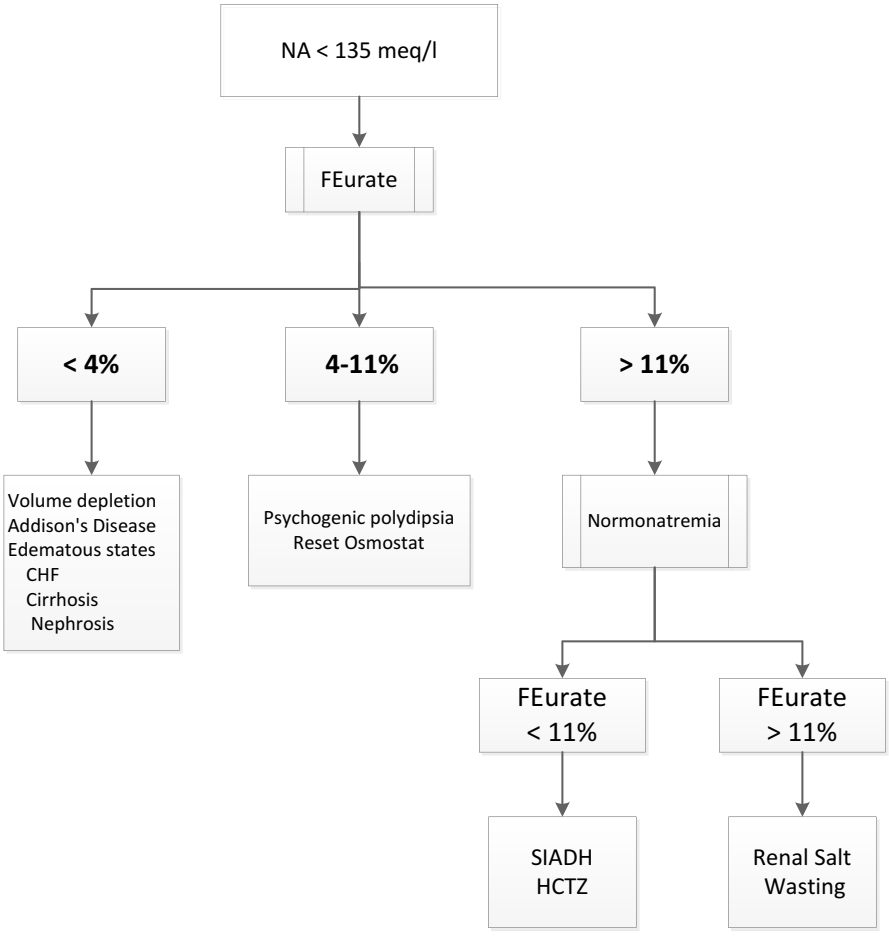

Fig. 40.2 Revised approach to hyponatremia based on FEurate

$$\text{FEurate} = \left(\left(\text{urine urate} / \text{plasma urate}\right) / \left(\text{urine creatinine} / \text{serum creatinine}\right)\right) \times 100$$

$$\text{FEurate} = \left(\left(\text{UNa} \times \text{serum urate}\right) / \left(\text{SNa} \times \text{Urine creatinine}\right)\right) \times 100$$

It should be noted that both SIADH and cerebral/renal salt wasting syndromes are associated with intracranial diseases, have normal renal, thyroid and adrenal function and have similar electrolyte abnormalities (see below) [3].

Findings common to both SIADH and RSW

- Hyponatremia
- Concentrated urine
- Urine Na >40 mEq/L
- Hyperuricemia with increased FEurate

Most patients with hyponatremia are "asymptomatic" and have a plasma sodium concentration above 120 mEq/L. In these patients there is no urgency in correcting the serum sodium concentration and treatment should occur over a number of days. Treatment typically consists of isotonic saline if the patient has true volume depletion or water restriction in the syndrome of inappropriate ADH secretion (SIADH). More aggressive therapy is indicated in those patients who have symptomatic or severe hyponatremia (plasma sodium concentration below 110 mEq/L). In this setting, hypertonic saline can be given initially to raise the plasma sodium concentration (to ~120 mEq/L), although the rate at which this occurs must be carefully monitored to minimize the risk of central demyelinating lesions (see below). Hyponatremia in the setting of effective intravascular volume depletion and edema (congestive cardiac failure and cirrhosis) results from release of ADH in response to "hypovolemia" and carries a poor prognosis. Such patients require volume expansion with albumin and attempts to correct the underlying hemodynamic derangement. The role of ADH antagonists in these patients is unclear [6, 7].

The treatment of hyponatremia requires either the addition of sodium or removal of water. When excess water (e.g. SIADH) rather than sodium deficit is the main mechanism of hyponatremia, removal of water alone is indicated. Net water removal can be achieved by the removal of sodium and water with a loop diuretic administered simultaneously with sodium in the form of normal saline or hypertonic saline. The administration of hypertonic saline alone will also induce sodium and water diuresis, resulting in net loss of water, but the urine concentration is less predictable in this situation. SIADH is usually treated by fluid restriction. Fluid restriction is frequently problematic in critically ill patients, particularly in neurosurgical patients in whom maintenance of a high intervascular volume is necessary to maintain cerebral perfusion. In these patients the use of a ADH receptor antagonist may be preferable (since the problem is water overload and no sodium deficiency). However, as alluded to above it may be exceedingly difficult to distinguish SIADH for CSW syndrome. In these patients it may be preferable to treat the patient with hypertonic saline, monitoring the change in serum sodium (carefully) and FEurate. In those patients who clearly have SIADH (very low BUN and features of hemodilution) an

ADH receptor antagonist may be preferable whereas in patients who clearly have CSW (increased BUN and features of volume depletion) treatment with normal saline is preferable.

Patients with SIADH are euvolemic and have traditionally been treated with volume restriction, demeclocycline, salt tablets, hypertonic saline and/or fludrocortisone [1, 8–11]. These interventions are not particularly effective and are unpredictable. Furthermore, volume restriction may result in intravascular volume depletion and impaired cerebral perfusion. Arginine vasopressin (AVP) binds to vasopressin-2 (V_2) receptors located on the epithelial cells of the renal collecting ducts increasing apical cell membrane water permeability, which stimulates water reabsorption, thereby decreasing serum sodium [12]. Thus, a potentially valuable pharmacologic approach for correcting dilutional hyponatremia is AVP-receptor antagonism to block this antidiuretic cascade. Conivaptan is a high-affinity nonpeptide antagonist of AVP V_2 and V_{1A} receptors that produces aquaresis, the renal excretion of solute-free water that is electrolyte sparing. Conivaptan is available in an intravenous formation. Tolvaptan is as selective V_2 receptor antagonist that is only available in an oral formulation. We have previously reported our experience with the use of a single dose of 20 mg conivaptan (infused over 30 min) in 32 neurocritical care patients with presumed SIADH [13]. The mean 24 h natremic response was 4.3 ± 2.6 mEq/L (range of 1–13 mEq/L), with the greatest change occurring within the first 8 h. Eighteen (56 %) patients met the primary end-point of an increase in serum sodium of $\geq$4 mEq/L in 24 h. The change in serum sodium from 24 to 48 h was 0.5 ± 1.3 mEq/L. We noted no side effects or cases of phlebitis. These results are similar to those reported in the literature and allows for a controlled and predictable increase in the serum sodium concentration [12]. Murphy et al. reported that the maximal response to a single dose of 20 mg conivaptan was maximal at 12 h with the effect being sustained over 72 h [14]. In the study by Murphy et al. the increase in urine output was maximal at 2 h and returned to baseline at 12 h. Rapid and excessive correction of sodium has not been reported with conivaptan [15, 16]. The largest 24 h natremic response in our study was 13 mEq/L. Similar results were reported by the Conivaptan Study group [12]. Conivaptan may act optimally when given as bolus doses rather than as a continuous infusion. Infusion-site reactions and venous phlebitis occurred in up to 73 % of patients receiving a 20 mg/day infusion in company-sponsored trials [16]. Repeat dosing together with the use of normal saline (and a small dose of a loop diuretic) is suggested in those who respond poorly to conivaptan. In all patients receiving AVP antagonists and hypertonic saline the serum sodium must be very closely monitored and corrective action taken if the serum sodium is increasing to quickly (see below). Conivaptan (but not tolvaptan) has a number of important drug interactions. Conivaptan is a sensitive substrate of CYP3A. Conivaptan is a potent mechanism-based inhibitor of CYP3A and can increase the serum levels of midazolam, simvastatin and amlodipine [16].

The optimal rate of correction of hyponatremia varies with the clinical state of the patient. Acute symptomatic hyponatremia (less than 48 h) results in cerebral edema to due water movement into the brain. In contrast, chronic hyponatremia allows time for cerebral adaption to occur, resulting in the return of brain volume

towards normal and usually causes no neurological symptoms. "Rapid" initial correction of hyponatremia is warranted in symptomatic patients, but overly rapid correction can be deleterious (osmotic demyelinating syndrome), particularly in patients with chronic hyponatremia [17]. The rate at which this correction should occur will depend on the presence of symptoms and the rate at which the disorder occurred. Alcoholic patients are particularly prone to cerebral demyelinosis. A recently convened panel of experts recommended that, based on the results of cohort studies and literature reviews, the optimal rate of sodium correction to avoid osmotic demyelination syndrome in patients with chronic hyponatremia is less than 12 mEq/L per 24 h and less than 18 mEq/L in 48 h [10]. In asymptomatic or mildly symptomatic patients the plasma sodium concentration should be raised at a maximal rate below 0.5 mEq/L per hour [18]. More rapid correction is indicated in patients with symptomatic hyponatremia who present with seizures or other severe neurologic manifestations; these findings are primarily due to cerebral edema induced by acute hyponatremia. In this setting, the plasma sodium concentration can be raised at an initial rate of 1.5–2 mEq/L per hour for the first 3–4 h, since the risk of persistent severe hyponatremia is greater than the possible danger of overly rapid correction. Despite the more rapid initial rate of correction with symptomatic hyponatremia, the total increase in the plasma sodium concentration over the first 24 h should not exceed 12 mEq/L, the same limit noted with asymptomatic patients.

The amount of Na^+ required to raise the plasma Na^+ concentration to a safe level (120 mEq/L) can be calculated from the following formula:

$$\text{Na} + \text{deficit} = 0.6 \times \text{lean body weight}\left(\text{kg}\right) \times \left(120 - \text{plasma}\left[\text{Na}^+\right]\right)$$

(Substitute 0.6 for 0.5 in women)

Since 3 % saline contains ~500 mEq/L, the total amount of this solution (in liters) required to increase the serum sodium to 120 mEq/L can be calculated as follows:

$$\text{Total volume of 3\% saline}\left(\text{liters}\right) = \text{Na}^+ \text{ deficit} / 500$$

When 3 % saline is used the initial rate is usually between 50 and 100 mL/h; the serum sodium should be checked after 2 h and then 2 hourly until the sodium has stabilized. An alternative (and perhaps safer) approach in "euvolemic" hyponatremic patients is to use a 0.9 % saline infusion together with furosemide, to increase the free water loss.

Hypernatremia

Hypernatremia is not uncommon in ICU patients primarily due to excessive resuscitation with 0.9 NaCl ($[Na^+]$ 154 mEq/L). Hypernatremia may also occur in dehydrated patients in whom thirst is impaired (e.g. bed ridden or altered mental status). The treatment of the former is free water (e.g. 200 mL water

orally q 4–6 h). In hypertonic dehydration volume status should be corrected first (Ringers Lactate) followed by correction of tonicity (0.45 % saline and/or free water). Rapid correction of hypernatremia can induce cerebral edema, seizures, permanent neurological damage and death. To minimize these risks the plasma Na^+ concentration should be corrected slowly. The maximum rate at which the plasma Na^+ should be corrected is 0.5 mEq/L/h or 12 mEq/L per day, a rate equivalent to that of hyponatremia. The water deficit can be calculated using the following formula:

$$\text{Water deficit} = 0.5 \times \left(\left(\left[\text{Na}^+ \right] / 140 \right) - 1 \right), \text{substitute } 0.5 \text{ with } 0.4 \text{ in women.}$$

Hypokalemia

Only a small fraction of the total body K^+ is extracellular. Therefore serum K^+ levels do not accurately reflect the total body K^+. The degree of K^+ deficit is dependent on the duration of the precipitating cause (time for equilibration) and the serum K^+ level. In patients with chronic hypokalemia 1 mEq fall in serum K^+ is approximately equal to a 200 mEq total body deficit. In critically ill ICU patients it is generally recommended to keep the serum $[K^+] \geq 4.0$ mEq/L. In patients with severe hypokalemia ($K < 3.0$ mEq/L) both PO and as well as IV potassium is recommended.

IV replacement therapy of KCl

- No more than 20 meq/h should be given via a central line infusion
- 20 meq in 50 mL over 1 h
- 40 meq in 100 mL over 2 h
- Peripheral line infusion
- 10 meq in 100 mL over 1 h
- 20 meq in 200 mL over 2 h

Hyperkalemia

Acute hyperkalemia is usually the result of renal failure. Hyperkalemia may also occur with overzealous potassium replacement and in patients receiving ACE inhibitors and potassium sparing diuretics. Factors such as the duration of hyperkalemia, the plasma Ca^{2+} concentration and the acid–base balance modify the toxicity of hyperkalemia. However, a $K^+ > 6.5$ mEq/L or hyperkalemia associated with ECG changes should be regarded as life-threatening requiring immediate treatment.

Clinical features usually occur when the $K^+ > 6.5$ mEq/L and include

- Weakness
- Paresthesia

- Ileus
- Paralysis
- cardiac arrest

ECG changes include:

- peaked T waves
- flattened P
- prolonged PR interval
- widening of the QRS complex
- sine wave leading to V. fibrillation or asystole

The rate of progression of the ECG changes is not predictable and patients may progress from minor ECG changes to dangerous conduction disturbances or arrhythmias within minutes. The ECG changes are exacerbated by coexisting hyponatremia, hypocalcemia, hypermagnesemia and acidosis.

Patients should be treated when the K^+ is greater than 5.5 mEq/L; urgent treatment is required when the K^+ >6.5 mEq/L. The goals of treatment are to:

- protect the heart from the effects of K^+ by antagonizing the effect on cardiac conduction (calcium)
- to shift the K^+ from the extracellular to intracellular compartment
- reduce the total body potassium

Life threatening arrhythmia may occur at any time during therapy, hence, continuous ECG monitoring is required. Patients with a serum K^+ >6.5 mEq/L and/or significant ECG changes should be treated immediately with calcium gluconate, followed by a glucose/insulin infusion and then an iron exchange resin.

Hypophosphatemia

Phosphorus is an essential component of phospholipid, nucleic-acids and plays an essential role in energy metabolism. Only about 1 % of the total body phosphorus is extracellular with the major phosphate store being in bone and the intracellular compartment. The normal range of serum phosphorus concentration in the serum is between 2.2 and 4.4 mg/dL, of which about 55 % is in an ionized form that is physiologically active. The serum phosphate concentration is a poor indicator of the total body phosphorus and rapid shifts of phosphate between the extracellular and intracellular compartments only confound this situation. Interpretation of the serum phosphate is further complicated by a normal diurnal variation, which may be as large as 0.5 mg/dL. However, hypophosphatemia may cause severe life threatening complications, particularly in patients with depleted phosphate stores.

Causes of severe hypophosphatemia

- alcohol abuse and withdrawal
- refeeding after starvation
- respiratory alkalosis

- malabsorption
- oral phosphate binders
- TPN
- severe burns
- therapy of diabetic ketoacidosis

There is a poor correlation between serum phosphate levels and symptoms. Although hypophosphatemia becomes life threatening when the serum levels are less than 1 mg/dL, symptoms may develop when the serum phosphate is less than 2 mg/dL.

Manifestations include:

- myocardial depression
- weakness, rhabdomyolysis and respiratory failure
- confusion, stupor, coma, seizures
- hemolysis, platelet dysfunction, leukocyte dysfunction

Management

Therapy is usually empiric and level levels must be closely followed to prevent hyperphosphatemia. It has been recommended that patients with severe hypophosphatemia (serum phosphate level less than 1 mg/dL) be given an infusion of phosphate at a rate of 6 mg/kg/h (or 0.1 mM phosphate/kg in 500 mL 0.45 NS over 6 h), with serum levels being checked every 6 h and discontinued when the serum phosphate level exceeds 2 mg/dL. Thereafter the patients should receive oral phosphate to replace the intracellular stores. Phosphate solutions should be used with extreme caution in patients with renal failure. Charron et al. demonstrated that a potassium phosphate solution may be given at a faster rate in patients with severe hypophosphatemia if the serum potassium is less than 4 mEq/L; these authors reported using an infusion of 30 mmol in 40 mL/NS over 2 h and 45 mmol/L in 100 mL/NS given over 3 h [19].

Patients with mild to moderate hypophosphatemia (serum phosphate between 1.0 and 2.2 mg/dL) should receive oral supplementation (1 g Neutra-Phos/day) unless diarrhoea precludes using this route of supplementation.

Hypomagnesemia

Magnesium in the fourth most abundant cation in the body and the second most prevalent intracellular cation. Approximately 53 % of total Mg stores are in bone, 27 % in muscle, 19 % in soft tissues, 0.5 % in erythrocytes, and 0.3 % in serum. Serum Mg is 67 % ionized, 19 % protein bound, and 14 % complexed. Standard clinical determinations of serum total Mg reflect all three forms. Of note, protein-bound and complexed Mg are unavailable for most biochemical processes. Since serum contains only 0.3 % of total body Mg stores, serum total Mg measurements poorly reflect total body status. Serum total Mg concentrations normally average 1.7–2.3 mg/dL.

Mg^{2+} is essential for the function of important enzymes, including those related to the transfer of phosphate groups, all reaction that require ATP, for the replication and transcription of DNA, as well as cellular energy metabolism, membrane stabilization, nerve conduction and calcium channel function. Magnesium plays an essential role in the function of the cell membrane sodium–potassium ATPase pump. Hypomagnesemia is reported to be common in ICU patients (~60 %) and an important prognostic marker. The causes of "hypomagnesemia" include:

- alcoholism and alcohol withdrawal
- emesis
- diarrhoea
- naso-gastric suction
- parenteral nutrition
- refeeding syndrome
- diabetes
- drugs
  - loop diuretics
  - aminoglycosides
  - amphotericin B
  - cis-platinum
  - cyclosporin

The reported manifestations of hypomagnesemia include:

- hypokalemia and hypocalcemia
- lethargy, confusion, coma, seizures, ataxia, nystagmus
- prolonged PR and QT interval on ECG
- atrial and ventricular arrhythmias

Assessing Mg status in the critically ill beyond serum total Mg levels is difficult. As for calcium, normal total Mg levels may coexist with ionized hypomagnesemia and vice versa. A major advance in evaluating Mg deficiency is the ability to measure Mg^{2+}. The incidence of ionized hypomagnesemia in ICU patients has been reported to be between 14 and 18 % [20]. The clinical significance of this finding is unclear. Serum total Mg levels are not correlated with serum Mg^{2+} in the critically ill because of accompanying variations in plasma protein concentrations, acid–base balance, metabolic derangements, and drugs that affect Mg balance [21].

Management of Hypomagnesemia

Most episodes of hypomagnesemia in intensive care are asymptomatic. In theory, symptoms and signs occur when the serum total Mg concentrations fall below 1.2 mg/dL. In light of the above information the value of routinely measuring the serum magnesium is in question. However, it is probably prudent to measure the serum magnesium level in patients at risk of magnesium deficiency and to treat

those who have severe hypomagnesemia (<1.2 mg/dL). Treatment of hypomagnesemia (aiming for a serum magnesium level of ~2.5 mg/dL) may be particularly important in patients with arrhythmias and those with seizures. Magnesium should be replaced cautiously in patients with renal impairment. The recommended dose is 2 g $MgSO_4$ over 10 min intravenously, followed either by an infusion at 0.5 g/h for 6 h or a 1 g bolus hourly for 4 h; followed by a repeat serum magnesium level. In renal failure the dose should be halved.

Disorders of Calcium Homeostasis

Calcium is a critical intracellular messenger and regulator of cell function. Calcium is essential for excitation-contraction coupling in muscle, neurotransmission, cell division, hormonal release, phagocytosis, chemotaxis, and numerous other activities. Although these functions are usually beneficial, calcium also regulates processes that can injure and kill cells such as digestive enzyme activation, cytokine release, free radical production, inhibition of ATP synthesis, and vasoconstriction. Thus, calcium is truly a double-edged sword.

Calcium circulates in the blood in three fractions:

- a protein-bound fraction (primarily albumin)
- a chelated fraction
- and an ionized fraction

It is the ionized fraction that is physiologically active and homeostatically regulated. Most critically ill patients have low concentrations of albumin and will have low total calcium concentrations in the blood. However, the ionized calcium fraction may be elevated, normal, or decreased. Thus, it is important to assess circulating calcium concentrations by ionized calcium measurement.

Circulating concentrations of ionized calcium are primarily maintained within a narrow range by the combined actions of parathyroid hormone and vitamin D. These hormones increase gastrointestinal absorption of calcium, decrease urinary loss of calcium, and increase calcium mobilization from bone. It is important to realize that dietary calcium is not required to maintain normal circulating calcium concentrations, because adequate calcium can be mobilized from bone. When interpreting concentrations of parathyroid hormone or calcitriol, it is important to consider the concentrations of ionized calcium. Normally, concentrations of these hormones should be high during hypocalcemia and decreased during hypercalcemia. Failure of parathyroid hormone to increase during ionized hypocalcemia suggests parathyroid gland suppression or insufficiency. On the other hand, elevated concentrations of parathyroid hormone in the context of ionized hypercalcemia suggest hyperparathyroidism. Normal ionized calcium concentrations in the context of elevated parathyroid hormone concentrations suggests that parathyroid hormone is appropriately compensating for some other factor that is lowering the ionized calcium concentration (such as a chelator).

Hypocalcemia

Hypocalcemia is a common electrolyte abnormality in critically ill patients. Hypocalcemia is best defined as an ionized calcium <4.65 mg/dL (1.16 mmol/L). Depending on the definition used and population studied hypocalcemia is reported to occur in 12–88 % of critically ill patients. Generally the incidence and degree of hypocalcemia correlates with disease severity and mortality [22].

Ionized calcium should be measured to confirm hypocalcemia in patients with low total serum calcium. Measuring magnesium, creatinine, phosphate, vitamin D levels, amylase, lipase, and CPK will help determine the etiology of hypocalcemia. Serum intact PTH is the most valuable test as an inappropriately normal or low level in the face of hypocalcemia confirms hypoparathyroidism.

Decreased circulating concentrations of ionized calcium are common in critically ill patients with sepsis. Patients with pancreatitis, burns, and multiple trauma are also predisposed to ionized hypocalcemia. Hypocalcemia secondary to blood transfusion is usually transient and often not clinically significant unless >5 units of packed red blood cells are given.

The cause of ionized hypocalcemia in critically ill patients is frequently multifactorial [23, 24]. Many critically ill patients (especially those with infection) have suppressed or inappropriately low parathyroid hormone concentrations in the context of ionized hypocalcemia. Hypomagnesemia contributes to hypoparathyroidism in some of these patients. It has also been suggested that elevated intracellular calcium or magnesium concentrations during sepsis suppress the parathyroid glands. Elevated concentrations of intracellular divalent cations may occur despite decreased circulating concentrations of the ions. Another proposed mechanism for hypocalcemia is suppression of the parathyroid glands via the direct or indirect effects of circulating mediators such as cytokines. In addition, ionized hypocalcemia may result from lack of activated vitamin D (calcitriol).

Vitamin D deficiency (25-hydroxyvitamin D <15 ng/mL) is common in critically ill patients and is reported to be an independent predictor of short term and long term mortality [25–27]. In the study by Lee et al. hypovitaminosis D was associated with adverse outcomes independent of hypocalcaemia, with vitamin D supplementation not being protective [25]. Vitamin D has numerous and diverse biological functions which may explain the increased mortality noted in critically ill patients with deficiency of this vitamin. Most notably vitamin D receptors have been identified on nearly all immune cells with vitamin D having numerous effects on both innate and adaptive immunity [28, 29]. Vitamin D deficiency appears to increase the production of pro-inflammatory mediators. Vitamin D deficiency may occur on admission to the ICU and/or develop during the patients ICU stay [26, 27]. The cause of the hypovitaminosis D is postulated to be due to lack of exposure to sunlight as well as alterations in vitamin D and parathyroid metabolism. While vitamin D deficiency is associated with increased mortality in critically ill patients, it is not clear that supplementation with vitamin D will improve the outcome of these patients. Ongoing clinical trials may help resolve this issue [30].

Elevated concentrations of intracellular calcium have been linked to cell dysfunction and death during sepsis and ischemia [31, 32]. It has been hypothesized

that hypocalcemia may be a protective mechanism in critical illness. Thus, parathyroid gland suppression, secondary to release of various inflammatory mediators, may have evolved to be protective during these states. If this premise is correct, one would hypothesize that administration of calcium would be detrimental during ischemia and sepsis. Indeed, this appears to be the case. Calcium administration increases cellular injury during ischemia. Calcium administration increases mortality in animals administered endotoxin, as shown by Malcolm et al. and after cecal ligation and puncture and as shown by Zaloga et al. [33, 34]. It is noteworthy that in these studies although intravenous calcium increased blood pressure, mortality increased. Furthermore, calcium antagonists appear to be beneficial during sepsis. Experimental studies have demonstrated that verapamil, nifedipine and diltiazem decrease production of pro-inflammatory mediators, increase IL-10 (anti-inflammatory mediator), improve the hemodynamic profile and reduce the mortality in liposaccharide-induced septic shock [35–39]. Todd and Mollitt demonstrated that sepsis increased RBC intracellular calcium and that this effect could be partly ameliorated by calcium-channel blockade [31].

Should Hypocalcemia Be Corrected in Critically Ill Patients?

This is controversial as hypocalcemia may be an adaptive response to severe stress. Furthermore, there is inadequate data currently available to make strong recommendations with regards to treatment of this common electrolyte disorder in the critically ill [40]. Most recommendations are therefore based on expert opinion [22, 41, 42]. While hypocalcemia may decrease cardiac contractility [43] and while intravenous calcium chloride has been demonstrated to increase the blood pressure and cardiac function [44] the effect of this intervention on patient outcome is unknown [40]. It is plausible that intravenous calcium has short term beneficial hemodynamic effects which are outweighed by the longer term effects on cell function. Consequently most experts suggest that symptomatic hypocalcemia (tetany, etc) warrants treatment, however "asymptomatic" hypocalcemia should not be not be treated until the serum ionized calcium is <3.2 mg/dL (0.8 mmol/L) [22, 41, 42].

This data suggests that hypocalcemia may have a protective effect in acute critical illness. Treatment of hypocalcemia may be akin to treating stress hyperglycemia…. it normalizes the numbers, but increases mortality! *We should not mess with that which we don't understand.*

Treatment

- Correct hypomagnesemia.
- Treat hyperphosphatemia
- Intravenous calcium gluconate is indicated for acutely symptomatic patients and following an acute fall in serum calcium. 1–2 g (90–180 mg of elemental

calcium) injected in 50 mL of 5 % dextrose slowly over 10–20 min with EKG monitoring. Rapid injection may precipitate cardiac arrest in systole.
- Treatment with IV calcium is contraindicated in concomitant hyperphosphatemia for fear of precipitation of the calcium–phosphate product
- As vitamin D has pleiotropic effects on immunity, endothelial and mucosal function and glucose metabolism, replacement with 1,25 hydroxyvitamin D may have a role in critically ill patients, particularly the chronically critically ill.

Hypercalcemia

Hypercalcemia is defined as an increase in serum calcium >1 mg/mL above the normal range (8.5–10.2 mg/dL or 2.2–2.5 mmol/L)

- Mild hypercalcemia 10.2–11.9 mg/dL
- Moderate hypercalcemia 12–13.9 mg/dL
- Severe hypercalcemia ≥14 mg/dL

The most common cause of asymptomatic hypercalcemia in an outpatient setting is primary hyperparathyroidism. The most common cause of inpatient hypercalcemia is malignancy [45, 46]. 20–30 % of patients with cancer have hypercalcemia at some point in the course of their disease Primary hyperparathyroidism can co-exist with cancer in up to 15 % of cases

The most common cancers associated with hypercalcemia are

- Breast
- Squamous-cell cancer (head and neck, esophagus, cervix or lung)
- Renal
- Ovarian/endometrial
- HTLV-associated lymphoma
- Multiple myeloma
- Lymphoma

Malignancy associated hypercalcemia results from any of four mechanisms

- Local osteolytic hypercalcemia from increased osteoclastic resorption of bone surrounding malignant cells in the bone marrow
- Humoral hypercalcemia of malignancy (HHM) caused by secretion of parathyroid hormone related protein (PTHrP) from the cancer cells
- Secretion of the active form of Vitamin D
- Ectopic secretion of PTH which is very rare

In chronically critically ill patients bone hyperabsorption is an important cause of hypercalcemia. Other less common causes include:

- Tertiary hyperparathyroidism—from autonomous parathyroid glands in end-stage renal disease
- Chronic granulomatous disease-from increased production of active vitamin-D

- Drug induced
  - Vitamin D intoxication
  - Lithium
  - Thiazide diuretics
  - Vitamin A toxicity
  - Theophylline
- Hyperthyroidism
- TPN

Hypercalcemia must be confirmed by ionized calcium measurements as albumin affects values of total but not ionized calcium (total serum calcium falls 0.8 mg/dL for every 1 g/dL reduction in serum albumin). Intact PTH levels help aid in the diagnosis, with high levels indicating primary hyperparathyroidism and low levels indicating other causes. Plasma 1, 25 dihydroxyvitamin D levels may be useful in sarcoidosis or other granulomatous disorders. An EKG may show shortened QTc from shortening of the myocardial action potential and there have been reports of ST segment elevation and arrhythmias though uncommon

Treatment

- Rehydration and calciuresis
  - Normal saline 200–500 mL/h
  - Guided clinically by volume status and evidence of fluid overload and cardiovascular status
  - Use of loop diuretics is controversial and should not be used until volume resuscitation is complete
- Intravenous bisphosphonates
  - Block osteoclastic bone resorption
  - Superior to all other modes of treatment
  - Pamidronate 60–90 mg IV over 2 h in 50–200 mL of saline or 5 % dextrose in water
  - Zoledronate 4 mg IV over 15 min in 50 mL saline or 5 % dextrose in water
  - Both drugs are associated with renal failure, flu-like symptoms, chills and fever
  - A response is noted in 2–4 days with the nadir in serum calcium occurring in 4–7 days
  - Lasts for 1–3 weeks

Second Line

- Glucocorticoids
  - In lymphomas with elevated levels of active vitamin D
  - 60 mg of prednisone for 10 days

- Calcitonin
  - Maximal response occurs in 12–24 h
  - reductions in serum calcium are small and transient (1 md/dL)
  - can cause flushing and nausea
- Mithramycin
  - Effective but limited by adverse effects like thrombocytopenia, anemia, leucopenia, hepatitis and renal failure
- Gallium nitrate
  - 100–200 mg/m^2 body surface area IV continuously over 24 h for 5 days
  - can cause renal failure

Additional Therapies

- Hemodialysis
  - In patients with acute or chronic renal failure who cannot be hydrated safely and in whom bisphosphonates may not be safe
  - The dialysate contains little or no calcium
  - Especially when the GFR is <10–20 mL/min

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Chapter 41
Acute Kidney Injury

Acute kidney injury (formally known as acute renal failure) is a common problem in the ICU. AKI is a syndrome characterized by the rapid loss of the kidney's excretory function and is typically diagnosed by the accumulation of the end products of nitrogen metabolism (urea and creatinine) or decreased urine output or both [1, 2]. Although serum creatinine (Scr) is not a perfect marker of GFR, it is frequently used as a surrogate to estimate GFR. Currently, additional biomarkers are undergoing investigation as more sensitive indicators of AKI (cystatin C, IL-18, neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, etc.) [2, 3]. AKI is defined as a twofold or greater increase in Scr, a GFR decrease of >50 % or urine output of 0.5 ml/kg/h for 12 h [2]. AKI represents a spectrum from risk to kidney injury to kidney failure to complete loss of kidney function. The RIFLE criteria have been used to define and classify AKI (see Table 41.1) [4]. In critically ill patients AKI is usually the result of extrarenal insults, most commonly sepsis, trauma, hypovolemic "shock", and rhabdomyolysis. The pathophysiology of AKI in patients with sepsis is complex and poorly understood; however decreased renal blood flow does not appear to play a role [2]. AKI occurs in up to two-thirds of ICU patients and increasing severity of AKI is associated with increasing mortality [5]. Even modest degrees of AKI not resulting in dialysis treatment increase the risk of death approximately fivefold [6]. Coca and colleagues demonstrated that elevations of the Scr less than used in the RIFLE classification are associated with a twofold risk of short-term death [7]. In this study patients with a 10–24 % increase in Scr had a relative risk of death of 1.8 (95 % CI, 1.3–2.5). The mortality of patients who require dialysis has remained in excess of 50 % despite improvements in renal-replacement therapy and aggressive supportive care [8]. It is therefore essential that all efforts be made to avoid this complication; i.e. appropriate fluid resuscitation and avoidance of potentially nephrotoxic drugs. The therapeutic intervention of choice in patients with intravascular volume depletion and oliguria is fluid resuscitation and not furosemide/Lasix™. However, as discussed in Chap. 9, excessive volume resuscitation with a high central venous pressure will "paradoxically" impair renal function

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Table 41.1 RIFLE criteria [4]

	Serum creatinine criteria	Urine output criteria
Risk	Inc 1.5–2 × baseline	<0.5 mL/hg/h for 6 h
Injury	Inc 2–3 × baseline	<0.5 mL/kg/h for 12 h
Failure	Inc > 3 baseline or Scr > 4 mg/dl	<0.3 mL/kg/h for 24 h or anuria for 12 h
Loss	Persistent renal failure > 4 weeks	
End-stage renal disease	Persistent renal failure > 3 months	

(see Chap. 8). A rational evidence-based approach to fluid resuscitation is therefore essential to reduce the risk of renal dysfunction in critically ill patients.

While low-dose dopamine increases renal blood flow and urine output in patients with normal renal function, dopamine does not improve renal function, reduce the need for dialysis or alter the course of AKI in critically ill patients [9]. In addition, studies have demonstrated that furosemide is of no value in modifying azotemia, reducing the need for dialysis, altering the time to recovery of renal function, reducing hospital stay or impacting survival in established AKI [10–12]. Indeed, diuretics have been reported to be associated with a significant increase in the risk of death and non-recovery of renal function [13]. A meta-analysis concluded that furosemide was not associated with any significant clinical benefit and perhaps an increased risk of harm [14]. Diuretics in any form (bolus, continuous infusion, topical) have no role in the management/prevention of acute renal failure (the only exceptions are patients with hypercalcemia/tumor lysis as part of a forced diuresis protocol). Optimization of intravascular volume, cardiac output and mean arterial pressure remains the cornerstone of both the prevention and treatment of AKI. No pharmacologic intervention has yet to be demonstrated to (positively) alter the clinical course of patients with renal dysfunction. In patients who remain oliguric/anuric after adequate fluid resuscitation it is important to exclude urinary tract obstruction (and urinary catheter obstruction), as this as an immediately reversible cause of acute renal failure. In patients with compromised renal function nephrotoxic drugs (particularly aminoglycosides and contract agents) should be avoided.

Pre-Renal Azotemia

While some experts have suggested that the term pre-renal azotemia is biologically flawed [2], others contend that the concept of pre-renal azotemia has clinical utility. Pre-renal azotemia refers to the syndrome of oliguria and an increased BUN/creatinine ratio in the setting of volume depletion, which resolves in 2–3 days with fluid administration. Patients with pre-renal azotemia have a urinary Na < 40 meq/l and an increased serum BUN/Creatinine ratio. The fractional excretion of sodium (FENa) has been used to distinguish pre-renal azotemia form AKI. Prerenal azotemia is indicated by a FENa less than 1 % whereas FENa greater than 1 suggests AKI. However, FENa may be spuriously low in patients with severe sepsis as well as in

patients with severe heart failure (cardio-renal syndrome) and cirrhosis (hepato-renal syndrome). The FENa may be falsely elevated in patients on diuretics, with glucosuria or with preexisting renal insufficiency.

$$\text{FENa} = (\text{urine Na} \times \text{Scr})/(\text{serum Na} \times \text{urine creatinine}) \times 100$$

Patients with pre-renal azotemia should be managed by targeted fluid resuscitation. Glomerular filtration is highly dependent on renal blood flow and renal perfusion pressure (MAP). When renal blood flow and/or renal perfusion pressure falls, the GFR and urine output fall sharply. Patients with pre-renal azotemia should be adequately fluid resuscitated to achieve an adequate MAP (>65 mmHg) and cardiac output (CI > 2.5 L/minM2). In the elderly and in patients with diseases affecting the integrity of the afferent arterioles, lesser degrees of hypotension may cause a decline in renal function and oliguria. In these patients a higher MAP (70–75 mmHg) may be preferable.

Contrast Agents and the Kidney

Contrast-induced nephropathy, defined as an increase in serum creatinine greater than 25 % (or >0.5 mg/dL) within 3 days of intravascular contrast administration in the absence of an alternative cause, is a common cause of AKI in hospitalized patients [15, 16]. Contrast induced nephropathy develops in up to 10 % of patients with normal renal function. However the incidence may be as high as 25 % in high risk patients, namely those with:

- preexisting renal dysfunction, esp. diabetic nephropathy
- Congestive heart failure
- Dehydration
- Multiple myeloma
- Concomitant drugs
  - angiotensin-converting-enzyme inhibitors
  - nonsteroidal antiinflammatory drugs

All attempts should be made to avoid iodinated contrast agents in patients with pre-renal azotemia and in patients with acute renal insults. In all patients receiving intravenous contrast agents vigorous pre-hydration is required. There is evidence that low-osmolality contrast agents lowers the risk of nephrotoxicity in patients with elevated serum creatinine concentrations (>1.5 mg/dL) [17].

Prevention of Contrast Induced AKI

- Effective interventions [1, 18–20]
  - Volume expansion
  - Avoidance of high-osmolar contrast agents

  - Minimization of volume of contrast media
  - Discontinue NSAIDS, diuretics, etc.
- Potentially effective interventions [18, 21]
  - *N*-acetylcysteine [22, 23]
  - Na Bicarbonate [24, 25]
  - Ascorbic acid [26]
  - Theophylline
  - Statins
- Ineffective or potentially harmful interventions [18, 21]
  - Dopamine
  - Fenoldopam
  - Atrial natriuretic peptide
  - Diuretics
  - Mannitol

Acetylcysteine and vigorous pre-hydration (? with $NaHCO_3$) should be considered in all patients at high risk of contrast induced nephrotoxicity [1]. Acetylcysteine should be given as 600 or 1,200 mg by mouth (or IV) twice daily the day before and the day of the procedure [19, 20]. Since ascorbic acid has a very favorable side-effect profile the addition of this agent (2 g BID, PO) should also be considered [27]. It is likely, though not proven, that a combination of agents may have a greater reno-protective effect than anyone agent alone [1]. In patients with acute renal failure in whom the use of contrast agents is essential, dialysis immediately after the contrast procedure may limit additional renal compromise (contrast agents are dialyzable). However, post procedure dialysis is not required in patients on chronic hemodialysis who receive an intravenous contrast agent unless the patient becomes volume overloaded.

Extreme caution should be exercised when using contrast agents in patients with cirrhosis. These patients have a diminished intravascular volume which is frequently exacerbated by the use of diuretics. Contrast induced renal failure is a devastating complication in these patients. Should contrast be required all cirrhotic patients should be vigorously volume resuscitated (5 % albumin) and given acetylcysteine.

"Common" Nephrotoxic Agents

- Interstitial nephritis
  - Beta-lactams (esp. ampicillin)
  - Quinolones
  - NSAID
  - rifampicin
  - sulphonamides
  - acyclovir

  - vancomycin
  - cisplatin
  - cimetidine
  - allopurinol
  - omeprazole and lansoprazole
- Tubular cell toxicity
  - aminoglycosides
  - amphotericin B
  - antiretrovirals
  - cisplatin
- Crystal nephropathy
  - foscarnet
  - ganciclovir
- Altered intraglomerular hemodynamics
  - cyclosporine
  - tacrolimus
  - NSAID
  - ACE

Management of Established Acute Renal Failure

Acute renal failure is a reversible process in the majority of cases and often requires only careful fluid and electrolyte management and an adjustment of drug dosage according to the level of the glomerular filtration rate. Multiple pharmacologic agents including dopamine, fenoldopam, loop diuretics, atrial natriuretic peptide, insulin growth factor-1 and thyroxine are effective for the treatment of AKI in animal models. However, similar success has not been observed in human studies [28]. Indeed, once the patient is in established acute renal failure no intervention or therapy has been demonstrated to hasten recovery of renal function. However, further kidney insults should be rigorously avoided as this will delay renal recovery.

The kidney is pretty much a stupid organ. Once it decides to stop working there is not much you can do about it!

When to Initiate Renal Replacement Therapy (RRT)

The "classic" criteria for initiating renal replacement therapy include:

- hyperkalemia ($K > 6.5$ mmol/L)
- progressive acidosis with $pH < 7.20$
- fluid overload with pulmonary edema

- pericardial effusion
- uremic symptoms, i.e. nausea, vomiting, altered mental status, asterixis
- increase of serum creatinine >2 mg/dL/day

These recommendations were formulated for patients with chronic renal failure. However, most intensivists (and critical care nephrologists) contend that there is no reason to wait for significant physiological derangements (hyperkalemia, severe acidosis, fluid overload, uremic complication) to develop in the already physiologically fragile, critically ill patient before initiating RRT. The early initiation of RRT facilitates early nutritional support, simplifies fluid management and may prevent complications. However, there is no solid data to support this strategy and a review of the literature does not allow recommendations regarding the optimal timing of renal replacement therapy [29].

Mode of Renal Replacement Therapy

Continuous renal replacement therapies (CRRT) have been developed to enable the critically ill patient with acute renal failure to be treated more effectively. Acute renal failure in the critically ill patient almost always develops in the setting of shock, sepsis, major surgery and/or major trauma, and is invariably associated with multi-organ dysfunction and/or failure. In addition these patients usually have hemodynamic and respiratory abnormalities that make conventional intermittent hemodialysis both technically difficult and fraught with many complications. The patients' fluid, electrolyte and acid-base status fluctuate widely within a 24 period; intermittent dialysis is not suited to these changing circumstances. Continuous renal replacement therapies were developed with the aim of providing a more physiological method of renal replacement therapy; i.e., to function more like a normal kidney. Over the last two decades CRRT has undergone a remarkable revolution, the major aspects of which include the introduction of countercurrent dialysate flow, the use of double lumen venous access and development of modular, portable CVVHD machines

Advantages of CRRT Therapy Include

- hemodynamically well tolerated
- minimal change in plasma osmolarity
- better control of azotemia and electrolytes and acid-base balance
- very effective in removing fluid
- technically simple
- membrane capable of removing cytokines in septic patients
- better membrane biocompatibility

From a conceptual standpoint, it seems logical that the use of CRRT with its gradual fluid and solute removal would be superior to the rapid volume and solute

flux associated with IHD in the critically ill patient with hemodynamic instability. However, clinical trials have not demonstrated outcome benefits associated with CRRT [29–32]. Based on current data, IHD and CRRT appear to lead to similar clinical outcomes for patients with AKI.

Dosing of RRT

Until recently, the optimal dosing of IHD and CRRT in the ICU was unclear with data suggesting that more aggressive RRT (daily IHD or CVVHD at an ultrafiltration rate of at least 35 mL/kg/h) was associated with improved renal recovery [29, 33]. The VA/NIH Acute Renal Failure Trial Network randomized 1,124 patients with AKI to receive intensive or less intensive RRT [8]. Hemodynamically stable patients underwent intermittent HD (6 vs. 3 times per week) and hemodynamically unstable patients underwent CVVHD (35 vs. 20 mL/kg/h). There was no difference in clinical outcomes between the two groups of patients. The RENAL Replacement Therapy Study Investigators randomized 1,508 patients with AKI to continuous venovenous hemodiafiltration with a flow of either 40 mL/kg/h (higher intensity) or 25 mL/kg/h (lower intensity) [34]. In this study there was no difference in the primary end point (mortality at 90 days) between the two groups.

Summary of Recommendations for RRT in Patients with AKI [35]

- RRT should be initiated in patients with life threatening changes in fluid, electrolyte and acid-base balance
- Continuous RRT (CRRT) rather than intermittent hemodialysis (IHD) should be used in patients with hemodynamic instability
- An uncuffed, non-tunneled dialysis catheter should be used at the initiation of CRRT. The right internal jugular vein is the preferred choice for insertion of a catheter. The second choice is the femoral vein and the last choice is the subclavian. This catheter should be replaced by a tunneled catheter in patients who require RRT for longer than 7 days [35].
- In patients undergoing CRRT who are not already receiving systemic anticoagulation regional citrate anticoagulation is recommended.
- An effluent flow rate of 20–25 mL/kg/h is recommended for CRRT

Rhabdomyolysis

Rhabdomyolysis is characterized by muscle breakdown and necrosis resulting in the leakage of the intracellular muscle constituents into the circulation and extracellular fluid. Rhabdomyolysis ranges from an asymptomatic illness with elevation in the

creatine kinase (CK) to a life-threatening condition associated with extreme elevations in CK, electrolyte imbalances, AKI, and disseminated intravascular coagulation (DIC) [36, 37]. The cause of rhabdomyolysis is usually easily identified; however, in some instances the etiology is elusive. Muscular trauma is the most common cause of rhabdomyolysis. Less common causes include muscle enzyme deficiencies, electrolyte abnormalities, infectious causes, drugs, toxins and endocrinopathies. Rhabdomyolysis is commonly associated with myoglobinuria, and if this is sufficiently severe, it can result in AKI. Weakness, myalgia and tea-colored urine are the main clinical manifestations. The most sensitive laboratory finding of muscle injury is the CPK; a level greater than 5,000 U/L indicates serious muscle injury in the absence of myocardial or brain infarction. The management of patients with rhabdomyolysis includes vigorous hydration and dialysis in patients with established AKI. The use of alkalizing agents and osmotic diuretics, while commonly used, remains of unproven benefit [36, 37].

Epidemiology

About 10–40 % of patients with rhabdomyolysis develop AKI [36]. It has been suggested that rhabdomyolysis from all causes leads to 5–25 % of cases of AKI. Patients with severe injury who develop rhabdomyolysis induced AKI have a mortality of approximately 20 %. Mortality is higher in patients with multiorgan dysfunction syndrome. Rhabdomyolysis occurs in up to 85 % of patients with traumatic injuries.

Etiology

There are multiple causes of rhabdomyolysis, which can be classified as physical and non-physical causes [36]:

Physical Causes

- Trauma and compression
- Crush injuries
- Motor vehicle accidents
- Confinement/incapacitation without changing position
- Prolonged surgery without changing position
- Vessel occlusion
- Embolism/in vitro thrombosis
- Vessel clamping during surgery
- Compartment syndrome

- Excessive muscle activity
- Delirium tremens
- Epilepsy
- Overexertion (marathon running)
- tetanus
- electrical current
- cardioversion
- high-voltage electrical injury
- lightning
- Hyperthermia
- Exercise
- Malignant hyperthermia
- Serotonin-syndrome
- Neurolept-malignant syndrome
- Sepsis

Non Physical Causes

- Inborn errors of metabolism
- Drugs
  - Cocaine
  - Ethanol
  - Heroin
  - Statins
  - Fibrates
  - Anti-depressants
  - Benzodiazepines
- Insect and snake venoms
- Infections
  - Legionella
  - Streptococcal (necrotizing fasciitis)
  - Coxsackie
  - Herpes virus
  - influenza A and B
  - Epstein-Barr
  - Adenovirus
  - HIV
  - Cytomegalovirus
- Electrolyte imbalances
  - Hyperosmotic conditions
  - Hypernatremia
  - Hypocalcemia
  - Hyponatremia

  - Hypokalemia
  - hypophosphatemia

The major causes of rhabdomyolysis in patients admitted to the emergency department of an urban population in the USA are cocaine, exercise and immobilization. In the United States rhabdomyolysis is commonly diagnosed in intoxicated patients subjected to prolonged muscle compression as they lay motionless, in elderly patients following a fall or stroke and in patients with seizure disorders. Trauma and crush injuries following motor vehicle accidents and collapse of buildings are other common causes of rhabdomyolysis. All trauma patients should be screened for rhabdomyolysis [38]. Acute alcohol-induced rhabdomyolysis can occur after binge drinking or a sustained period of alcohol abuse, and is associated with pain and swelling of muscles, particularly the quadriceps. Rhabdomyolysis has rarely been reported when a surgical procedure is performed in an improper position or following the prolonged use of a tourniquet. Myoglobinemia and myoglobinuria and a mild elevation of CPK may occur after strenuous physical exertion. However, when physical exertion is extreme, it can cause myolysis with severe rhabdomyolysis; this is especially likely to occur when strenuous exercise is performed under condition of high temperature and humidity. Hypokalemia increases the risk of rhabdomyolysis during strenuous exercise. Athletes who abuse diuretics are therefore at a high risk of developing rhabdomyolysis during strenuous exercise. Medications and recreational drugs are important causes of rhabdomyolysis. Drug-induced rhabdomyolysis encompasses a large group of substances that can affect muscles by different mechanisms.

Statins (3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors) are an important cause of myositis and rhabdomyolysis [39, 40]. Risk factors for the development of a statin induced myopathy include:

- high dosages
- increasing age
- female sex
- renal and hepatic insufficiency
- diabetes mellitus
- concomitant therapy with drugs such as
  - fibrates
  - cyclosporine
  - azole antifungals
  - macrolide antibiotics
  - warfarin
  - digoxin

Individual statins may differ in their risk of inducing rhabdomyolysis with some patients developing this syndrome when switching from one statin to another. Other patients develop rhabdomyolysis when exposed to any statin. It is probable that genetic factors play a role in the pathogenesis of this syndrome [41].

Pathophysiology

Muscle injury, regardless of mechanism, results in a cascade of events that leads to leakage of extracellular calcium ions into the intracellular space [37, 42]. The excess of calcium causes a pathologic interaction of actin and myosin and activates cellular proteases with muscle destruction and fiber necrosis. The final common effector pathway is thought to be an increase in free cytosolic ionized calcium, which may start a cascade of effects leading to major cell permeability and capillary leak. With muscle injury large quantities of potassium, phosphate, myoglobin, CK and urate leak into the circulation. Myoglobin in the renal glomerular filtrate can precipitate and cause renal tubular obstruction, leading to renal damage.

Mechanisms of Acute Renal Failure in Rhabdomyolysis Patients

It has been suggested that there are two crucial factors in the development of myoglobinuric AKI; these include hypovolemia/dehydration and aciduria [42]. Three main mechanisms influence heme protein toxicity: renal vasoconstriction with diminished renal circulation, intraluminal cast formation and direct heme protein-induced cytotoxicity. In the absence of hypovolemia and aciduria, heme proteins have minimal nephrotoxic effects, however, when these conditions are present heme proteins can induce renal dysfunction by a variety of mechanisms [43]. Released heme proteins produce a synergistic effect on renal vasoconstriction initiated through hypovolemia and activation of the cytokine cascade. Pigmented casts are a characteristic of rhabdomyolysis-associated acute renal failure. These are a result of the interaction of Tamm-Horsfall protein with myoglobin which is enhanced at a low pH.

Clinical Manifestations

There is a wide variation in the clinical presentation of rhabdomyolysis. The “classic” triad of symptoms include muscle pain, weakness and dark urine. The most frequently involved muscle groups are the calves and lower back. The muscles can be tender and swollen, and there can be skin changes indicating pressure necrosis. However, these classic features are seen in less than 10 % of patients. Some patients experience severe excruciating pain. The calf pain may erroneously result in a work-up for deep venous thrombosis and the back pain can mimic renal colic. Similarly, involvement of the chest musculature can present with “anginal” type chest pain. Over 50 % of the patients may not complain of muscle pain or weakness. The initial clinical sign of rhabdomyolysis may be the appearance of discolored urine. Urine can range from pink-tinged, to cola colored, to dark black.

Severe hyperkalemia occurs secondary to massive muscle breakdown, causing cardiac dysrhythmias and possibly cardiac arrest. Hepatic dysfunction occurs in 25 % of patients with rhabdomyolysis [44]. Proteases released from injured muscle cause hepatic injury. AKI and DIC are late complications, developing 12–72 h after the acute insult.

Laboratory Findings

Although history and physical examination can provide clues, the diagnosis of rhabdomyolysis is confirmed by laboratory studies. CK levels are the most sensitive indicator of myocyte injury in rhabdomyolysis. Normal CK enzyme levels are 45–260 U/L. In rhabdomyolysis, CK rises within 12 h of the onset of muscle injury, peaks in 1–3 days, and declines 3–5 days after cessation of muscle injury. The peak CK level may be predictive of the development of renal failure. Abnormal CK levels are commonly seen in injured ICU patients and a level of 5,000 U/L or greater is related to renal failure [38, 45]. The half-life of CK is 1.5 days and so it remains elevated longer than serum myoglobin levels

Both AKI and the increased release of creatinine from skeletal muscle increase the serum concentrations of urea nitrogen and creatinine. However the creatinine is elevated to a greater extent than the blood urea nitrogen (BUN), narrowing the normal 10:1 ratio of urea nitrogen to creatinine to 6:1 or less. Other findings include hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, and elevated levels of other muscle enzymes like lactate dehydrogenase, aldolase, aminotransferases, and carbonic anhydrase III.

Management

The treatment of rhabdomyolysis includes initial stabilization and resuscitation of the patient while concomitantly attempting to preserve renal function. Retrospective analysis have suggested that early fluid replacement with saline is beneficial in minimizing the occurrence of AKI. The longer it takes for rehydration to be initiated, the more likely it is that AKI will develop [46]. Forced diuresis, when started within six hours of admission has been reported to minimize the risk of AKI [47]. Mannitol and bicarbonate are commonly employed following the initial resuscitation with saline [48, 49]. It has been suggested that mannitol may be protective due to the associated diuresis which minimizes intratubular heme pigment deposition and mannitol may act as a free radical scavenger, thereby minimizing cell injury. Furosemide and other loop diuretics have been advocated for use in patients with myoglobinuric renal impairment in an attempt to initiate diuresis and convert anuric to oliguric renal failure.

Traditionally normal saline has been recommended for the volume expander of choice in patients with rhabdomyolysis [1, 37]. This has been based on the

assumption that LR will cause a greater increase in potassium than normal saline [37]; however as reviewed in Chap. 9 this is incorrect. "Normal saline" is likely to exacerbate the metabiotic acidosis common in patients with rhabdomyolysis. A small RCT compared the effects of LR vs 0.9 % saline administered at 400 mL/h in patients with mild rhabdomyolysis secondary to doxylamine [50]. At the end of 12 h of infusion, the serum and urine pH were higher in the LR group. The study was not powered to detect a difference in clinical outcomes. However, this study suggests that LR maybe the fluid of choice in patients with rhabdomyolysis, and certainly establishes that this fluid is not contraindicated in this condition.

Alkalinization of the urine has been suggested to minimize renal damage after rhabdomyolysis. After resuscitation and restoration of normal renal perfusion, the kidneys clear a large acid load resulting in an acidic urine. It has been postulated that these patients may be unable to alkalinize their urine without the administration of bicarbonate, and this increases the risk of tubular cast development and renal injury. However, others have argued that large volume infusion of crystalloid alone creates a solute diuresis sufficient to alkalinize the urine [51]. Furthermore, large doses of bicarbonate may worsen the degree of hypocalcemia especially if hypovolemia is corrected.

While mannitol and bicarbonate are considered the standard of care in preventing AKI, there is little clinical evidence to support the use of these agents [37]. While randomized controlled trials are lacking the available evidence suggests that mannitol and bicarbonate have no benefit over and above aggressive fluid resuscitation alone [52]. In a retrospective study of 24 patients Homsi et al. demonstrated that volume expansion with saline alone prevented progression to renal failure and that the addition of mannitol and bicarbonate had no additional benefit [53]. Using their Trauma Registry and ICU database, Brown and colleagues reviewed the case records of 1,771 trauma patients with increased CK levels [38]. Overall 217 patients (12 %) developed AKI, with 97 requiring dialysis. In this study, peak CK >5,000 U/L was associated with an increased risk of developing AKI. Of the 382 patients with CK >5,000 U/L, 154 patients (40 %) received mannitol and bicarbonate whereas 228 patients did not. There was no significant difference in the incidence of AKI (22 % versus 18 %), of dialysis (7 % versus 6 %) or of mortality (15 % versus 18 %) between the two groups. Based on these data it would appear that mannitol and bicarbonate have little additional benefit over aggressive volume replacement with saline alone. A recent consensus statement suggested that sodium bicarbonate administration is not necessary and not superior to normal saline diuresis in increasing urine pH [1].

Dialysis

Despite optimal treatment, some patients will develop AKI; severe acidosis and hyperkalemia can also be present. These patients will require RRT to correct fluid and electrolyte abnormalities. Daily hemodialysis or CRRT may be required initially to remove urea and potassium that are released from damaged muscles.

Normalization of potassium is the priority, because hyperkalemic cardiac arrest is a life-threatening early complication. The removal of myoglobin by plasma exchange has not showed benefit. A unique management issue in rhabdomyolysis-induced AKI is the development of hypercalcemia during the recovery phase in 20–30 % of patients. To minimize this complication, the administration of calcium should be avoided during the renal failure phase, unless the patient has symptomatic hypocalcemia or severe hyperkalemia.

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Chapter 42
Acute Ischemic Stroke

Stroke causes 9 % of all deaths worldwide and is the second most common cause of death after ischemic heart disease. In over 75 % of cases the stroke is ischemic in nature. However, unlike acute myocardial infarction, therapeutic interventions which attempt to limit infarct size have been of limited success. Only two interventions in a small subset of patients (less than 5 % of patients) have been demonstrated to improve the outcome of patients suffering an acute ischemic stroke (AIS). The single most important intervention to alter the natural history of AIS and improve the patients' functional outcome is the administration of a thrombolytic agent (intravenous rt-PA) in the appropriate patient within the narrow 3–4.5 h window [1]. Endovascular therapy represents an alternative therapy to intravenous rt-PA in patients who are not candidates for intravenous rt-PA, but has no advantage over intravenous rt-PA [2]. Hemispheric decompression in patients less than 60 years of age with malignant middle-cerebral-artery-territory infarction and space occupying brain edema has been demonstrated to improve outcome. An individual patient meta-analysis demonstrated a marked improvement in neurological recovery and survival with decompressive craniectomy [3]. Despite initial enthusiasm, neuroprotective agents have failed to show a benefit in the management of AIS [4, 5], as has tight glycemic control [6], high dose albumin [7], and the use of anti-hypertensive agents [8–11]. Considering this data, the rationale for admitting patients to an ICU needs to be evaluated. Furthermore, aspects of medical care which maximize the potential for recovery and limit complications need to be explored. In most instances such treatment is best provided by specialized "low-technology" Stroke Units.

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Stroke ICU's, Medical ICU's or Stroke Units

Stroke Intensive Care Units were abandoned in the 1970s after it was demonstrated that such units had very little impact on the outcome of patients following a stroke. The situation is not much different today; for the overwhelming majority of patients suffering a stroke acute medical intervention in an ICU have not been established to improve outcome, and in fact, certain interventions may be harmful [12]. Admission to and aggressive management in an ICU may only serve to prolong the dying process of a patient who has suffered a catastrophic neurological event. In patients who have had an AIS the requirement for mechanical ventilation appears to be associated with both a high short- and long-term mortality. Using a large administrative database covering 93 counties in the eastern half of the United States, Golestanian and coworkers evaluated the outcomes of 31,301 patients suffering an AIS [13]. The 30-day and 1-year mortality was 64 and 81 % respectively in those patients who required mechanical ventilation compared to 16 % and 35 % in those patients who did not require mechanical ventilation. Similarly, Burtin and colleagues evaluated 199 stroke patients who underwent mechanical ventilation in an ICU [14]. The 1 year survival rate was just 8 %. These data suggest that patients intubated and ventilated for coma (or neurologic deterioration) may not benefit from mechanical ventilation. A small group of patients who suffer a stroke may benefit from admission to the ICU if they develop a reversible/treatable medical complication. Endotracheal intubation should be reserved for patients with reversible respiratory failure or comatose patients who are likely to have a good prognosis for a functional recovery. Furthermore, it is arguable that endotracheal intubation and mechanical ventilation will reduce the risk of atelectasis and pneumonia in patients with an impaired level of consciousness, when compared to good nursing and respiratory care without endotracheal intubation. The notion that intubation "protects the airway" is not true; intubation alters the normal airway protective mechanisms and likely "unprotects the airway."

Profiles Predictive of Futility After Devastating Stroke [15]

- Aneurysmal SAH
  - Persistent coma after attempts to lower ICP
  - Massive intraventricular hemorrhage with hydrocephalus
  - Presence of delayed global edema on CT
- Lobar intracerebral hemorrhage
  - Coma with extensor posturing and absent pontomesencephalic reflexes
  - Coma with septum pellucidum shift >6 mm on CT
- Ganglionic intracerebral hemorrhage
  - Coma with hydrocephalus and hematoma size >60 cm^3

- Pontine hemorrhage
  - Coma with hyperthermia and tachycardia
  - Coma with acute hydrocephalus and hemorrhage extension into thalamus
- Cerebellar hemorrhage
  - Absent corneal reflexes
  - Absent oculocephalic response with hydrocephalus
- Hemispheric ischemic infarction
  - Clinical deterioration with coma and loss of pontomesencephalic reflexes
  - Shift of pineal gland >4 mm on CT scan performed within 48 h
- Cerebellar ischemic infarction
  - Persistent coma after decompressive surgery

The failure of specific intervention to improve the outcome of patients suffering a stroke should not imply that physicians should adopt a fatalistic approach when managing these patients [12]. A number of well conducted clinical trials have demonstrated that the mortality and functional recovery of patients following a stroke is significantly improved when these patients are cared for in a specialized stroke unit as compared to a general medical ward. These units provide specialized nursing care and a well-organized multidisciplinary rehabilitation program. Stroke unit care reduces the medical complications in stroke patients and allows for earlier and more intense rehabilitation. The Stroke Council of the American Heart Association (AHA/ASA) recommends "rapid transfer of a patient to a hospital that has a specialized stroke care unit" [16].

Acute Ischemic Stroke (AIS)

Ischemic stokes may be conveniently classified as:

- large vessel atherosclerotic
- cardioembolic
- small artery (lacuna)
- stroke of other identified cause (e.g. vasculitis)
- stroke of undetermined cause (likely cardioembolic).

Imaging

Non-contrast enhanced CT scans (NECT) are recommended in all patients suffering AIS. NECT excludes parenchymal hemorrhage and can assess for other exclusion criteria for rt-TPA such as widespread hypoattenuation [16]. NECT is however insensitive in detecting acute and small infarctions, especially in the posterior fossa. A "subtle" sign of cerebral ischemia within the first few hours of symptom onset on

NECT is loss of gray-white differentiation. This sign may be manifest as a loss of distinction among the basal ganglia or as a blending of the densities of the cortex and underlying white matter [16]. Another sign of cerebral ischemia is swelling of the gyri that produce sulcal effacement. Another useful CT sign is that of increased density within the occluded artery, such as the hyperdense middle artery (MCA) sign. Diffusion-weighted MRI imaging (DWI) is currently the most sensitive and specific technique for the diagnosis of AIS. DWI imaging has a sensitivity of 88–100 % in the diagnosis of AIS within minutes of symptom onset. CT perfusion and MRI perfusion and diffusion imaging allow measurement of the size of the infarct core and the penumbra. However, reperfusion therapy based on the mismatch between infarct size and penumbra has not been proven to improve outcome [17].

Thrombolytic Therapy

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial demonstrated that rt-PA given to patients within 3 h of the onset of stroke resulted in an 11–13 % absolute increase in the chance of minimum or no disability at 3 months [18]. Studies with a longer time window for enrollment have demonstrated a higher mortality in the treatment group, largely due to an increased incidence of intracerebral hemorrhage. In the European Cooperative Acute Stroke Study (ECASS) patients with moderate to severe acute ischemic strokes were randomized (<6 h) to placebo or rt-PA. Patients with infarction involving more than one third of the middle cerebral artery territory on CT scan were excluded. At 30 days there was a higher mortality in the rt-PA group (17.9 % vs. 12.7 %) [19]. Large parenchymal hemorrhages were increased threefold in the rt-PA group. In the second European Cooperative Acute Stroke Study (ECASS II) no benefit for rt-PA was demonstrated; furthermore, treatment differences were similar whether patients were treated within 3 h or 3–6 h [20]. ECASS III reported the results of a study in which alteplase (0.9 mg/kg) or placebo was administered between 3 and 4.5 h after the onset of acute ischemic stroke [21]. Patients with severe stroke were excluded from this trial. Although mortality did not differ between groups, more patients has a favorable outcome with alteplase than with placebo (52.4 vs. 45.2 %; OR 1.34 95 % CI 1.02–1.76, $p=0.04$). The Third International Stroke Trial (IST-3) randomized 3,035 patients to 0.9 mg/kg rt-TPA or placebo within 6 h of suffering an AIS; this study had no exclusion criteria based on age [22]. Patients who had a clear indication for rt-TPA were commonly treated with rt-TPA; hence this study included patients with clinical equipoise. In this study, 53 % of the patients were older than 80 years (an exclusion criteria in previous studies). Furthermore, 38 % of patients received rt-TPA after a delay of 3.0–4.5 h while 33 % received therapy after a delay of 4.5–6.0 h. At 6 months, 37 % of patients in the rt-TPA group as compared to 35 % in the control group were alive and independent (primary outcome variable; NS). However, an ordinal analysis demonstrated a significant shift in the Oxford Handicap Score (OHS) towards a favorable outcome with thrombolytic therapy (OR 1.27;

95 % CI 1.10–1.47). It is noteworthy that patients over the age of 80 years appeared to benefit the most from rt-TPA, emphasizing that age alone should not be used as a "contraindication" to treatment with rt-TPA. Furthermore, only patients treated within 3 h of the onset of the ictus benefited from treatment with rt-TPA. Wardlaw performed an updated meta-analysis which included data from the IST-3 trial [23]. This meta-analysis included 12 trials (7,012 patients) of rt-TPA given within 6 h of the onset of stroke symptoms. rt-TPA significantly increased the odds of being alive and independent at final follow up (46.3 % vs. 42.1 %, OR 1.17, 95 % CI 1.06–1.29, $p=0.001$). However, the benefit of rt-TPA was noted only in patients given rt-TPA within 3 h. There was a trend towards an increased risk of death for patients treated between 3 and 6 h (OR 1.16; 95 % CI 1.00–1.35; $p=0.06$). Symptomatic ICH occurred in 7.7 % of patients receiving rt-TPA as compared to 1.8 % in the placebo group. These data suggest that suitable patients with AIS treated within 3 h of the onset of symptoms benefit from treatment with rt-TPA (see contraindications below). The use of rt-TPA beyond this narrow window is controversial. To help resolve the time to treatment issue, Lees et al. performed a pooled analysis investigation time to treatment and outcome [1]. This meta-analysis predated the publication of the IST-3 study. The adjusted odds for a favorable 3 months outcome were 2.55 (95 % CI 1.44–4.52) for 0–90 min, 1.64 (1.12–2.40) for 91–180 min, 1.34 (1.06–1.68) for 181–270 min (4.5 h) and 1.22 (0.92–1.61) for 271–360 min in favor of rt-TPA. This data would suggest that "selected" patients (low risk of bleeding) may benefit from TPA up to 4.5 h and that the risks outweigh the benefits beyond 4.5 h. Drug regulatory authorities have taken contradictory actions with regards to the extended treatment window for rt-TPA, with the European Medicines Agency expanding the approval to 4.5 h while the US FDA have declined to do so [16]. The most recent guidelines (January 2013) published by the AHA/ASA state "Intravenous rt-TPA is recommended for administration to eligible patients who can be treated in the time period of 3–4.5 h after stroke onset (Class 1; Level of evidence B) [16]. In addition to the exclusion criteria for patients treated within 3 h (listed below), the AHA/ASA include the following additional exclusion criteria for treatment between 3 and 4.5 h: Age > 80 years, those taking an oral anticoagulant regardless of the INR, those with an NIHSS score > 25, >1/3 MCA territory stroke and those with a history of both stroke and diabetes.

The most recent guidelines from the AHA/ASA suggest the following inclusion and exclusion criteria for thrombolytic therapy [16]:

Inclusion Criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <3 h before beginning treatment
- Age >18 years

Exclusion criteria

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggestive of subarachnoid hemorrhage
- Arterial puncture at a noncompressible site in previous 7 days

- History of previous intracranial hemorrhage
- Intracranial neoplasm, AV malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated BP (SBP > 185 or DBP > 110 mmHg)
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to
  - Platelet count <100,000/mm^3
  - Heparin received within 48 h, resulting in abnormally elevated aPTT greater than the upper limit of normal
  - Current use of anticoagulant with INR > 1.7
  - Current use of a direct thrombin inhibitor or direct factor Xa inhibitor with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, ECT, TT or factor Xa activity assay)

Relative exclusion criteria (risk and benefits must be carefully considered on a case by case basis)

- Only minor or rapidly improving stroke symptoms
- Pregnancy
- Seizure at onset with postictal residual neurological impairment
- Major surgery or serious trauma in 14 days
- Recent GI or urinary tract hemorrhage (within 21 days)
- Recent acute myocardial infarction (within 3 months)

Treatment of Acute Ischemic Stroke With Intravenous rtPA [16]

- Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min with 10 % of the dose given as a bolus over 1 min
- Admit the patient to an ICU or stroke unit for monitoring
- Perform neurological assessments every 15 min during the infusion and every 30 min thereafter for the next 6 h, then hourly until 24 h after treatment
- If the patient develops severe headache, acute hypertension, nausea or vomiting discontinue the infusion (if rtPA being administered) and obtain emergency CT scan
- Measure blood pressure every 15 min for the first 2 h and subsequently every 30 min for the next 6 h, then hourly until 24 h after treatment
- Increase the frequency of BP measurements if SBP > 180 or if DBP > 105; administer antihypertensive medication to maintain BP below these levels
- Delay placement of NG tubes, CVC'c, bladder catheters or intra-arterial catheters
- Obtain a follow-up CT scan at 24 h before starting anticoagulants or antiplatelet drugs

Angioedema is estimated to occur in between 1 and 5 % of patients who receive rt-TPA. The angioedema is usually mild, transient and contralateral to the ischemic hemisphere. Empiric treatment with H2RA's, anti-histamines and corticosteroids are recommended [16].

Endovascular Interventions

Intravenous thrombolytic therapy has a number of limitations, most notably the low recanalization rate which is reported to be about 6 % for the internal carotid artery, 30 % for the proximal segment of the middle cerebral artery and 33 % for the basilar artery. In contrast to rt-TPA endovascular treatment offers the potential for significantly higher rates of recanalization which may limit secondary brain injury [24]. Furthermore, emergency endovascular treatments could be prescribed for those patients who do not improve following rt-TPA and those who have contraindications for rt-TPA. Consequently, a number of endovascular treatment options for AIS have been developed over the past decade, including intra-arterial fibrinolysis, mechanical clot retrieval, mechanical clot aspiration angioplasty and stenting and a combination of these approaches. Despite initial encouraging results, three RCT's published in 2013 failed to demonstrate a benefit from acute endovascular interventions [2, 17, 25]. These trials are summarized in Table 42.1. The MR RESCUE trial compared endovascular therapy with standard care in patients within 8 h of stroke onset. Patients were sub grouped according to the presence of an ischemic penumbra. In this study patients with an ischemic penumbra had better outcomes than patients without a penumbral pattern, but endovascular therapy provided no advantage in either group. Currently endovascular interventions for AIS are of unproven benefit and should only be performed within the setting of a RCT. Endovascular therapies can be considered otherwise suitable candidates who have clear cut contraindications to rt-TPA.

Table 42.1 Pivotal trials of endovascular therapy for acute ischemic stroke

Trial	n	Test Rx	Control Rx	Window to randomization	Rate of disability free survival at 90 days
IMSI III [25]	656	IV-TPA followed by EVT	IV rt-TPA	IV rt-TPA within 3 h	EVT = 40.8 %
					IV rt-TPA = 38.7 %
Synthesis Expansion [2]	362	EVT	IV rt-TPA	4 h	EVT 42 %
					IV rt-TPA 46.4 %
MR RESCUE [17]	127	EVT	Standard care	8 h	EVT 14 % penumbral group
					9 % non-penumbral group
					SC 23 % penumbral group
					10 % penumbral group

EVT endovascular therapy

Antiplatelet Therapy and Anti-Coagulation

The International Stroke Trial (IST) randomized (using a factorial design) over 19,000 patients within 48 h of an AIS to 14 days of treatment with placebo, heparin (5,000 or 12,500 U q 12 hourly) or aspirin 300 mg daily [26]. Aspirin resulted in a 1.1 % absolute reduction in recurrent ischemic strokes at 14 days; both heparin regimens had no effect on outcome. Additional studies have demonstrated that heparin, low-molecular-weight heparin (LMWH) and heparinoids do not improve outcome following a stroke [27, 28].

Low-dose unfractionated heparin and LMWH are commonly prescribed for the prevention of DVT and pulmonary embolism in patients with stroke. Furthermore, prophylactic doses of heparins for patients with stroke who are deemed at high risk of venous thromboembolism and a low risk of bleeding has been recommended [29]. However, a meta-analysis by Whiteley et al. found no evidence that patients with ischemic stroke who were at higher risk of thrombotic events or lower risk of hemorrhagic events benefited from treatment with heparin [30]. In this study higher age, greater stroke severity, and the presence of atrial fibrillation were associated with an increased risk of both thrombotic and hemorrhagic events. Therefore, patients at a higher predicted risk of thrombotic events were also at a higher risk of hemorrhagic events, and no single variable discriminated reliably between the risk of thrombosis and hemorrhage. The current AHA/ASA guidelines do not recommend urgent anticoagulation for patients with moderate to severe strokes because of an increased risk of serious intracranial hemorrhage. Nor do they recommend anticoagulant therapy following rtPA [16]. However, these guidelines recommend treatment with aspirin (initial dose of 325 mg) within 24–48 after stroke onset. In addition, DVT prophylaxis with sequential compression devices (SCD's) is recommended. The CLOTS-3 study demonstrated that SCD's were an effective method of reducing the risk of DVT and possibly improving survival in patients who were immobile after stroke [31].

Anticoagulation in Cardio-Embolic Stroke

Hemorrhage into the infarct occurs in about 30 % of cases of all embolic infarcts; it may however, require 3 or 4 days or longer to become apparent on the CT scan. However, magnetic resonance imaging has demonstrated that by 3 weeks, hemorrhagic conversion occurs in up to 70 % of patients. Hemorrhage ranges from the usual cortical petechiae to confluent hematomas. In non-anticoagulated patients infarct volume seems to be the only independent predictor of hemorrhagic conversion.

Chronic anticoagulant therapy has been demonstrated to reduce the risk of recurrent embolization in patients who have suffered an embolic stroke. Approximately 80 % of patients who have suffered a cerebral embolic stroke will suffer a subsequent embolic stroke without anticoagulation. In the IST trial recurrent ischemic stroke

(during the study period) occurred in 4.9 % of patients with cardioembolic stoke randomized to receive placebo compared to 2.8 % who received heparin [26]. However, hemorrhagic transformation occurred in 2.1 % of patients receiving heparin compared to 0.4 % who received placebo. The role of transesophageal echocardiography (TEE) in these patients is unclear. However, it may be prudent to perform TEE in patients at high risk of early recurrent embolization, and to commence anticoagulation earlier if clot is visualized within the cardiac chambers and CT scan does not show evidence of hemorrhagic transformation. The HAEST study compared LMWH and aspirin in 449 patients with AIS and atrial fibrillation [32]. In this study the frequency of recurrent ischemic stroke during the first 14 days was 8.5 % in the LMWH group and 7.5 % in the aspirin group. There was no difference in the rate of ICH between the treatment groups. These data suggest that patients with embolic stroke and atrial fibrillation should receive aspirin during the acute phase of the stroke with the initiation of chronic oral anticoagulation between 10 and 14 days.

Raised ICP and Decompressive Surgery

Hemispheric decompression in young patients with malignant middle-cerebra-artery-territory infarction and space occupying brain edema has been demonstrated to improve outcome. An individual patient meta-analysis demonstrated a marked improvement in neurological recovery and survival with decompressive craniectomy [3]. This combination occurs in about 1–10 % of patients with supratentorial hemispheric infarcts and usually arises between 2 and 5 days after stroke. Juttler et al. performed a RCT in 112 patients over the age of 60 years with malignant MCA syndrome [33]. Hemicraniectomy improved the primary outcome; the proportion of patients who survived without severe disability was 38 % in the hemicraniectomy group, as compared with 18 % in the control group (odds ratio, 2.91; 95 % confidence interval, 1.06–7.49; $P = 0.04$). However the majority of the survivors had moderate disability and required assistance with most bodily needs. Hemicraniectomy should therefore be limited in this group of patients. In cerebellar stokes with increased edema suboccipital craniectomy should be considered in patients who deteriorate neurologically [34].

While not specifically recommend by the AHA/ASA guidelines for the management of cerebral swelling following AIS, it would appear logical to administer hypertonic saline (100–200 ml 3 % Saline q 4–6 hourly) to patients with large MCA strokes to limit or prevent the development of severe edema. Unlike mannitol hypertonic saline is a volume expander and likely to maintain MAP and cerebral perfusion pressure. A small prospective study suggested that hypertonic saline is more effective than mannitol at reducing ICP after AIS [35]. Furthermore, a meta-analysis which included five prospective trials demonstrated that hypertonic saline was more effective in reducing ICP than mannitol [36]. High dose albumin is of no proven benefit in this situation [7].

Treatment of Hyperglycemia

Poststroke hyperglycemia is an independent predictor of poor functional outcome and death in the acute phase of stroke [37–39]. Furthermore, animal studies have suggested that hyperglycemia increases infarct size [40]. Clinical guidelines have therefore recommended tight glycemic control in patients who have suffered an AIS. However, as reviewed in Chap. 13 hyperglycemia is a marker of illness severity rather than a cause of excess morbidity. Furthermore, glucose is the predominant fuel for the brain and it is likely that even moderate hypoglycemia will increase infarct size. INSULINFARCT was a RCT designed to test the benefit of tight glycemic control (blood glucose <126 mg/dL) in patients with an AIS [6]. The major outcome of this study was infarct growth as determined by an MRI performed on admission and at 3-months. Infarct growth was almost threefold greater in the tight glycemic control group than the standard care group (10.8 cm^3 vs 27.9 cm^3, $p=0.04$). The study was not powered to detect a difference in functional outcomes nor death which were similar between groups. Current AHA/ASA guidelines recommend maintaining the blood glucose between 140 and 180 mg/dl and advise against tight glycemic control [34].

Treatment of Fever

Fever has been shown to worsen the prognosis in acute stroke. A meta-analysis demonstrated a twofold increase in short term mortality in patients with hyperthermia within the first 24 h [41]. It is therefore reasonable to treat fever in stroke patients with antipyretics [42]. The goal should be to keep patients normothermic. A large RCT evaluating whether early treatment with acetaminophen improved functional outcome by reducing body temperature and fever found no difference between groups [43]. In animal models of focal cerebral ischemia, hypothermia significantly reduces infarct size improves outcome [44]; however the role of induced hypothermia in patients with ischemic stroke has yet to be determined.

Treatment of Post Stroke Hypertension

The vast majority of patients with cerebral ischemia present with acutely elevated BP regardless of the sub-type of infarct or pre-existing hypertension [45, 46]. The BP elevation spontaneously decreases over time. The elevated BP is not a manifestation of a hypertensive emergency, but rather a protective physiologic response to maintain cerebral perfusion pressure to the vascular territory affected by ischemia. Lowering the BP in patients with ischemic strokes may reduce cerebral blood flow, which because of impaired autoregulation, may result in further ischemic injury. The common practice of "normalizing" the BP following a cerebrovascular accident

is potentially dangerous. When a proximal arterial obstruction results in a mild stroke, a fall in BP may result in further infarction involving the entire territory of that artery. It should be noted that the Intravenous Nimodipine West European Trial of intravenous nimodipine for acute stroke was stopped because of increased neurological deterioration in the treatment group, which the investigators attributed to the effects of hypotension [47, 48]. A meta-analysis evaluating the use of oral or intravenous calcium channel blockers initiated at 6 h to 5 days after symptom onset in acute ischemic stroke patients found that intravenous administration, higher doses, and administration within 12 h of symptom onset were associated with an increased risk of poor outcomes [49]. The increased risk of poor outcomes is probably limited to patients treated very aggressively or to specific antihypertensive agents.

The SCAST study randomized 2,049 patients with an acute stroke (ischemic or hemorrhagic) and a SBP>140 mmHg to candesartan (an angiotensin receptor blocker) or placebo within 30 h of symptom onset [8]. During the 6 months followup the risk of the composite vascular end-point did not differ between treatment groups. Ordinal functional outcome according to the modified Rankin Score suggested a shift in favor of placebo (OR 1.17, 1.00–1.38; $p=0.48$). Subgroup analysis was unable to detect any group that benefited from treatment with candesartan with no difference in outcome between patients with an AIS or hemorrhagic stroke. The authors of this study performed a meta-analysis investigating the effect of antihypertensive treatment in patients with acute stroke. The meta-analysis which included 11 studies (7,055 patients) showed no difference in the major end-point of death or dependency (RR 1.04, 95 % CI 0.97–1.12). More recently the results of the CATIS study were published [9]. This study randomized 4,071 patients with an AIS to receive antihypertensive treatment aimed at lowering systolic blood pressure by 10–25 % within the first 24 h after randomization and achieving blood pressure less than 140/90 mmHg or to the discontinuation of all antihypertensive medications during hospitalization. The primary outcome was a combination of death and major disability (modified Rankin Scale score ≥3) at 14 days. The primary outcome did not differ between treatment groups nor did the secondary composite outcome of death and major disability at 3-month posttreatment.

The current recommendations regarding BP management in AIS are based on two observations:

(i). BP reduction is associated with an increased risk of neurological deterioration and worse outcome in patients with AIS in some studies, although a causal relationship has not been demonstrated conclusively and
(ii). the benefit of acute BP lowering (unlike chronic treatment) in patients with AIS remains unproven.

In the absence of definitive benefit, both the AHA/ASA and the European Stroke Initiative are consistent in not recommending routine lowering of BP in patients with AIS unless it is repeatedly exceeds 200–220 mmHg systolic or 120 mmHg diastolic in the acute period [16, 50]. In these patients the aim is to reduce the pressure by no more than 10–15 % in the first 24 h. While the drug of choice is unclear a short acting intravenous agent is currently recommend; i.e. labetalol, nicardipine

or clevidipine (see Chap. 28). Both the AHA/ASA and European Stroke Initiative guidelines recommend the reduction of BP according to the eligibility thresholds for inclusion in the NINDS rtPA efficacy trial before thrombolytics are administered [16, 50]. Anti-hypertensive therapy is therefore required for SBP > 185 or DBP > 110 mmHg with a targeted SBP of 180 and a DBP of 105 mmHg. The role of acute lowering of blood pressure in hemorrhagic stroke is reviewed in the section of hemorrhagic stroke.

Supportive Medical Therapy

- At present, no intervention with putative neuroprotective actions has been established as effective in improving outcomes after stroke and therefore none currently can be recommended [5, 11, 16]. Similarly, hemodilution, volume expansion, vasodilators and induced hypertension cannot be recommended [11, 16].
- General measures are aimed at maintaining an adequate cerebral perfusion pressure and preventing complications.
- Maintain euvolemia; hypovolemia will compromise cardiac output and cerebral perfusion thereby extending the size of the infarct. Avoid hypotonic solutions which will increase cerebral edema. Stroke patients may develop the "Cerebral Salt Wasting Syndrome," which requires aggressive volume replacement (see Chap. 40). While "normal" saline increases the risk of complications and death in medical and surgical patients (see Chap. 9) the use of balanced salt solutions versus 0.9 % saline has not been studied in patients with AIS. However, in patients with AIS, 0.9 % saline may limit the development of cerebral edema and is therefore the preferred fluid. European and US guidelines recommend the use of 0.9 % saline for fluid replacement in AIS [16, 50]. Despite promising preclinical data on the use of 25 % albumin in AIS, a large RCT found no benefit on outcomes at 90 days compared with saline [7].
- As reviewed in Chap. 14 hyperoxia may be particularly bad in the setting of ischemia-reperfusion injuries. Hyperoxia is toxic to the injured brain and worsens outcome [51]. Supplemental oxygen should only be provided for an arterial saturation below 90–92 %, targeting a saturation between 92 and 96 %.
- Attempts at increasing cerebral oxygenation with the use of blood transfusions is likely harmful. A strong body of evidence supports the concept that targeting a Hb > 10 g/dl in acutely ill patient increases the risk of death, infections and thrombotic complications (see Chap. 38). While the role of blood transfusion in patients with AIS has not been studied, data from in patients with SAH and traumatic brain injury suggest worse outcomes with blood transfusion [52, 53]. These data suggest that patients with an AIS should receive a blood transfusion only when the Hb <7 g/dL.
- Bed rest with elevation of the head to 20–35°

- Laxatives
- DVT prophylaxis with SCD's.
- Mild sedation/anxiolysis for agitated patients. In patients who require deeper sedation/hypnosis (for example to facilitate mechanical ventilation) propofol is a useful agent. This drug decreases ICP (and CBF proportionately) and allows frequent neurological assessment due to is short duration of action
- Regular chest physiotherapy and physical therapy
- Speech and swallowing assessment. The ability of the patient to swallow should be assessed as abnormalities of swallowing occur in up to 40 % of patients. In patients with swallowing dysfunction enteral feeding should be achieved using a small bore feeding nasoenteric tube. In the majority of patients swallowing function will recover in 7–10 days. Occasionally prolonged supportive feeding may be required necessitating placement of a gastrostomy/gastrojejostomy
- Fever should be treated with acetaminophen
- Corticosteroids have no role in the management of cerebral edema and increased intracranial pressure after stroke.
- The frequency of seizures during the acute period after stroke is reported to be between 4 and 43 %. Recurrent seizures occur in approximately 20–80 % of cases. There are no data concerning the value of prophylactic administration of anticonvulsants after ischemic stroke. Until such data becomes available, stroke patients who are seizure-free should not receive anticonvulsant drugs.

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Chapter 43
Intracerebral and Subarachnoid Hemorrhage

Intracerebral Hemorrhage

Approximately 15 % of all strokes are hemorrhagic [1]. Intracerebral hemorrhage (ICH) is one of the most devastating forms of stroke. The mortality rate in the first 30 days after ICH is 40 % with more than half of the deaths occurring in the first 2 days; only 12–39 % of patients achieve functional independence [1]. The incidence of ICH increases with age and is more common in Asians than Caucasians or blacks. Clot volume at presentation is the most powerful predictor of outcome. Clot volume can be measured using computer algorithms available in some CT scanners or it can be approximated by the ellipsoid method [2]: ellipsoid volume = (AP × LAT × HT)/2. Generally a good functional outcome is associated with a hematoma volume of less than 30 mL [3–8]. Other important variables are clot expansion, patient age, baseline neurologic status, site of hemorrhage and intraventricular hemorrhage volume. Basal ganglia bleeds generally have the best prognosis followed by lobar hemorrhages; patients with pontine and brain stem bleeds have the worst prognosis [3, 6]. The most common sites of ICH are listed in Table 43.1. In patients who present within 3 h of symptom onset, 26 % of hematomas expand more than 33 % over the first hour, and another 12 % expand this amount over the next 20 h [9, 10]. In warfarin-associated ICH up to 50 % of patients develop hematoma expansion [11]. A number of prognostic scoring systems have been developed to risk stratify patients with ICH [5, 8, 12]. The modified ICH prognostic score and the Functional Risk Stratification Score (FUNC) are based on hematoma volume, age GCS, hematoma location intraventricular hemorrhage and pre-morbid cognitive status (see Table 43.2) [4, 7]. The STITCH investigators have developed a prognostic score based on the GCS at presentation, the patients' age and hematoma volume: 10 × GCS − (age − 0.64 × volume). A score of 27.67 discotomizes patients into a poor and good prognostic group [13–15].

Risk factors for ICH include:

- Hypertension
- Age
- Previous CVA

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Table 43.1 Common sites for ICH

%	Location
50	Basal ganglia
15	thalamus
10–15	Pons
10	Cerebellum
10–20	Cerebral white matter
1–6	Brain stem

Table 43.2 ICH prognostic score

Variable	Modified ICH score	FUNC score
Hematoma volume (mL)		
<30	0	4
30–60	1	2
>60	1	0
Age (yr)		
<70	0	2
70–79	0	1
>79	1	0
Glasgow Coma Scale		
3–4	2	0
5–8	1	0
9–12	1	2
13–15	0	2
Hematoma location		
Lobar	0	2
Deep	0	1
Infratentorial	1	0
Intraventricular hemorrhage	1	–
Pre-ICH cognitive impairment	–	No = 1, Yes = 0

ICH score: ranges from 0 (best) to 6 (worst)
FUNC score: ranges from 0 (worst) to 11 (best)
FUNC functional ocutome risk stratification scale

- Moderate/heavy alcohol consumption
- Amyloid angiopathy
- Recreational drugs
- Male
- Oral anticoagulants
- AVM's
- Hemorrhagic transformation of AIS especially post rt-TPA
- Brain tumor
- Venous thrombosis
- Eclampsia
- Post-partum cerebral angiopathy

Medical Management

Current practice (at least in the US) and clinical practice guidelines suggest that all patients with ICH be referred to a tertiary care center, be admitted to an ICU and undergo emergent neurosurgical evaluation [16]. However, as will be reviewed below, and with few exceptions, there is little data that neurosurgical interventions favorably alter patient outcomes. Patients with small (hematoma volume <15 mL) basal ganglia, thalamic and lobar hemorrhages without intraventricular involvement are unlikely to require a neurosurgical intervention. Likewise patients with catastrophic bleeds (hematoma volume >60 mL) are unlikely to benefit from any intervention. Patients with cerebellar bleeds are likely to require a neurosurgical intervention and therefore likely to benefit from transfer to a tertiary care center. While placement of a ventriculostomy is common in patients with intraventricular hemorrhage, it is not clear that this intervention improves functional outcomes (see below). Nevertheless, patients with IVH or those at greatest risk of developing this complication (hematoma volume >15 mL) [17] and who have a reasonable prognosis for functional recovery (hematoma volume <60 mL) are probably best managed at a tertiary care facility with the availability of neurosurgeons. Patients with ICH who have an elevated blood pressure (SBP>150 Hg) at presentation will likely require a continuous infusion of an anti-hypertensive agent (see below); these patients require transfer to an intensive care unit. Similarly, patients taking an oral anticoagulant will require emergent reversal of the anticoagulant; this is best facilitated in an ICU. However, similar to the situation of patients with AIS, non-hypertensive patients with ICH and those unlikely to require a neurosurgical intervention can be adequately managed in a stroke unit. A proposed triage scheme is illustrated in Fig. 43.1 It should be emphasized that this triage scheme should only be used as a starting point and the patients age, neurological deficit, co-morbidities,

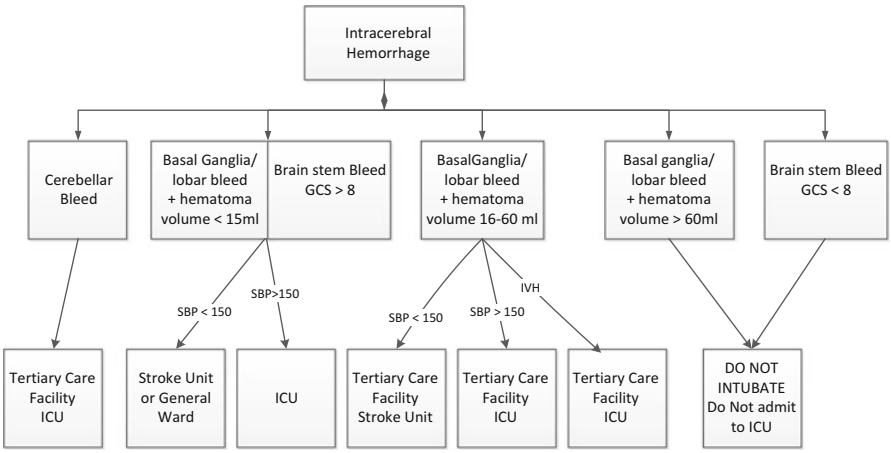

Fig. 43.1 Proposed triage scheme for intercerebral hemorrhage

pre-morbid functional status and advance directives should be used to develop an individualized treatment plan. For example, a 25 year old female with hemorrhagic conversion of a venous sinus thrombosis in a non-dominant hemisphere resulting in ICH >60 mL may benefit from aggressive supportive care in an ICU.

The principles of the medical management of intracerebral hemorrhage are similar to those of acute ischemic stokes, with a few exceptions, notably blood pressure control. A NECT has a high sensitivity and specificity for the diagnosis of ICH. Common sites of bleed in patients with hypertension include the basal ganglia, thalamus and brainstem. Cerebral amyloid angiopathy is associated with lobar bleeds. Secondary causes of hemorrhage, including arteriovenous malformations, tumors, moyamoya, and cerebral vein thrombosis should be excluded in patients with unusual (noncircular) hematoma shape, the presence of severe edema, unusual location for hemorrhage, and the presence of other abnormal structures on imaging [16]. MRI/angiogram/venogram and CT angiogram/venogram are reasonably sensitive at identifying secondary causes of hemorrhage. An MR or CT venogram should be performed if hemorrhage location, relative edema volume, or abnormal signal in the cerebral sinuses on routine neuroimaging suggest cerebral vein thrombosis. A urine toxic screen should be obtained as part of the initial evaluation in ICH patients, particularly the young and the normotensive; substances implicated in the causation of ICH include cocaine, amphetamines, methylphenidate, talwin-pyribenzamine, phencyclidine and phenyl-propanolamine.

Patients undergoing treatment with oral anticoagulants constitute 12–14 % of patients with ICH, and with the increased use of these agents for the treatment of non-valvular atrial fibrillation and venous thromboembolism the proportion appears to be increasing. The risk of death is twice as high in those patients with ICH taking warfarin. In patients taking warfarin rapid reversal of the anticoagulant is recommended (see Chap. 38). Reversal of the newer oral anticoagulants is somewhat problematic. Emergent hemodialysis is suggested in patients taking dabigatran with residual anticoagulant activity (as evidenced by a prolonged PTT or ECT). In patients with ICH and mechanical heart valves temporary interruption of anticoagulation therapy seems safe in patients without previous evidence of systemic embolization. Discontinuation of anticoagulation for 1–2 weeks should be sufficient to observe the evolution of a parenchymal hematoma [16, 18]. Recommendations in patients with non-valvular atrial fibrillation is somewhat more complex. Studies of survivors of a first hemorrhagic stroke have identified rates of recurrent ICH of 2.1–3.7 % per patient-year, substantially higher than these individuals' rate of subsequent ischemic stroke [19, 20]. The most consistently identified risk factor for recurrent ICH is lobar location of the initial ICH. Based on this information resumption of anticoagulation is not recommended in patients with a previous lobar ICH [11, 16]. In patients with a non-lobar hemorrhage and well controlled hypertension resumption of anticoagulation can be considered in those with a high risk of embolic stoke (based on the $CHAD_2$ score) [11]. The effects of antiplatelet agents on ICH recurrence and severity appear to be substantially smaller than for anticoagulation, suggesting that antiplatelet treatment may be a safer alternative to anticoagulation after ICH [11].

Prior use of antiplatelet drugs is associated with an increased risk of death and worse outcomes following an ICH [21–23]. However, the role of platelet transfusion in patients taking anti-platelet drugs is controversial, with no clear benefit [22–24]. The AHA/ASA guidelines do not recommend routine platelet transfusion in these patients [16]. There is currently an ongoing study, the Platelet Transfusion in Cerebral Hemorrhage trial, which aims to answer this question [25]. A phase II study demonstrated an improvement in neurological outcome and mortality in patients with an ICH treated with activated recombinant factor VII (fVIIa) [26]. However, a large phase III trial (FAST) was unable to reproduce these findings [27]. Patients who are thrombocytopenic (platelet count <100,000) should be transfused with platelets.

Two randomized trials showed no benefit on regional blood flow, neurological improvement, mortality, and functional outcomes from the regular use of intravenous mannitol boluses [28, 29]. Patients with ICH are at an increased risk of DVT and PE. Prophylaxis with SCD's is recommended in these patients. In immobile patients at increased risk of DVT, low dose s/c unfractionated heparin or LMWH can be considered if after 48 h there is no evidence of ongoing hematoma expansion [11, 16]. Prophylactic anticonvulsant medication are not recommended [16].

Blood Pressure Control

The acute hypertensive response in intracerebral hemorrhage is characterized by its high prevalence, self-limiting nature, and prognostic significance. In an analysis of 45,330 patients with intracerebral hemorrhage, 75 % had systolic blood pressure greater than 140 mmHg and 20 % greater than 180 mmHg at presentation [30]. The high blood pressure may be secondary to uncontrolled chronic hypertension, with disruption of central autonomic pathways by intracerebral hemorrhage. Alternately the high blood pressure may be an autoregulatory response to increased intracerebral pressure (ICP). High blood pressure is associated with hematoma enlargement and poor outcome [31, 32]. Systolic blood pressure reduction may reduce hematoma expansion in patients who are initially seen with an acute hypertensive response. However, reduction in blood pressure will reduce the cerebral perfusion pressure which may increase neuronal injury in the penumbral area. Until recently the risk/benefits of acute blood pressure reduction in ICH were unclear.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage trial (ATACH I) was a pilot study that investigated the role of blood pressure reduction in 60 patients with ICH and a SBP > 170 mmHg [33]. SBP was reduced using intravenous nicardipine targeting three tiers of sequentially escalating SBP reduction goals (170–199, 140–149 or 110–140 mmHg). In this study hematoma expansion and poor 3-month outcome were greater in the group of patients having less aggressive BP reduction; due to the small sample size these difference were not statistically significant however aggressive BP lowering appeared to be safe.

The INTERACT2 trial randomized 2,839 patients with a spontaneous ICH within the previous 6 h and an elevated blood pressure to antihypertensive treatment

to lower the SBP < 140 mmHg within one hour or a control group with a target SBP < 180 mmHg [34]. The primary outcome of death or major disability at 90 days did not differ between groups. However, an ordinal analysis showed significantly lower modified Rankin scores with intensive treatment. Subgroup analysis failed to demonstrate a group of patients who were harmed by intensive lowering of blood pressure. The use of antihypertensive agents was not standardized with urapidil (an alpha adrenergic blocker) being the most common agent prescribed (32.5 % of patients in the intensive blood pressure lowering group). Furthermore, drugs such as nitroglycerin, diuretics, nitroprusside and hydralazine which are "relatively contra-indicated" in these patients (see Chap. 28) were prescribed in 45 % of patients in the intensive therapy group!!! In addition mannitol was prescribed in 62 % of patients. There were no significant absolute or relative change in hematoma growth in the intensive-treatment group as compared with the standard-treatment group; hence the reason for the apparent benefit of intensive blood pressure lowering in this study is unexplained. Despite the significant limitations of this study it would appear that lowering the SBP < 140 mmHg in patients with a spontaneous ICH is safe and may improve functional outcomes.

The ATACH II Trial is a large (n = 1,280) RCT designed to determine the efficacy of early, intensive, antihypertensive treatment (SBP < 140 mmHg compared to SBP < 180 mmHg) using intravenous nicardipine initiated within 3 h of onset of ICH and continued for the next 24 h in subjects with spontaneous supratentorial ICH [35]. The results of ATACH II should provide additional data on the safety and outcomes benefit of acute reduction of BP in hypertensive patients with an ICH. The SAMURI study demonstrated that in patients with ICH an infusion of nicardipine was highly effective in lowering the SBP < 160 mmHg with no obvious adverse effects [36]. ACCELERATE was a pilot study evaluating the role of clevidipine in patients with ICH and a SBP > 160 mmHg [37]. Clevidipine monotherapy was effective and safe for rapid BP reduction in this cohort of critically ill ICH patients. The median time to achieve SBP target range was 5.5 min Overall, patients showed minimal hematoma expansion with BP reduction, suggesting that rapid BP control with clevidipine may have a beneficial impact on hematoma expansion. Until the results of the ATTACH II study are available it would appear reasonable to lower SBP to <140 mmHg in patients with ICH and a SBP > 150 mmHg. However as discussed in Chap. 28, this should be achieved with the use of a continuous infusion of a short acting, titratable, intravenous antihypertensive agent (nicardipine or clevidipine only) in the controlled environment of an ICU.

Surgical Interventions

The STITCH trail randomized 1,033 patients with intracerebral hemorrhage to early surgery combined hematoma evacuation (within 24 h of randomization) or medical treatment [38]. Forty percent of hemorrhages were lobar, 40 % were in the basal ganglia/thalamus and about 20 % involved both sites with an average hematoma

volume of 40 mL. Twenty-six percent of early surgery patients had a favorable outcome compared with 24 % randomized to initial conservative group (OR 0.89; 95 % CI 0.66–1.19). The mortality rate at 6 months for the early surgery group was 36 % compared with 37 % for the initial conservative treatment group (OR 0.95. 95 % CI 0.73–1.23). Patients with hematomas extending to within 1 cm of the cortical surface had a trend toward more favorable outcome with surgery within 96 h, although this finding did not reach statistical significance (OR; 0.69; 95 % CI 0.47–1.01). Patients with lobar hemorrhages and a GCS score of 9–12 also had a trend toward better outcome. By contrast, patients with ICH >1 cm from the cortical surface or with a GCS score of ≤8 tended to do worse with surgical removal as compared with medical management.

The STITCH II trial randomized 601 conscious patients with superficial lobar intracerebral hemorrhage (<1 cm from cortical surface of the brain) of 10–100 mL and no intraventricular hemorrhage to early surgery compared with an initial conservative treatment approach [14]. The primary outcome was a prognosis-based favorable or unfavorable outcome dichotomized from the Extended Glasgow Outcome Scale at 6 months. Seventy-five percent of patients had a GCS ≥ 12 on admission. Fifty-nine percent of patients in the early surgery group had an unfavorable outcome versus 62 % in the initial conservative treatment group (OR 0.86; 0.62–1.20). STITCH II enrolled patients most likely to benefit from clot evacuation and found no benefit. Based on the STITCH 1 and II trials there is therefore little data to support surgical evacuation of hematoma in patients with ICH. It should be noted that similar to almost all large multi-center studies, the patients in these trials were treated in neurosurgical centers of excellence. Such centers are more likely to have better outcomes than centers with lower surgical volumes and less expertise [39–41]. Therefore in the best of circumstances it would appear that surgical clot evacuation has little clinical benefit. It is likely that in centers with lower surgical volumes such surgery would be harmful.

Observational data strongly suggest that surgical decompression in patients' with cerebellar hematomas greater than 3 cm in diameter or with brain stem compression improves outcome [42–44]. Due to the lack of clinical equipoise patients with cerebellar bleeds were excluded from the STITCH trials. The current AHA/ASA guidelines (which predate the publication of the STITCH II trial) states that "for most patients with ICH, the usefulness of surgery is uncertain but recommend surgery in patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression". Furthermore these guidelines recommend that "initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended." [16]

Intraventricular hemorrhage (IVH) is a frequent complication of ICH. In the STITCH trial, 23 % of patients had IVH on presentation of whom 55 % developed hydrocephalus [45]. In a series of 216 patients, Maas et al. reported that 21 % of patients with no IVH on presentation subsequently developed IVH [17]. In this study patients who developed a delayed IVH had a significantly greater clot volume than those who did not develop this complication. Furthermore, despite initially better clinical function compared with patients with initial IVH, patients

with delayed IVH fared as poorly as the patients with an initial IVH in terms of mortality and severe disability. The severity of IVH varies from sedimentation of blood in the posterior horns to complete filling of all ventricles. Massive IVH is associated with a very poor outcome [46]. In the absence of any specific treatment, risks of death and severe disability in patients with IVH are reported to be 72 % and 86 %, respectively [47]. The risk of death and severe disability with placement of an external ventricular drain (EVD) is reported to be 58 % and 87 % respectively [47]. An EVD in the context of obstructive hydrocephalus would appears to decrease mortality compared to conservative treatment [46]. However, placement of an EVD does not improve the functional outcomes of the survivors. Placement of an EVD should therefore be considered in select patients with ICH who develop hydrocephalus with neurological deterioration. In patients with massive IVH, EVD may reduce mortality but result in severe functional disability. Intraventricular administration of rt-TPA is of uncertain benefit and is not routinely recommended [16]. The endoscopic retrieval of intraventricular blood has been recently described and appears to be to be as efficient as ventriculostomy, but its use is limited to specialized centers [46].

Subarachnoid Hemorrhage

Subarachnoid Hemorrhage (SAH) is a common and devastating condition. SAH accounts for about 5 % of all strokes and affects as many as 30,000 Americans each year [48]. Despite improved management the outcome following SAH remains poor; with an overall mortality of approximately 25 % and significant morbidity amongst the survivors [48]. The vast majority of patients with SAH have a ruptured aneurysm. In general the prognosis is related to the amount of blood in the subarachnoid space. SAH causes profound reductions in cerebral blood flow, reduced cerebral autoregulation, and acute cerebral ischemia [48]. These pathophysiological processes are linked to raised intracranial pressure, decreased cerebral perfusion pressure, vasoconstriction, platelet aggregation, with decreased microvascular perfusion and increased permeability [48, 49]. Despite advances in the understanding of the mechanisms of SAH-induced brain injury, few effective treatments exist. Furthermore, while numerous therapeutic interventions including putative neuroprotective agents been studied, few have demonstrated improved patient outcomes. Once the aneurysm has been secured treatment is essentially supportive. Scrupulous attention to the patients' hemodynamic status may limit complications. As these patients are at risk of serious multisystem complications they are best managed in an ICU or a specialized neurology/neurosurgical unit.

The most serious complications following the initial bleed are rebleeding and cerebral vasospasm; management of patients with SAH is therefore is largely directed to avoiding these complications [48]. The risk of rebleeding (with conservative therapy) is highest in the first month, with a rate of between 20 and 30 %. The mortality rate is approximately 70 % for patients who rebleed. Angiographic

vasospasm probably develops to some degree in most patients who suffer a SAH. However, clinically manifest vasospasm occurs in approximately 40 % of patients. Fifteen to 20 % of these patients will suffer a stroke or die despite aggressive management.

Diagnosis and Evaluation

- CT scan and lumbar puncture. Non-contrast CT scanning is the diagnostic test of choice following a suspected SAH [48]. If the scan is performed within 24 h of the event, clot can be demonstrated in the subarachnoid space in approximately 90 % of patients. The diagnostic sensitivity of the CT scan declines after the first day. A diagnostic lumbar puncture should be performed in a patient with a suspected SAH if the initial CT scan is negative. A normal CT scan and a normal spinal fluid examination excludes a SAH and predicts a favorable prognosis in the setting of the sudden onset of a severe headache.
- Clinical Classification**.** The Hunt and Hess Classification system is the most commonly used grading system to assess the severity of a SAH [48]. The Hunt and Hess grade has important therapeutic and prognostic implications.
  I. Asymptomatic or slight headache
  II. Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
  III. Drowsiness, confusion or mild focal deficit
  IV. Stupor, moderate to severe hemiparesis
  V. Deep coma, decerebrate rigidity
- Cerebral angiography. Selective catheter angiography is currently the standard for diagnosing cerebral aneurysms as the cause of SAH. Approximately 20–25 % of cerebral angiograms performed for SAH will not indicate a source of bleeding. It is generally recommended to repeat the angiogram in 2 weeks, because vascular spasm may have obscured the aneurysm. However, only a very small percentage of repeat angiograms will demonstrate an aneurysm. The risk of rebleeding in patients with normal angiograms is low; less than 4 % are reported to rebleed when followed for up to 10 years. CT angiography has improved to the point where some centers use it as the primary test to identify an aneurysm.

Initial Management

- Bed rest with elevation of the head to 20–35°
- Nimodopine has been shown in multiple RCT to significantly improve outcome after SAH, by reducing delayed cerebral ischemia and is considered the standard of care [50, 51]. Contrary to common belief, nimodopine does not

appear to reduce the incidence of vasospasm [51]. The mechanisms by which nimodipine exerts its beneficial effects is not well understood but may involve neuronal as well as vascular factors. Nimodipine 60 mg q 4 per NG/oral should be started as soon as feasible. The dosage should be reduced (not stopped) in patients who develop hypotension [50].

- Mild sedation/anxiolysis for grade I and II patients.
  - Ativan 0.5 mg q 4–6 PRN IV
- Agitation/delirium:
  - Haloperidol (Haldol) 2.5–5 mg IV PRN and then q 2–4 as reqd. Check QTc interval
  - Quetiapine (Seroquel) 25–50 mg BID (oral)
  - Dexmedotomidine infusion
- Pain
  - Tylenol Max 2,600 mg/day (oral, suspension, rectal)
  - Fentanyl 25–50 ug q 4 PRN IV
  - Morphine 2–4 mg q 4 PRN IV
- Temperature/fever
  - Fever is common in patients with SAH (41–72 %) and is more common with poor-grade SAH patients who have more subarachnoid blood [52–54].
  - Retrospective studies suggest that fever is independently associated with poor outcome [52–54].
  - It is important to exclude infective causes of fever (blood cultures, CXR, BAL, PVL's, *CSF*, etc.). Serum procalcitonin (PCT) has been shown to be useful in distinguishing between the systemic inflammatory response (SIRS) following SAH from infection [55]. In febrile patients a baseline PCT should be obtained and repeated every 2–3 days as indicated.
  - Fever should be treated ***aggressively*** and kept below 37.5 °C
    Acetaminophen, Max 2,600 mg/day (oral, suspension, rectal)
    Naproxen 250–750 BID or ibuprofen 300–800 mg TID (not contraindicated in patients with SAH) [50, 56].
    In a prospective RCT the combination of ibuprofen and acetaminophen were shown to be more effective in reducing fever than either agent alone [56].
    If fever not controlled with acetaminophen and a NSAID then active cooling with a cooling blanket/ external cooling device or an intra-vascular cooling system is recommended [57]. The patient may require anti-shivering medications (meperidine, dexmedetomidine).
- Fluid management
  - Maintain euvolemia; on presentation most patients with SAH are volume depleted and require volume resuscitation. However patients with SAH have a very complex hemodynamic pattern that requires very careful hemodynamic management (see transpulmonary thermodilution hemodynamic assessment).

  - Careful fluid management is required to avoid hypovolemia which may increase the risk of delayed cerebral ischemia. However "hypervolemia" (volume overload) is also associated with worse neurological outcomes.
  - Despite being widely advocated, data supporting the use of prophylactic "hypervolemia" does NOT EXIST. Two RCT investigating the use of prophylactic hypervolemia demonstrated no benefit on CBF, vasospasm or patient outcome [58, 59]. However, the incidence of complications, primarily pulmonary edema was increased with "hypervolemia". The concept hypervolemia is a misnomer and reflects a lack of understanding of cardiovascular physiology and the Frank-Starling mechanism (see Chap. 9).
  - 0.9 % NaCl at 100 ml/h (adjusted according to cardiac, pulmonary, renal and electrolyte status)
- Sodium
  - Keep Sodium between 140 and 145 meq/L.
  - Na < 135—check serum and urine electrolytes (including uric acid) and osmolarity. Calculate fractional excretion of urate (see Chap. 40).
  - SIADH—one dose of 20 mg conivaptan and follow Na (ensure patient not hypovolemic); repeat conivaptan as required [60].
  - Cerebral salt wasting—0.9 % NaCl. Salt tablets although commonly prescribed are probably useless. 3 % hypertonic saline can also be considered however the sodium should be closely monitored (see below).
  - Patients with SIADH have hyponatremia with features of water overload (hemodilution) while patients with cerebral salt wasting have hyponatremia with evidence of hemoconcentration. Transpulmonary thermodilution with measurement of the global end-diastolic volume (GEDVI) may help in the determination of volume status. Alternatively, the sodium can be corrected with an infusion of 3 % saline at 50–100 mL/h (the serum sodium should be checked after 2 h and then 2 hourly until the sodium has stabilized) with re-calculation of the fractional excretion of urate once the sodium has corrected (see Chap. 40).
  - Diabetes insipidus; replace with 0.45 NaCl and administer desmopressin 2 mg SQ bid
- Magnesium
  - Magnesium has putative neuroprotective properties. The Magnesium for Aneurysmal Subarachnoid Hemorrhage (MASH-2) study did not demonstrate an outcome benefit from intravenous magnesium (64 mmol/day) [61]. While hypermagnesemia does not appear to be beneficial hypomagnesemia should be avoided to limit the risk of arrhythmias and other possible complications. As per usual ICU practice the Mg level should be kept >2 mg/dL.
- Glucose control
  - Hyperglycemia is common following SAH [62, 63]. Hyperglycemia is associated with poorer clinical grade and worse prognosis [62, 63]. However, in keeping with ICU patients in general hyperglycemia is a reflection of the degree of activation of the stress response and DOES NOT

imply a causal relationship between hyperglycemia and poor outcome (see Chap. 13).
  - A study of SAH patients treated with an insulin infusion targeted to keep the blood glucose between 80 and 110 mg/dL (tight glycemic control) found an increase in episodes of hypoglycemia, and this was associated with more vasospasm and a less favorable 3-month outcome [64].
  - Microdialysis findings in patients with SAH have demonstrated cerebral metabolic crisis and low cerebral glucose in patients treated with insulin infusions, even in the absence of systemic hypoglycemia [65, 66].
  - Keep glucose between 140 and 200 mg/dL in keeping with general ICU practice. Tight glycemic control is likely to increase the risk of poor outcomes.
  - NPH and Sliding scale insulin is recommended for glycemic control. Insulin infusions should only for used for severe hyperglycemia. Bolus feeding with a low glycemic index formula is likely to reduce the degree of hyperglycemia (see Chap. 32).
  - Corticosteroids have no proven benefit in patients with SAH, are likely to increase the risk of hyperglycemia (and myopathy) and should NEVER be prescribed.
- Blood pressure control
  - Stop home (PO) anti-hypertensive medications and diuretics (not Beta blockers)
  - The role of anti-hypertensive agents in preventing rebleeding is controversial.
  - It is generally advised that the SBP be kept below 150 mg/Hg prior to securing the aneurysm. In this situation Nicardipine. Clevidipine or labetalol infusions are the preferred agents (see Chap. 28).
  - Mild sedation and control of pain may adequately control an elevated blood pressure
  - Exclude vasospasm in patients with increasing BP.
  - An increase in BP may be a manifestation of an increased ICP. Lowering of the blood pressure in this circumstance may have serious adverse sequela. Such therapy should only be considered in patients where the ICP and CPP are being monitored. In such situations Nicardipine. Clevidipine or labetalol infusions are the preferred agents.
  - Antihypertensive agents should be used with great caution as an excessive reduction of blood pressure may cause cerebral ischemia and infarction.
- Laxatives (Bisacodyl, lactulose)
- Anemia
  - Transfuse only for Hb < 7 g/dL (one unit at a time). Blood transfusion is associated with an increased risk of vasospasm, worse neurological outcome and increased risk of death in patients with SAH [67, 68].

- DVT prophylaxis
  - SAH induces a prothrombotic state that may lead to an increased risk of DVT and PE [50].
  - Sequential compression devices are recommended on admission.
  - Prophylactic heparin 5,000 u s/c q 12, LMWH or fondaparinux are recommended 48–72 h after coiling/craniotomy [50].
  - Consider screening PVL's every 4–5 days
- Mechanical ventilation
  - Sedation with propofol is recommended (keep dose <50 ug/kg/min). Fentanyl may be added as needed. Dexmedetomidine is an alternative agent.
  - Keep $PaCO_2$ 35–40 mmHg
  - Keep arterial saturation between 92 and 96 %
  - Keep plateau pressures <30 cmH_2O
  - Monitor iPEEP; keep <5 cmH_2O
- Nutrition
  - Start within 24 h.
  - Bolus tube feeds (see Chap. 32).
- Statins. Preliminary data suggested that statins improved the outcome after SAH. However, recent meta-analyses have failed to demonstrate a benefit in terms of the risk of vasospasm, delayed cerebral ischemia, poor outcome or mortality [69, 70]. Based on this data statins are not routinely recommended, however, a statin should not be stopped in patients already taking these agents (increases the risk for developing sepsis).
- Stress ulcer prophylaxis: SUP is not required if patients are receiving enteral nutrition or taking a normal diet (see Chap. 33).
- Transcranial Doppler's (TCD's): Daily TCD's are recommended starting on the 3rd ICU day and continued for 7–10 day or as indicated. A CT angiogram's is suggested if flow velocities are increasing (see below).
- Brain tissue oxygen monitoring and cerebral microdialysis have been described in a number of observational studies [71–77]. While a brain tissue oxygen tension <20 mmHg, a lactate/pyruvate ratio >40 and a brain glucose concentration <13 mg/dL are associated with poor outcomes it is not clear that these monitoring techniques result in improved patient outcomes.
- Screening ECHO (to assess LV function) and ECG (to exclude myocardial ischemia) on admission
- The routine use of phenytoin has been associated with cognitive impairment and is not recommended [78]. Keppra is the preferred agent when the patient deemed at high risk of seizures
- Corticosteroids have no proven benefit in SAH and are not recommended.

Specific Therapeutic Issues

Antifibrinolytic Therapy

The role of antifibrinolytic agent in preventing rebleeding is controversial. While antifibrinolytic agents reduce the rate of bleeding the benefits are offset by a higher incidence of cerebral infarction [79]. A more recent RCT (n = 505) demonstrated that an early short course of antifibrinolytic therapy reduced the risk of early rebleeding pending repair of the aneurysm [80]. Delayed and prolonged therapy with these agents is not recommended [50]. While a short course of therapy prior to securing the aneurysm may be beneficial these agents have generally fallen out of favor and are not widely recommended [50].

Surgical and Endovascular Methods of Treatment

In 1991, Guglielmi et al. described the technique of occluding aneurysms from an endovascular approach with electrolytically detachable platinum coils (Guglielmi detachable coils) [81]. Guglielmi detachable coils are introduced directly into the aneurysm through a microcatheter and detached from a stainless steel microguidewire by an electric current. The aneurysm is packed with several coils. The coils induce thrombosis, thereby excluding the aneurysm from the circulation. As clinical experience with the technique has increased and technological advances in coil design and adjunctive methods have improved, endovascular treatment has been used with increasing frequency [48].

The ISAT trial compared neurosurgical clipping versus endovascular coiling in 2,143 patients with ruptured aneurysms [82]. In this study which enrolled patients with ruptured intracranial aneurysms suitable for both treatments, endovascular coiling was more likely to result in independent survival at 1 year than neurosurgical clipping; the survival benefit continued for at least 7 years. The risk of epilepsy was substantially lower in patients allocated to endovascular treatment, but the risk of late rebleeding was higher.

Management of Cerebral Vasospasm

After aneurysmal SAH, angiographic vasospasm is seen in 30–70 % of patients, with a typical onset 3–5 days after the hemorrhage, maximal narrowing at 5–14 days, with a gradual resolution over 2–4 weeks. Digital subtraction angiography is considered the gold standard for the detection of arterial narrowing [50, 83]. CT angiography (CTA) has a high specificity and negative predictive value and has largely replaced DSA [83]. Cerebral vasospasm is associated with reduced

CBF. The changes in CBF are coupled to changes in oxygen delivery so that cerebral hypoperfusion leads to inadequate oxygen delivery. In about one half of cases, vasospasm is manifested by the occurrence of a delayed ischemic neurological deficit (DIND), which may resolve or progress to cerebral infarction. In contemporary series, 15–20 % of such patients suffer a stroke or die of vasospasm despite maximal therapy [48]. The development of a new focal deficit, unexplained by hydrocephalus or rebleeding, is the frequently the first objective sign of symptomatic vasospasm. In addition, unexplained increases in mean arterial pressure may occur as cerebral arterial autoregulation attempts to improve cerebral circulation to prevent ischemia. Monitoring for vasospasm with transcranial Doppler (TCD) technology, in addition to clinical observation is controversial [50]. Overall, TCD is generally considered to have fairly high specificity but only moderate sensitivity for the detection of vasospasm as compared to DSA [50]. However, in view of its widespread availability, low cost, ability to perform the test at the beside and its non-invasiveness, TCD's have become a common method for screening for vasospasm in patients with SAH [83].

The goal for the management of cerebral vasospasm is to reduce the threat of ischemic neuronal damage by controlling intracranial pressure, decreasing the metabolic rate of oxygen use, and improving CBF. Since 1976, when Kosnik and Hunt reported on the reversal of neurologic deficits by use of induced hypertension and hypervolemia in SEVEN patients who had deteriorated due to vasospasm, the use of "Triple-H" therapy in the management of patients with cerebral vasospasm after SAH has been widely accepted [84]. Despite being widely advocated, data supporting the use of Triple-H therapy are scant and the relative contribution of each component is debated.

"Hypervolemia" has no physiological basis and no proven clinical benefit and only serves to increase cerebral edema and worsen the alveolar-capillary leak syndrome. Hypervolemia damages the endothelial glycocalyx and inhibits lymphatic function increasing interstitial edema (see Chap. 9). While hypovolemia may increase the risk of vasospasm, induced hypervolemia has no proven benefit and should be avoided. Muench et al. studied the three components of "Triple-H" therapy in patients with SAH [85]. Induction of hypertension resulted in a significant increase of regional cerebral blood flow and brain tissue oxygenation at all observation time points. In contrast, hypervolemia/hemodilution induced only a slight increase of regional cerebral blood flow while brain tissue oxygenation did not improve. Finally, Triple-H therapy failed to improve regional cerebral blood flow more than hypertension alone and was characterized by the drawback that the hypervolemia/hemodilution component reversed the effect of induced hypertension on brain tissue oxygenation. Using a xenon blood flow tomography-based system, Joseph et al. showed that hypervolemia does not increase CBF. Furthermore, in a clinical series, Ekelund et al. demonstrated no effect of hypervolemic therapy on CBF and a pronounced reduction in oxygen delivery capacity. In a series of 413 patients Ibrahim et al. demonstrated that a positive fluid balance was associated with worse neurological outcomes [86]. Martini et al. demonstrated that a positive fluid balance was independently predictive of vasospasm and increased length of hospital stay [87]. These

data suggests that the two "H's (hypervolemia + hemodilution) should be dropped from "Triple H" therapy. Observational studies suggest improved neurologic outcome with induced hypertension (alone) in patients with vasospasm [88–92]. Induced hypertension has been shown to increase CBF, and this effect maybe greater in patients with angiographic vasospasm or in brain regions that are hypoperfused.

Cerebral autoregulation is disturbed in patients after SAH, with cerebral perfusion being directly dependent on cerebral perfusion pressure. Vasoactive agents are used to increase the cerebral perfusion pressure. Blood pressure targets should be based on the mean arterial pressure (MAP) and not the systolic pressure (cerebral perfusion is dependent on the MAP). This concept is reviewed in Chap. 14. When a vertriculostomy is in place the cerebral perfusion pressure (CPP) is a more important variable to follow than the MAP. Schmidt et al. determined that the minimally acceptable cerebral perfusion pressure threshold above which the risks of brain tissue hypoxia and oxidative metabolic crisis are reduced in patients with poor grade SAH was 70 mmHg [77]. Based on this and other data it is recommended that the CPP be maintained between 80 and 120 mmHg and titrated according to the patients clinical status [93]. Assuming an ICP of 20 mmHg this translates into a MAP of between 100 and 140 mmHg (see below). Norepinephrine is the agent of choice; dopamine is associated with an increased risk of tachycardia and arrhythmias. In addition, this drug suppresses pituitary and immune function and is best avoided. Phenylephrine tends to decrease cardiac output (and therefore cerebral blood flow) and should only be used as second line therapy. Dobutamine is recommended in patients with a cardiac index of <3.5 L/min/m^2 (see transpulmonary thermodilution hemodynamic assessment). Angioplasty of the implicated vessel, high-dose intravenous nicardipine, intraarterial papaverine and verapamil has been reported in patients with refractory vasospasm [93–95]. The role of these therapeutic interventions remains to be determined.

Endothelin is a potent, long-lasting endogenous vasoconstrictor that has been implicated in the pathogenesis of DIND. Therefore, endothelin receptor antagonists (ETAs) have emerged as a promising therapeutic option for SAH-induced cerebral vasospasm. A meta-analysis by the Cochrane group which included 4 studies demonstrated that ETAs reduced the incidence of DIND (RR 0.80; 95 % CI 0.67–0.95) and angiographic vasospasm (RR 0.62; 95 % CI 0.52–0.72) but did not reduce the incidence of unfavorable outcomes (RR 0.87; 95 % CI 0.74–1.02) or mortality (RR 1.05; 95 % CI 0.77–1.45). ETAs increased the incidence of hypotension (RR 2.53; 95 % CI 1.77–3.62) and pneumonia (RR 1.56; 95 % CI 1.23–1.97) [96]. An updated meta-analysis demonstrated that ETA's tended to increase the risk of poor functional outcome (RR, 1.12; 95 % CI 0.97–1.28) despite a decreased incidence of angiographic vasospasm [97]. Based on this data ETAs are not recommended.

TCD Monitoring

- While the use of transcranial Doppler (TCD) in the diagnosis of vasospasm is controversial, TCD's are non-invasive and inexpensive and proven to have clinical utility in the management of patients with SAH [83].

- TCD's have poor diagnostic performance for anterior circulation vasospasm; angiography is required in patients with unexplained neurological deterioration and "normal" TCD's [83].
- The trends in the mean velocity are as important as the individual measurements
  - Normal <120 cm/s
  - Moderate Vasospasm 120–200 cm/s
  - Severe Vasospasm >200 cm/s

(a) *Asymptomatic vasospasm*

- Monitor patients closely
- Maintain euvolemia and MAP > 80 mmHg
- In patients with progressive increase in daily TCD velocities, single daily increase ≥ 50 cm/s or velocity > 200 cm/s initiate induced hypertension with goal of MAP > 90 mmHg and CPP > 70 mmHg. CT angiogram (CTA) and perfusion CT scan is required. Hemodynamic assessment and management by transthoracic thermodilution is recommended in these patients (see below).

(b) *Symptomatic Vasospasm*

- *Obtain a STAT CT* scan to exclude other causes; i.e. rebleed, hydrocephalus. If no rebleed/hydrocephalus obtain STAT CTA and perfusion CT imaging. Exclude other causes of altered mental status including hypoxia (ABG), electrolyte abnormalities and sepsis (cultures).
- Initiate induced hypertension with a target MAP of 100–140 mmHg titrated to clinical effect. Generally MAP is increased by 20 mmHg and the effect on neurological status closely monitored. Vasopressors should be titrated to an adequate MAP, CPP (>80 mmHg) and clinical effect.
- The goal of therapy is to maintain euvolemia, while *increasing cardiac output, cerebral perfusion pressure and cerebral blood flow.*
- Patients who do not improve within 6–12 h of induced hypertension should be referred to interventional radiology for angiography and possible endovascular therapy (IV verapamil or angioplasty)
- Hemodynamic assessment and management by transthoracic thermodilution is recommended in patients with clinical evidence of vasospasm to optimize cardiac preload and cardiac output while liming the increase in intravascular lung water (and cerebral edema).

Transpulmonary Thermodilution (TPTD) Hemodynamic Assessment

Hemodynamic monitoring with the CVP, pulmonary artery catheter (PAC), pulse pressure variation (PPV), un-calibrated pulse contour analysis [98] or similar technology has no place in patients with SAH and MUST be abandoned

(immediately). TPTD provides a detailed (and accurate) hemodynamic assessment (see Chap. 10) and has demonstrated to have significant clinical utility in the management of patients with SAH. Patients with SAH typically have an increased CI, low global end-diastolic volume (GEDV), high (normal to high) extravascular lung water (EVLW) and high systemic vascular resistance (SVR) at presentation [99, 100]. This complex hemodynamic pattern is typical of a hyperadrenergic and volume depleted state with increased microvascular permeability (sympathetic hyperactivity with hyperdynamic and hypovolemic state). The poorer the grade of SAH the more deranged this hemodynamic pattern [99–101]. These hemodynamic variables tend to normalize with time (and with appropriate treatment). The goals of hemodynamic management in these studies were as follows: CI > 3.0 L/min/m^2 (CI > 3.5 l/min/m^2 with DIND), GEDVI 700–900 mL/m^2 and a EVLW < 14 mL/kg.

Mutoh et al. performed a small (n = 100) RCT in patients with SAH that compared hemodynamic management with a CVP (and PAC for DIND) as compared to TPTD [102]. In this study patients managed by TPTD had a significantly reduced risk of vasospasm, DIND, cerebral infarction and cardiopulmonary complications compared with those managed with the CVP/PAC ($p < 0.05$) with a trend towards improved functional outcomes at 3 months ($p = 0.06$). Based on these data we suggest that patients with severe vasospasm and/or DIND be managed by TPTD. Fluid boluses with normal saline are recommended in patients who are volume responders (see Chap. 9). The goal of fluid management is to achieve a CI > 3.5 L/min/m^2, a GEDVI > 800 mL/m^2 and an EVLW < 14 mL/kg. Norepinephrine should be used to achieve the MAP targets as discussed above. Dobutamine (2.5–20 ug/kg/min) is suggested for low cardiac output.

Subdural Hematoma

The collection of fresh blood under the dura mater is referred to as an acute subdural hematoma (SDH). Data from the traumatic Coma Data Bank indicates the 21 % of all severely injured patients have subdural hematomas. Traumatic subdural hematomas are common in elderly patients and most commonly associated with falls [103]. In blunt trauma, a SDH is observed more commonly on the contrecoup side (ie, side opposite to the blow) as opposed to epidural hematomas, which are found more commonly on the coup side (ic, side of the blow) and usually adjacent to a skull fracture. An acute SDH also may occur with deceleration or rotational mechanisms, without an actual impact. A SDH usually results from venous bleeding, specifically from bridging veins from the cortex to the superior sagittal sinus. These bridging veins are stretched in older patients, with an associated increased chance of tearing. Acutely, the blood collection is thick and jelly-like, explaining its bright appearance on CT scan. It remains acute for approximately 3 days, after which it will begin to liquefy becoming subacute for 2–3 weeks, after which it will have completely liquefied. At this point, the SDH is considered chronic.

The clinical presentation includes a wide spectrum of neurological findings secondary to either mass effect or direct brain injury. On CT scan the lesion is seen as a hyperdense extraaxial collection that is crescent shaped. Patients presenting with acute neurological deficits and a CT scan demonstrating an acute subdural hematoma should undergo emergent surgery. Surgical intervention may not be required for patients with small lesions less than 3 mm thick on CT scan or those who present neurologically after a significant delay.

Traditionally patients who have had a Burr-hole evacuation of a subdural hematoma are nursed supine to prevent recurrent subdural hematoma formation [104]. However, not all studies have demonstrated an increased recurrence rate in patients placed in a sitting position with the head of the bed raised 30–40° [105]. Due to the increased risk of aspiration patients placed in a supine position cannot be fed and this position increases the risk of atelectasis and pneumonia. However, the risk of aspiration is equivalent with the head of bed at 20° as compared to 45° [106]. Based on this data it would appear reasonable to nurse patients at 20° for the first 3 days following surgery.

Epidural Hematoma

Like subdural hematoma, epidural hematomas are most commonly associated with head trauma, especially in association with skull fractures. They are rarely seen in adults over the age of 60 years, because after this age the dura adheres tightly to the inner table of the calvarium. The most common locations are temporal and frontal. When identified the most common source is the middle meningeal artery. The primary therapy for an acute epidural hematoma is surgery, usually urgently. Mannitol, furosemide and hyperventilation are used when patients deteriorate clinically from an awake state to one of decreased arousal or agitation.

Increased Intracranial Pressure (ICP)

Increased intracranial pressure (ICP) may occur in patients who have cerebral hemorrhage, cerebral infarction with associated edema, primary or metastatic brain tumors, encephalitis, global anoxic or ischemic brain injury, or following traumatic brain injury (TBI). Most of the information concerning raised ICP is derived from studies on TBI; it is unclear if this information can be extrapolated to other clinical situations.

Cerebral blood flow (CBF) in humans' averages about 50 mL/100 g brain tissue/min. Irreversible neuronal damage occurs if CBF drops below 18 mL/100 g/min for a prolonged period of time. Cerebral blood flow is equal to the cerebral perfusion pressure (CPP), which is defined as the difference between the MAP and the ICP, divided by the cerebral vascular resistance (CVR). Because the CBF is difficult to measure clinically the CPP is used as a guide to assessing the adequacy of cerebral perfusion.

Both the ICP and MAP need to be measured to determine the CPP. The normal ICP is between 0 and 10 mmHg. While earlier studies and recommendations centered on the importance of ICP per se, current evidence emphasizes the importance of the CPP. The guidelines proposed by the Brain Trauma Foundation recommend that the CPP should be maintained at a minimum of 70 mmHg in the brain injured patient, although the exact target number and methodology for achieving that target remains controversial [107]. A higher threshold may be required in patients with chronic hypertension [108]. These guidelines use 20 mmHg as the threshold for intracranial hypertension. A lower target CPP (50–60 mmHg) may be adequate in patients with cerebral edema associated with fulminant hepatic failure.

Measurement of ICP

ICP cannot be reliably estimated from any specific clinical feature or CT finding and must be measured. Different methods of monitoring ICP have been described but two methods are commonly used in clinical practice: intraventricular catheters and intraparenchymal catheter-tip, microtransducer systems. Subarachnoid and epidural devices have much lower accuracy and are currently rarely used. The "gold standard" technique for ICP monitoring is a catheter inserted into the lateral ventricle, usually via a small right frontal burr hole. This can be connected to a standard pressure transducer via a fluid filled catheter. The reference point for the transducer is the foramen of Munroe, although, in practical terms, the external auditory meatus is often used. Some ventricular catheters have a pressure transducer within their lumen and the ICP wave form is generally of better quality than traditional fluid-filled catheters connected to an external transducer. Ventricular catheters measure global ICP and have the additional advantages of allowing periodic external calibration, therapeutic drainage of CSF, and administration of drugs (e.g., antibiotics). However, placement of the catheter may be difficult if there is ventricular effacement or displacement due to brain swelling or intracranial mass lesions. The use of intraventricular catheters is complicated by infection in up to 11 % of cases. Microtransducer-tipped ICP monitors can be sited in the brain parenchyma or subdural space, either through a skull bolt, a small burr hole or during a neurosurgical procedure. They are almost as accurate as ventricular catheters. Fiberoptic, strain gauge or pneumatic technologies are used to transduce pressure in modern microtransducer devices.

Indications for ICP Monitoring

There is no data from randomized controlled trials that can clarify the role of ICP monitoring in acute coma [109]. Indeed, there is very little data that ICP monitoring improves patient outcome. With the exception of monitoring after TBI, the

indications for ICP monitoring are not well established. ICP monitoring has become an integral part of the management of patients with severe head injuries in virtually all trauma centers in the U.S. The Brain Trauma Foundation recommends ICP monitoring in all patients with a severe TBI (Glasgow Coma Score 3–8) and either an abnormal CT scan or a normal scan and the presence of two or more of the following three risk factors at admission: age >40 year; unilateral or bilateral motor posturing; a systolic a BP < 90 mmHg [110].

A pivotal multicenter, controlled trial randomized 324 patients 13 years of age or older who had severe TBI to one of two specific protocols: guideline-based protocol based on ICP monitoring ICP or a protocol in which treatment was based on imaging and clinical examination [111]. The primary outcome was a composite of survival time, impaired consciousness, and functional status at 3 months and 6 months and neuropsychological status at 6 months. There was no difference in the primary outcome between groups. Cremer et al. reported a retrospective analysis of severe TBI patients managed at two different trauma centers who differed in the use of ICP monitoring [112]. One center with 122 patients that did not monitor ICP but used ICP lowering treatment (82 % sedatives and paralytics, 25 % mannitol, 22 % hyperventilation and 2 % ventricular drainage) was compared to another with 211 patients that used ICP monitoring in 67 % of severe TBI patients and treated ICP significantly more except for hyperventilation and ventricular drainage which was equally used in both centers. The length of mechanical ventilation was significantly longer in the patients who received ICP monitoring. There was however, no difference in mortality or 12-month GOS. These data seriously question the recommendation for routine ICP monitoring in patients with severe TBI.

Management of Raised ICP

After the establishment of an airway and ventilation, the restoration of blood pressure and normal circulating volume is of the utmost importance in patients with increased ICP. According to the Brain Trauma Foundation guidelines for the management of severe TBI, a MAP of 90 mmHg or greater should be targeted; this was chosen based on attaining cerebral perfusion pressures greater than 70 mmHg. These guidelines use 20 mmHg as the threshold for intracranial hypertension [110]. Patients should be resuscitated with Lactated Ringers' solution (see Chap. 9). Norepinephrine should be used to achieve the target MAP once an adequate preload is achieved. Even though the head injured patient may be comatose, they require analgesia and sedation as they still respond to painful and noxious stimuli, often with an increase in ICP and blood pressure. Most frequently, narcotics (morphine or fentanyl) should be considered first line therapy since they provide both analgesia and depression of airway reflexes, which is required in the intubated patient. Fentanyl has the advantage of having minimal hemodynamic effects. Other general principles in the management of patients with head injury include lowering the body temperature of patients with fever and prevention of jugular venous outflow

obstruction (keeping patient's head midline, avoiding extrinsic compression of the jugular veins by hematomas, masses). While some studies have suggested that CPP is optimal when patients are nursed flat, others have demonstrated that head elevation to 30° lowers ICP without decreasing CPP or cerebral blood flow [113].

Hyperventilation

Aggressive hyperventilation ($PaCO_2 \leq 25$ mmHg) has traditionally been considered a cornerstone in the management of raised ICP. Hyperventilation reduces ICP by causing cerebral vasoconstriction with a subsequent reduction in CBF. Hyperventilation results in a fall in ICP, however, this is associated with a significant fall in jugular venous O_2 saturation. Skippen and colleagues, using xenon-enhanced computed tomography and cerebral blood flow studies, demonstrated a two and a half fold increase in the number of regions of brain ischemia in children with TBI who were hyperventilated [114]. In 1991, Muizelaar and colleagues published the results of a prospective randomized clinical study in which they demonstrated that hyperventilation post head-injury was associated with a significantly worse neurological outcome when compared to patients who were kept normocapnic [115]. Based on this data chronic hyperventilation is no longer recommended [108, 116]. Initial target pCO_2 should be 35–40 mmHg [108, 116]. Short term hyperventilation, however, may have a role in reducing ICP in patients who are rapidly deteriorating before other measures can be instituted [117].

Volume Resuscitation

Volume resuscitation with isotonic fluids (0.9 % saline) and restoration of a normal intravascular volume is recommended in all patients with acute cerebral insults. Volume overload should however be avoided. Hypotonic solutions should be avoided. It should be noted that in the Safe Study a hypo-oncotic albumin solution was used (4 % albumin). This was associated with higher ICP and worse outcomes in patients with TBI [118, 119]. More concentrated albumin solutions (5 %, 20 %, 25 %) are not contraindicated in patients with acute cerebral insults [120].

Hyperosmotic Agents

If the ICP remains above 20 mmHg, despite adequate sedation and elevation of the head of the bed (to 30°), additional measures are required to lower the ICP. When a ventricular catheter is being used for ICP monitoring, CSF drainage should be used for ICP elevations [121]. If CSF drainage is ineffective, hyperosmotic agents such as mannitol or hypertonic saline are recommended. Mannitol is dosed 0.25–0.5 g/kg given every 2–6 h to increase the serum osmolarity to 310–320 mOsm/kg H_2O [122]. Mannitol acts acutely by expanding intravascular volume and decreasing blood viscosity thereby increasing

cerebral blood flow [123]. The osmotic movement of fluid out of the cellular compartment is followed by a diuresis which is delayed for 15–30 min while gradients are established between plasma and cells. The osmotic diuresis following mannitol lasts for between 90 min to 6 h. The prolonged administration of mannitol may lead to intravascular dehydration, hypotension, and prerenal azotemia. The benefit of mannitol in head injured patients has yet to be determined, and remarkably only one placebo controlled study has been reported to date [124]. In this study which compared the prehospital administration of mannitol against placebo, mannitol was associated with an increased relative risk for death (1.59; 95 % confidence interval 0.44–5.79). Similarly, mannitol has failed to show a benefit in patients with intracerebral hemorrhage [28, 29]. Hypertonic saline has been demonstrated to decrease ICP and increase CPP in patients with refractory intracranial hypertension and should be considered an alternative to treatment with mannitol [125]. Although both mannitol and hypertonic saline are effective in reducing brain water content and ICP, animal studies suggest greater short- and intermediate-term reduction in brain water with hypertonic saline [126]. A meta-analysis which included 5 clinical studies demonstrated that hypertonic saline was more effective than mannitol for the treatment of elevated ICP [127]. In addition, HTS is effective at achieving ICP control when mannitol therapy fails [128, 129]. Hypertonic saline has the advantage that unlike mannitol it is a volume expander and therefore likely to maintain the MAP with a greater increase in the CPP.

Other Interventions

The use of corticosteroids for increased ICP has only been efficacious in cerebral edema associated with tumors [130, 131]. In head injuries, steroids have been shown to lack efficacy and carry the risks of potential side effects (i.e. hyperglycemia, increased risk of infections, myopathy), and their use must be avoided. Indeed, in the CRASH study high dose corticosteroids were associated with an increased mortality [132].

Propofol is the hypnotic agent of choice in patients with an acute neurological insult as it is easily titratable and rapidly reversible once discontinued. Propofol has additional properties that may be beneficial in the head injured patient including a decrease in cerebral metabolic rate, decrease in intra-cranial pressure (ICP), potentiation of GABAminergic inhibition and inhibition of NMDA glutamate receptors and voltage-dependent calcium channels and prevention of lipid peroxidation.

Prophylactic Hypothermia

Although hypothermia is often induced prophylactically on admission and used for ICP elevation in the ICU in many trauma centers, the scientific literature has failed to consistently support its positive influence on mortality and morbidity. Meta-analyses of hypothermia in patients with TBI have concluded that the evidence was insufficient to support routine use of hypothermia [133]. While there is little data to support routine hypothermia, fever should be aggressively treated (see SAH recommendations).

Mechanical Ventilation

The ventilator settings should be adjusted to maintain the $PaCO_2$ between 35 and 40 mmHg and the PaO_2 above 70 mmHg. While it has been suggested that a high PaO_2 may improve brain tissue oxygenation [134], this goes against our understanding of human physiology, as tissue oxygen unloading is dependant primarily on the hemoglobin concentration, the P50 and the hemoglobin saturation. The dissolved oxygen fraction makes an insignificant contribution to oxygen transport. A high FiO_2 may, however, promote the formation of reactive oxygen species and increase lipid peroxidation. Hyperoxia appears particularly toxic to the injured brain (see Chap. 14). In a retrospective multi-center cohort study, Rincon et al. demonstrated that hyperoxia was independently associated with higher in-hospital mortality rate (OR 1.5, 95 % CI 1.02–2.4, p = 0.04) [135]. While it has been suggested that positive end-expiratory pressure (PEEP) and modes of ventilation that increase mean intrathoracic pressure be avoided in patients with elevated ICP, clinical studies do not support this contention [136–138]. However, in accord with current guidelines, the lowest level of PEEP that maintains adequate oxygenation and prevents end-expiratory alveolar collapse should be used. Continuous pulse oximetry is recommended with the arterial saturation maintained between 92 and 96 %. Although endotracheal suctioning does cause a transient rise in ICP it does not produce cerebral ischemia and is required to prevent atelectasis [139]. Airway pressure release ventilation (APRV) is an alternative approach to the low-tidal volume "open lung" ventilation strategy (See Chaps. 19 and 9). APRV is associated with a higher mean airway pressure than conventional ventilation. It has therefore been assumed that this mode of ventilation will result in a higher ICP and is therefore contraindicated in patients with acute neurological insults. We reported a patient with severe progressive hypoxemia following SAH who was converted from pressure-controlled mechanical ventilation to APRV [140]. This change in ventilatory mode was associated with a significant improvement in oxygenation and alveolar ventilation with an associated increase in cerebral blood flow and a negligible increase in ICP.

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Chapter 44
Seizures & Status Epilepticus

Seizures in the ICU

Seizures are common neurological complications in medical and postsurgical ICU patients and commonly arise from coexisting conditions associated with critical illness. Most seizures occur in ICU patients who did not have prior seizures or neurologic pathology as part of the primary admitting diagnosis. In general ICUs, metabolic abnormalities have been reported to account for 33 % of seizures, drug withdrawal for 33 %, drug toxicity for 14.5 %, and stroke for 9–39 % [1]. Hypoglycemia should always be excluded as this is imminently treatable and delayed diagnosis is associated with significant neurological injury. Status epilepticus as an admitting diagnosis is much less common than seizures occurring as a complication during the course of critical illness [2]. Most seizures that occur in the ICU setting manifest as generalized tonic-clonic convulsions.

It is important to emphasize that "all that shakes" is not a seizure [3]! Abnormal movements and "jerkiness" are common in ICU patients especially those with delirium. The distinction between seizures and abnormal movements is crucial as antiepileptic drugs (AEDs) are not indicated in those with abnormal movements and can cause further sedation and delirium in an already susceptible patient population. Seizures are unlikely in patients with jerking movements who are alert and responsive; these patients should NOT be treated with AEDs. In cases of diagnostic uncertainty bedside EEG-video recordings and a neurology consult are recommended. Benbadis et al. reviewed EEG-video recordings obtained for "possible seizures" in 52 ICU patients [3]. In this study only 14 patients (27 %) had epileptic seizures. Tremor-like movements, multifocal myoclonic jerks, and other abnormal movements were diagnosed in the 73 % of patients without seizures.

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Seizures Occurring as a Complication of Critical Illness

(a) Drug/substance toxicity

- Antibiotics
  - Carbapenems, esp. imipenem
  - Penicillins
  - Cephalosporins
  - Aztreonam
  - Fluoroquinolones
  - metronidazole
- Antidepressants
  - Tricyclics
  - bupropion
- Antipsychotics
  - chlorpromazine
- Immunosuppressants
  - tacrolimus
  - cyclosporine
- Other
  - Theophylline
  - Cocaine
  - Amphetamines

(b) Drug/substance withdrawal

- Alcohol
- Barbiturates
- Benzodiazepines
- Opioids

(c) Metabolic

- Hypoglycemia
- hypocalcemia
- Hypophosphatemia
- Hyponatremia
- Renal failure

(d) Eclampsia

(e) Posterior reversible encephalopathy syndrome (PRESS)

Seizures from Primary Neurological Disease

- "Primary" epilepsy with poor compliance (subtherapeutic AED levels)
- Previous stroke
- Acute ischemic stroke
- Intracerebral hemorrhage
- Intracranial tumor
  - Cortical primary
  - Cortical metastatic
- Traumatic head injury
- Cerebral sinus thrombosis
- Encephalitis
- Meningitis
- Brain abscess
- Non-infectious encephalitis
  - NMDA-receptor antibody
  - Paraneoplastic limbic
- Anoxic-Hypoxic brain injury
- Cerebral vasculitis

Management

Many seizures manifest as single, self-limited episodes. Such occurrences serve to alert the intensivist that a metabolic, drug or structural problems exists. The first step is to terminate the ictal activity followed by an evaluation as to the cause of the seizure. Neuro-imaging (CT scan) is always required to exclude a structural lesion even in the context of an identifiable metabolic/drug etiology. An EEG is required in patients who do not fully regain conscious (see Sect. "Status Epilepticus") and in those patients whose level of consciousness is difficult to assess (due to sedation, underlying disease, etc.).

Seizure Therapy

- Acute termination of ictal activity
  - Lorazepam 0.05–0.1 mg/kg
  - Midazolam 0.05–0.2 mg/kg

- Treatment of underlying cause
  - Drug induced; stop offending drug(s); consider hemodialysis if recurrent (theophylline)
  - Lorazepam for drug withdrawal
  - Alcohol (see Chap. 46)
  - Serotonin inhibitors (see Chap. 18)
  - Cocaine—benzodiazepine (see Chap. 45)
- Prophylaxis if risk persists (consult neurology)
  - Levetiracetam (drug of choice). Levetiracetam (Keppra) has distinct advantages over the other intravenous and oral anticonvulsants in the critically ill as it has few drug interactions and is usually well tolerated.
  - Valproic acid

Status Epilepticus

Status epilepticus is a relatively common condition. It accounts for 3–5 % of all ED admissions for seizure disorders and occurs in 2–16 % of all epilepsy patients [4]. Status epilepticus is a major medical emergency associated with significant morbidity and a mortality of up to 76 % in elderly patients with refractory status epileptics [5]. This clinical entity requires prompt management. The complications of status epilepticus include cardiac dysrhythmias, derangements of metabolic and autonomic function, neurogenic pulmonary edema, hyperthermia, rhabdomyolysis, and pulmonary aspiration. Permanent neurological damage occurs with prolonged uncontrolled convulsive activity.

Status epilepticus has previously been defined as continuous seizure activity lasting 30 min or as two or more discrete seizures between which consciousness is not fully regained [6]. Lowenstein, Bleck and Macdonald have proposed that status epilepticus be defined as a continuous, generalized, convulsive seizure lasting greater than five minutes or two or more seizures during which the patients does not return to baseline consciousness [7]. The rationale for this revised definition is based on the fact that a typical, generalized tonic-clonic seizure rarely lasts longer than 5 min, spontaneous termination becomes less likely in seizures greater than 5 min and the longer the seizure continues the more difficult the seizure becomes to control with antiepileptic drugs and the greater the degree of neuronal damage [8]. This definition is consistent with common clinical practice in which it would be unreasonable to wait 30 min before initiating antiepileptic drug therapy.

Refractory status epilepticus is usually defined as seizures lasting longer than 2 h, or seizures recurring at a rate of two or more episodes per hour without recovery to baseline between seizures, despite treatment with conventional antiepileptic drugs. However, from a clinical perspective it is preferable to consider

refractory status epilepticus as any patient who has failed first-line therapy [8]. Status epilepticus may be classified by the presence of motor convulsions (convulsive status epilepticus) or their absence (non-convulsive status epilepticus). They may be further divided into status epilepticus that affects the whole brain (generalized status epilepticus) or only part of the brain (partial status epilepticus) [6]. Status epilepticus appears to be more frequent among males, blacks and the aged.

Etiology

In many patients with a pre-existent seizure disorder no obvious precipitating factor can be determined. A fall in serum levels of AEDs due to poor compliance with medications or due to increased clearance associated with concurrent illness has been implicated in some patients. Adult patients with a new diagnosis of epilepsy may first present in status epilepticus.

Common Causes of Status Epilepticus Include

- Anti-epileptic drug non-compliance
- Alcohol related
- Cerebrovascular accidents
- Drug toxicity
  - cephalosporins
  - carbapenems
  - penicillins
  - ciprofloxacin
  - tacrolimus
  - cyclosporine
  - theophylline
  - cocaine
- Central nervous system infections
  - Meningitis
  - Encephalitis
- Central nervous system tumors (primary or secondary)
- Metabolic disturbances (i.e., electrolyte abnormalities, uremia)
- Head trauma
- Cerebral anoxia/hypoxia
- Hypoglycemia

Pathophysiology

It is likely that ineffective recruitment of inhibitory neurons together with excessive neuronal excitation play a role in the initiation and propagation of the electrical disturbance occurring in status epilepticus. A growing body of basic science and clinical observation supports the concept that status epilepticus becomes more difficult to control as its duration increases. It is been postulated that this may occur due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor mediated transmission [1]. Furthermore, as status epilepticus progresses, the $GABA_A$ receptors are internalized and become functionally inactivated, conferring benzodiazepine resistance, which is believed to be a major cause of treatment failure. This may explain why benzodiazepines (GABAergic receptor agonists) are very effective AEDs during the early period of status epilepticus however they become less effective as time passes [1]. In humans and experimental animals, sustained seizures cause selective neuronal loss in vulnerable regions such as the hippocampus, cortex and thalamus. The degree of neuronal injury is closely related to the duration of seizures, underscoring the importance of rapid control of status epilepticus.

Complications of Generalized Status Epilepticus

- Systemic
  - Acidosis
  - Hyperthermia
  - Rhabdomyolysis
  - Renal failure
  - Arrhythmias
  - Trauma
  - Aspiration
- Neurologic
  - Direct excitotoxic injury
  - Epileptogenic foci
  - Synaptic reorganization

Diagnosis

Status epilepticus may be divided into two stages [6]. The first phase is characterized by generalized convulsive tonic-clonic seizures that are associated with an increase in autonomic activity that results in hypertension, hyperglycemia, sweating, salivation and hyperpyrexia. During this phase cerebral blood flow is increased due to increased cerebral metabolic demands. After approximately 30 min of

seizure activity, patients enter the second phase characterized by failure of cerebral autoregulation, decreased cerebral blood flow, an increase in intracranial pressure and systemic hypotension. During this phase electromechanical dissociation may occur in which although electrical cerebral seizure activity continues the clinical manifestations may be restricted to minor twitching.

The diagnosis of status epilepticus is straightforward in patients with witnessed generalized convulsive tonic-clonic seizures. However, status epilepticus may not be considered in patients who have progressed to the non-convulsive phase of status epilepticus and present in coma. All comatose patients should therefore be carefully examined for evidence of minor twitching which may involve the face, hands or feet or present as nystagmoid jerking of the eyes. Towne and colleagues evaluated 236 patients with coma and no overt seizure activity. Eight percent of patients in this study were found to have non-convulsive status epilepticus by electroencephalographic monitoring [9]. An urgent EEG is therefore required in patients with unexplained coma.

Treatment

Status epilepticus is a medical emergency that requires rapid and aggressive treatment to prevent neurologic damage and systemic complications. The longer status remains untreated the greater the neurologic damage. In addition, the longer an episode of status continues the more refractory to treatment it becomes and the greater is the likelihood of chronic epilepsy. The management of status epilepticus involves the rapid termination of seizure activity, airway protection, measures to prevent aspiration, management of potential precipitating causes, treatment of complications, prevention of recurrent seizures and the treatment of any underlying conditions.

General Measures

- As with any critically ill patient, the first step in the management of a patient with status epilepticus should be to ensure an adequate airway and provide respiratory support.
- The patient should be positioned so that they cannot harm themselves from the seizure activity.
- Two large gauge intravenous catheters should be inserted to allow fluid resuscitation and pharmacotherapy. Should peripheral venous access be difficult placement of a central venous catheter is recommended.
- Despite the periods of apnea and cyanosis that occur during the tonic or clonic phases of their seizure, most patients in status epilepticus breathe sufficiently as long as the airway remains clear. An oral airway may be required once the seizure has terminated to prevent airway obstruction. Once the seizures are

controlled and if the patient is oxygenating and ventilating adequately endotracheal intubation may not be required for "airway protection" even if the patient remains comatose [10]. However, in this situation precautions should be taken to avoid aspiration and a nasogastric tube should be placed to ensure that the stomach is empty. Endotracheal intubation will be required in patients who continue to seizure despite first-line therapy (see below). There is no available data as to the pharmacologic agent(s) preferred for achieving endotracheal intubation. As these patients will be comatose and already have received lorazepam a hypnotic agent is usually not required. However, an anesthetic induction dose of propofol, midazolam or etomidate may terminate the seizure activity and facilitate intubation. Neuromuscular blockade will be required to facilitate intubation in patients who continue to have tonic-clonic seizure activity despite these pharmacologic interventions. Rocuronium (1 mg/kg), a short acting, non-depolarizing muscle relaxant, which is devoid of significant hemodynamic effects and does not increase ICP is the preferred agent. Succinyl-choline should be avoided if possible as the patient may be hyperkalemic as a consequence of rhabdomyolysis. Prolonged neuromuscular blockade should be avoided.

- Hypoglycemia must be excluded rapidly and corrective measures instituted if serum levels of glucose are low. If prompt measurement of blood glucose levels is not possible, the patient should receive 100 mg of intravenous thiamine followed by a 50-mL bolus of 50 % dextrose.
- Blood pressure, electrocardiogram, and temperature should be monitored. If the patient develops significant hyperthermia (>40 °C) then passive cooling is required.
- Blood specimens should be obtained for the determination of serum chemistries.
- Continuous motor seizures may lead to muscle breakdown with the release of myoglobin into the circulation. Maintenance of adequate hydration is necessary to prevent myoglobin-induced renal failure (see Chap. 41).
- Brain imaging with a computerized tomographic scan (CT) and/or magnetic resonance imaging (MRI) as well as a lumbar puncture will be required in patients presenting with a previously undiagnosed seizure disorder once the seizure activity has been controlled. It is important to emphasize that the first priority is to control the seizures. Imaging studies should only be performed once the seizure activity has been controlled. Endotracheal intubation and neuromuscular paralysis for the sole purpose of imaging the patient may increase morbidity and is strongly discouraged.

Pharmacotherapy

Because only a small fraction of seizures go on to become status epilepticus, the probability that a given seizure will proceed to status is small at the start of the seizure and increases as the seizure duration increases. If a seizure lasts longer than

5 min, clinical experience suggests that the likelihood of spontaneous termination decreases [1]. The goal of pharmacologic therapy is to achieve rapid and safe termination of the seizure and prevention of its recurrence without adverse effects on the cardiovascular and respiratory systems or altering the level of consciousness. Diazepam, lorazepam, midazolam, phenytoin, fosphenytoin and phenobarbital have all been used as first-line therapy for the termination of status epilepticus. These drugs have different pharmacodynamic and pharmacokinetic properties which determine their rapidity of clinical effect, efficacy in terminating status epilepticus and their duration of action. The benzodiazepines bind to the benzodiazepine receptor on GABA increasing GABAergic transmission, while the barbiturates act directly on the GABA receptor. The anti-seizure activity of phenytoin is complex, however, its major action appears to block the voltage sensitive, use dependent sodium channels.

The publication of the Veterans Administration Cooperative Trial in 1998 and the San Francisco EMS Study in 2001 allows for an evidence based approach to the choice of the first-line agent to terminate status epilepticus [11, 12]. The VA cooperative study randomized 384 patients with overt generalized status epilepticus into four treatment arms as follows:

- lorazepam 0.1 mg/kg,
- diazepam 0.15 mg/kg, followed by 18 mg/kg of phenytoin;
- phenytoin 18 mg/kg; and
- phenobarbital 15 mg/kg.

Successful treatment required both clinical and EEG termination of seizures within 20 min of the start of therapy, and no seizure recurrence within 60 min from the start of therapy. Patients who failed the first treatment received a second choice and if necessary, a third choice of study drug. The latter choices were not randomized, because this would have resulted in some patients receiving two loading doses of phenytoin, but the treating physician remained blinded to the treatments being given. Status epilepticus was terminated in:

- 64.9 % of patients randomized to lorazepam,
- 58.2 % to phenobarbital,
- 55.8 % to diazepam and phenytoin and
- 43.6 % to phenytoin ($p = 0.002$ for lorazepam vs. phenytoin).

There was no difference between arms in recurrence rates. The San Francisco EMS Study was a randomized, double-blind trial to evaluate intravenous benzodiazepine administration by paramedics for the treatment of out-of hospital status epilepticus [12]. In this study, 205 patients were randomized to intravenous diazepam (5 mg), lorazepam (2 mg) or placebo. An identical second injection was given if needed. Status epilepticus had terminated at arrival in the emergency department in 59.1 % of patients treated with lorazepam, 42.6 % of patients treated with diazepam and 21.1 % of patients given placebo (odds ratio of 1.9 [95 % CI of 0.9–4.3] for lorazepam compared to diazepam). The duration of the status epilepticus was shorter in the lorazepam group as compared to the diazepam group (adjusted

relative hazard, 0.65 [95 % CI 0.36–1.17]). This data is supported by a double-blind study reported by Leppick in 1983 in which 78 patients with status epilepticus were randomized to receive one or two doses of either 4 mg lorazepam or 10 mg diazepam [13]. Seizures were controlled 89 % of the episodes treated with lorazepam and in 76 % treated with diazepam. Although the dosages of lorazepam and diazepam differed in these three studies and phenytoin was added to diazepam in the VA study, the summed data indicate that lorazepam is significantly more effective in terminating seizures than is diazepam (odds ratio of 1.74 [95 % CI of 1.14–2.64], $p = 0.01$). Furthermore, the pharmacokinetic properties of lorazepam favor it over diazepam. The anticonvulsant effect of a single dose of diazepam is very brief (20 min) whereas that of lorazepam is much longer (greater than 6 h) and the risk of respiratory depression may be greater with diazepam [14]. Although diazepam has a much longer elimination half-life, due to its high lipid solubility it is rapidly redistributed from the brain to the peripheral fat stores accounting for its shorter antiseizure activity. Based on this data lorazepam in a dose of 0.1 mg/kg is recommended as first-line therapy for control of status epilepticus.

Many authorities recommend phenytoin 20 mg/kg (or fosphenytoin) following the administration of lorazepam [1]. While there is no data which demonstrates that phenytoin increases the response rate following the use of lorazepam, this agent may prevent recurrent seizures and is recommended in patients without a rapidly reversible process (e.g. the effect of sub-therapeutic anti-epileptic-drug concentrations) [15]. Continuous EEG monitoring is required in patients who do not recover consciousness once the convulsive seizure has aborted. In a study by DeLorenzo and colleagues, after cessation of convulsions, 48 % of patients continued to have seizure activity and 14 % of patients had persistent non-convulsive status epilepticus [16].

Management of Refractory Status Epilepticus

In the VA cooperative study 55 % of patients with generalized convulsive status epilepticus failed first-line therapy. The aggregate response rate to a second first-line agent (lorazepam, diazepam, phenytoin or phenobarbital) was 7 and 2.3 % to a third first-line agent. Only 5 % of patients with status epilepticus who did not respond to lorazepam and phenytoin therapy, responded to phenobarbital administration This data suggests that refractory status epilepticus is much more common than is generally appreciated and that phenobarbital should not be used as a second (or third-line) agent in patients who have failed to respond to lorazepam. Furthermore, the limited data available suggests that the administration of further doses of lorazepam will not be useful [13].

A variety of agents have been recommended for the treatment of refractory status epilepticus including, midazolam, propofol, high-dose thiopentone or pentobarbital, intravenous levetiracetam, intravenous valproate, topiramate, tiagabine, ketamine, isoflurane and intravenous lidocaine [1, 8]. Treatment guidelines are difficult as refractory status epilepticus has not been studied in a prospective clinical trial. Currently, however, a continuous intravenous infusion of midazolam or propofol together with continuous EEG monitoring is the preferred mode of treatment [8, 17,

18]. Both agents have been reported to be successful in the control of patients with refractory status epilepticus. It should, however, be pointed out that this recommendation is based on limited clinical data [17, 19]. Recently intravenous levetiracetam (Keppra) and intravenous valproic acid have become available and may have particular utility in status epilepticus both as a second line agent and as an "add-on" to another second line agent (midazolam or propofol) [1, 20, 21]. In a recent review of studies using levetiracetam after benzodiazepines in 334 patients with SE, its efficacy was reported as ranging from 44 to 94 % [22]. Overall, more than 700 patients with SE have been treated with an initial dosage of 2–3 g/day and with an estimated success rate around 70 % [23]. In a retrospective study of 181 episodes of status epilepticus failing to respond to benzodiazepine first-line treatment, valproic acid was more effective than levetiracetam for controlling status epilepticus [24].

The goal regarding the activity on the EEG remains a matter of debate. There is no prospectively collected evidence that a burst-suppression EEG pattern is required for, or is efficacious for, the termination of status epilepticus. Many patients can achieve complete seizure control with a background of continuous slow activity and do not incur the greater risks associated with higher doses of medication required to achieve a burst-suppression pattern.

- Midazolam is given as a loading dose of 0.2 mg/kg, followed by an infusion of 0.1–2.0 mg/kg/h titrated to produce seizure suppression by continuous EEG monitoring.
- Propofol is given as a loading dose of 3–5 mg/kg, followed by an infusion of 30–70 μg/kg/min titrated to EEG seizure suppression. After 12 h of seizure suppression the dose is gradually titrated by 50 % over the next 12 h and then titrated to off over the subsequent 12 h. If seizure activity should recur during the weaning period, a further loading dose 1–3 mg/kg should be given followed by an infusion the rate increased to obtain another 12 h seizure free period [25].
- Valproic acid is given as a loading dose of 20–40 mg/kg followed by an infusion at 5 mg/kg/h that is titrated down after 12 h of clinical and EEG seizure control.
- Levetiracetam (Keppra) in a dose of between 1,000 and 3,000 mg infused over 15 min has been successfully used in status epilepticus. Levetiracetam has essentially no drug-drug interactions, limited protein binding, no hepatic metabolism and is generally well tolerated.
- High dose barbiturate therapy is associated with hemodynamic instability and immune-paresis. Due to their side effects, barbiturates are reserved for those patients who fail second line therapy. Pentobarbital in a dose of 10–15 mg/kg/h, followed by 0.5–1.0 mg/kg/h is recommended.

The Management of Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus constitutes approximately 20–25 % of status epilepticus cases, occurring in about 8 % of all comatose patients without clinical signs of seizure activity, and persisting in 14 % of patients after generalized convulsive

status epilepticus. Some have suggested that nonconvulsive status epilepticus is a benign condition which does not require aggressive therapy. However, the prognosis of nonconvulsive status epilepticus depends upon the etiology and the level of consciousness, being associated with significant morbidity in those with a depressed level of consciousness. Comatose patients with nonconvulsive status epilepticus and nonconvulsive status epilepticus following generalized convulsive status epilepticus should be treated aggressively as outlined above for refractory convulsive status epilepticus. Levetiracetam may have particular utility in these patients [26].

Prevention of Seizure Recurrence Once Status Epilepticus is Terminated

Once status epilepticus is controlled, attention turns to preventing its recurrence. The best regimen for an individual patient will depend on the cause of the patient's seizure and any previous history of anti-epileptic drug therapy. A patient who develops status epilepticus in the course of ethanol withdrawal may not need antiepileptic drug therapy once the withdrawal has run its course. In contrast, patients with new, ongoing epileptogenic stimuli (e.g. encephalitis) may require high dosages of antiepileptic drugs to control their seizures.

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Chapter 45
Toxicology

This chapter provides a brief overview on the management of patients following an accidental or suicidal overdose. The reader is referred to toxicology texts and their local poison center for information on the management of specific intoxications.

General Measures

- Stabilization of patient, i.e. airway, breathing and circulation
  - Intubate comatose and seizing patients
- Obtain IV access
- Treat hypotension initially with volume expansion
- Comatose patients should be given naloxone 0.8 mg IV
- Specific antidotes are available for a limited number of intoxications (see Table 45.1)
- Flumazenil (a benzodiazepine antagonist), may be indicated in patients who present with obtundation or coma following the ingestion of benzodiazepines. Flumazenil is contraindicated in patients with mixed overdoses (tricyclic antidepressants and benzodiazepines) as well as patients with a history of seizures. An initial dose of 0.2 mg intravenously should be given over 30 s. Additional doses of 0.2–0.5 mg can be given up to a total of 3 mg
- Ipecac is not recommended for ingestions treated in hospital. May be used at home for accidental ingestions in children. Should not be given after ingestion of caustic substances and acids
- Gastric lavage is indicated in the following circumstances:
  - recent ingestion (<1 h) of a potentially life-threatening poison
  - ingestion of a substance that slows gastric emptying (e.g. anticholinergic medications)
  - ingestion of a poison that is slowly absorbed from the gastrointestinal tract

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Table 45.1 Toxic substances with specific antidotes

Agent	Antidote
Acetaminophen	*N*-acetylcysteine
Anticholinergic poisoning	Physostigmine
Anticoagulants	Vitamin K, protamine
Benzodiazepines	Flumazenil
Beta-adrenergic antagonists	Glucagon, calcium salts, isoproterenol
Carbon monoxide	Oxygen, hyperbaric oxygen
Cholinergic syndromes	Atropine
Digoxin	Fab antibody, Mg
Ethylene glycol	Fomepizole, thiamine, ethanol
Fluoride	Calcium and Mg salts
Heavy metals	BAL, DMSA, D-penicillamine
Iron	Desferoxime
Isoniazid	GABA antagonists, pyridoxime
Methemoglobinemia	Methylene blue
Opioids	Naloxone

  - ingestion of a substance that does not bind well to activated charcoal (see below)
  - ingestion of specific life-threatening poisons (e.g. tricyclic antidepressants, theophylline, cyanide)
  - Contraindicated in caustic ingestions

Technique for Performing Gastric Lavage

- Patients who cannot protect their airway MUST BE INTUBATED prior to performing gastric lavage
- Patient placed in head down lateral position
- Place large bore lavage tube through mouth
- Aspirate to empty stomach
- Lavage with 150–300 mL tepid tap water

Activated Charcoal

This is the cornerstone of the management of most ingestions. Activated charcoal is administered in a dose of 50–100 g.

- Drugs not well bound to activated charcoal
  - bromides
  - caustics

  - cyanide
  - ethylene glycol
  - heavy metals
  - iron
  - isopropyl alcohol
  - lithium
  - methanol
- Drugs amenable to repeat-dose activate charcoal therapy
  - carbamazepine
  - diazepam
  - digitalis
  - phenobarbital
  - phenytoin
  - salicylates
  - theophylline
  - tricyclic antidepressants

Hemodialysis/Hemoperfusion

Some drugs are cleared by hemodialysis/hemoperfusion; this technique should be instituted as clinical circumstances dictate.

- Hemoperfusion
  - acetaminophen
  - theophylline
  - methotrexate
  - phenylbutazone
  - procainamide
  - quinidine
- Hemodialysis
  - ammonium chloride
  - amphetamine
  - atenolol
  - meprobamate
  - methyldopa
  - nadolol
  - phenobarbital
  - procainamide
  - quinidine
  - sotalol
  - thallium
  - ethanol
  - methanol
  - ethylene glycol

  - isopropanol
  - aspirin
  - lithium
  - bromide
  - arsenic
  - dabigatran

In the evaluation of the patients with a possible drug overdose it is useful to look for symptom complexes or "toxidromes" that may help in identifying the type of drug ingested. The following toxidromes should be identified:

- Depressed level of consciousness
  - coma, stupor, lethargy, confusion
- Anticholinergic signs
  - mydriasis, increased blood pressure, tachycardia, warm dry skin, erythema, delirium, hallucination, urinary retention
- Cholinergic signs
  - salivation, lacrimation, urination, defecation (SLUD), miosis, bradycardia, sweating
- Sympathetic signs
  - high blood pressure, tachycardia, hyperthermia, mydriasis
- Serotonin syndrome
  - Confusion, myoclonus, hyperreflexia, diaphoresis, tremor, flushing, diarrhoea, fever
- Neurological signs
  - Nystagmus, tremors, hyperreflexia, seizures, extrapyramidal signs, hallucinations

Common Agents Responsible for

- Depressed level of consciousness
  - alcohols
  - anticholinergic
  - anticonvulsants
  - antidepressants
  - antihistamines
  - antipsychotics
  - barbiturates
  - benzodiazepines
  - carbon monoxide
  - opiates
  - sulfonylureas
- Seizures
  - phenytoin
  - beta-blockers

  - clonidine
  - theophylline
  - meperidine
  - amphetamines
  - cocaine
- Anticholinergic syndrome
  - antidepressants
  - antihistamines
  - antipsychotic
  - belladonna alkaloids
  - mushrooms
- Cholinergic syndrome
  - insecticides
  - mushrooms
  - nicotine
- Sympathetic syndrome
  - cocaine
  - amphetamines
  - phenycyclidine
- Serotonin syndrome
  - SSRI: fluoxetine etc
  - isoniazid
  - meperidine
  - clomipramine
- Extrapyramidal
  - antipsychotic
- Nystagmus
  - alcohols
  - lithium
  - carbamazepine
- Hallucinations
  - amphetamines
  - cocaine
  - phencyclidine
  - cannabinoids

Common Intoxications

Acetaminophen

Acetaminophen (acetyl-para-aminophenol or APAP) is an active ingredient of several hundred preparations and is the most common drug implicated in both accidental (children) and suicidal overdoses. In 2003, the American Association of Poison Control Centers reported more than 127,000 exposures involving

acetaminophen [1]. Of these exposures, 65,000 patients received treatment in a medical facility, and 16,500 received *N*-acetylcysteine (NAC). There were 214 deaths involving overdose where an analgesic agent was thought to be primarily responsible. In 62 of these cases, APAP was the single agent involved. APAP toxicity is the major cause of fulminant hepatic failure (FHF) and is implicated in as many as 39 % of cases presenting to tertiary care hospitals.

Acetaminophen is well absorbed, with peak levels about 4 h after an overdose. After therapeutic doses approximately 90 % of acetaminophen is conjugated by the liver to nontoxic inactive compounds which are renally excreted. About 5 % is excreted unchanged in the urine and about 5 % is oxidized by the P-450 mixed function oxidase enzyme to yield highly reactive toxic intermediates which are detoxified by reduced glutathione. After overdosage, the amount of drug metabolized by the P-450 route is increased. The same process occurs in the kidney, and while renal toxicity may occur with acetaminophen overdose it is far less common than hepatotoxicity. The hepatotoxicity may vary from asymptomatic elevation of liver enzymes to fatal liver failure. Pancreatitis and myocardial necrosis has also been described. It should be noted that stores of reduced glutathione are diminished in alcoholics and malnourished patients, predisposing to hepatic toxicity at therapeutic dosages. Ingestions of greater than 7.5 g in an adult should be considered potentially toxic.

Non-acute ingestions of APAP, frequently referred to as subacute or chronic, are ingestions that take place over a period longer than 4 h. In these cases, the nomogram (Fig. 45.1) offers no guidance in treatment, because it is intended only for use with acute ingestions. Most cases of nonacute ingestion of APAP that result in hepatotoxicity involve persons taking supra-therapeutic doses who are at increased risk for APAP-induced hepatotoxicity. However, hepatotoxicity has been reported in patients taking "therapeutic doses" (4 g/day); these patients usually have other risk factors including alcohol abuse, malnutrition, underlying liver disease or concomitant drugs (including phenytoin) [2, 3].

Watkins et al randomized 147 healthy volunteers to receive, acetaminophen (4 g day), an oral opiate, acetaminophen + an opiate, or placebo [4]. In this study, the daily intake of acetaminophen was associated with ALT elevation (>3 times) normal in up to 44 % of patients (risk not influenced by concomitant opiate). The AST levels began to rise on the 5th day and peaked on the tenth day when the drug was stopped. A prospective study of more than 600 patients from 22 US tertiary care centers found that acetaminophen related liver damage is the leading cause of acute liver failure in the country and that about half of such cases involved unintentional overdose [5]. In the unintentional group, 38 % took two or more acetaminophen preparations simultaneously. Based on the risks of hepatotoxicity with the "current dosage" recommendations the FDA has required a change in the labeling of these products, including reducing the maximum daily dose for both prescription and over-the counter acetaminophen products from 4 g per day to 3,250 mg per day (500 q 4 hourly or 650 q 6 hourly), limiting the dose in individual tablets, and adding to the labeling of these products a warning that individuals who chronically use alcohol should use an even lower dose of the drug [6, 7].

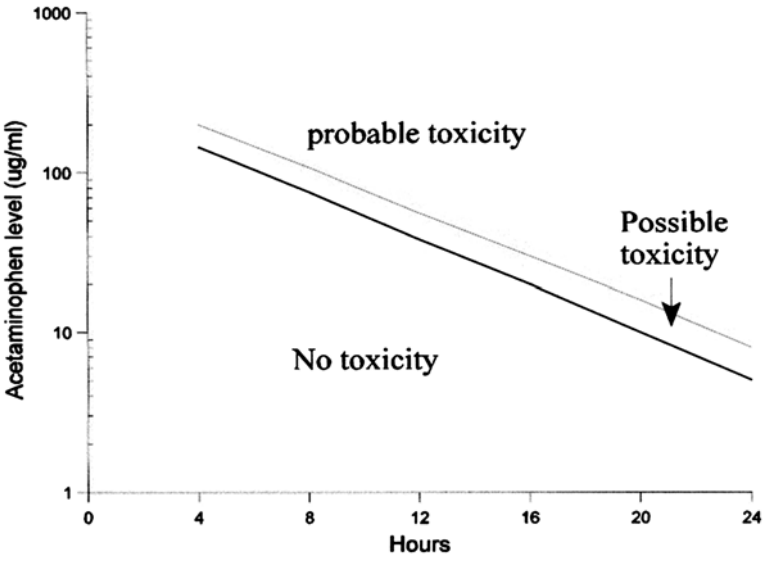

Fig. 45.1 Acetaminophen treatment nomogram

Signs and Symptoms

- Stage 1: 12–24 h after ingestion; asymptomatic or mild GI symptoms
- Stage 2: 24–72 h; right upper quadrant pain, nausea and vomiting, liver enzymes begin to rise.
- Stage 3: 72–96 h; maximal hepatic injury
- Stage 4: 4 days to 2 weeks; patient either improves with normalization of enzymes or progresses to acute hepatic necrosis with liver failure

Management

Analyzing the serum acetaminophen concentration is essential in all cases of acute overdose (see Fig. 45.1). A level prior to 4 h is difficult to interpret. High potential for toxicity exists when serum concentration is >200 μg/mL at 4 h, 50 μg/mL at 12 h and 7 μg/mL at 24 h after ingestion.

N-acetylcysteine (NAC) should be administered as soon as possible within the first 24 h of ingestion. However, antidotal therapy is optimal when given within 12 h of acetaminophen ingestion. NAC should be given if the patient has ingested more than 140 mg/kg (or 10 g) acetaminophen, if the serum level is above 140 μg/mL, or if the serum level is in the toxic range. The dose of *N*-acetylcysteine is 140 mg/kg as an initial oral loading dose, followed by 70 mg/kg every 4 h for a total of 17 doses. Nausea and vomiting are reported in 33 % of APAP overdoses before NAC and in an

estimated 51 % during oral NAC therapy. In 2004, *Acetadote* became the first NAC solution approved by the FDA for IV use, allowing the United States to join the rest of the industrialized world, which has been using IV NAC since its introduction in 1977 [8]. A 72-h oral, 48-h IV, and 20-h IV protocol have been reported. These protocols have been compared by retrospective study and through meta-analysis [9]. When started within 8 h of ingestion, no protocol shows advantage over another. However, the 20-h IV protocol is generally preferred; this is given as a loading dose of 150 mg/kg over 15 min, followed by 50 mg/kg infused over 4 h and 100 mg/kg administered over 16 h as a constant infusion. Although there is general consensus that IV administration is preferable in the face of intractable vomiting, no study shows clear evidence that IV therapy is more or less effective than oral NAC therapy.

It may be useful to measure a second level some time after starting *N*-acetylcysteine in order to determine the half life of acetaminophen. A half life greater than 4 h is suggestive of hepatic toxicity. *N*-acetylcysteine should not be stopped as the level fall to zero, as it is not acetaminophen that is toxic but rather its metabolites.

Salicylates

Signs and Symptoms

Gastric upset, tinnitus, increased depth of breathing, headache, seizures and coma. Anion gap metabolic acidosis and respiratory alkalosis.

Management

Serum salicylate levels are useful in confirming the diagnosis and assessing the severity of the toxicity, but are however not used in directing therapy.

- Supportive measures, GI decontamination, and activated charcoal.
- Forced alkaline diuresis (ion trapping and increased elimination). In cases of severe toxicity dialysis is useful.
- The decision to dialyze the patient is based on clinical grounds, i.e., seizures, altered level of consciousness.
- Blood level monitoring is useful to monitor drug elimination.

Tricyclic Antidepressants

The newer cyclic antidepressants (SSRI agents) are less toxic in overdose than the tricyclic drugs. Tricyclic antidepressants have anticholinergic and cardiac effects, however they can cause seizures, altered mentation and level of consciousness, leading to coma in overdose.

Signs and Symptoms

- Anticholinergic:-mydriasis, blurred vision, dry mouth, tachycardia, hyperpyrexia, urinary retention, decreased GI motility.
- CNS:- agitation, mental confusion, respiratory depression, seizures, coma.
- Cardiac:- Quinidine like action on heart; widened QRS, PR, and QT intervals, RBBB, torsades de pointe. The best predictor of cardiac arrhythmias and seizures is a QRS complex greater than 0.1 s or a prolonged QTc interval.

Management

- Antidepressants are highly tissue bound and therefore serum concentrations do not correlate with toxicity and have little clinical value.
- Supportive measures, GI decontamination and activated charcoal are essential.
- Alkalinization of the serum with bicarbonate to achieve an arterial pH of 7.5–7.55 should be instituted in patients with a prolonged QRS/QTc interval or cardiac arrhythmias. Alkalinization increases plasma protein binding (less free drug) and antagonizes the quinidine-like effects on the His-Purkinje system.
- Seizures are best treated with diazepam/midazolam or intravenous phenobarbital. Phenytoin is ineffective and may be dangerous.

Acute Ethanol Intoxication

Alcohol is the most common poison consumed by Americans, approximately a third of the population ingest this toxin on a chronic basis. The mechanism of action of alcohol is unclear; no specific ethanol receptors have been identified. It is postulated that ethanol influences multiple ion channels by causing alterations in their tertiary structure due to intercalation of ethanol into the bi-lipid cell membrane. Ethanol antagonizes the excitatory *N*-methyl-D-aspartate (NMDA) glutamate receptor and potentiates the inhibitory gamma-aminobutyric acid A receptor; these actions may explain the effect of alcohol on the central nervous system; ethanol is a CNS depressant.

Ethanol is readily absorbed from the gastrointestinal tract, with 80 % of the absorption occurring in the small intestine. Peak ethanol levels typically occur 30–60 min after ingestion. Metabolism occurs in the liver by first order kinetics (ie at a constant rate unaffected by the serum level), predominantly by alcohol dehydrogenase. The clinical features and associated blood levels of ethanol intoxication are listed in Table 45.2. The blood alcohol level can be estimated by the following formula: EtOH level = osmolar gap × 4.3. Serum ethanol levels decline by about 15–30 mg/dL/h. The treatment of acute alcohol intoxication is largely supportive; with prevention and

Table 45.2 Features of acute alcohol intoxication

Blood ethanol conc (mg %)	Symptoms and signs
50–150	Euphoria or dysphoria, uninhibited
	Impaired concentration and judgement
150–250	Slurred speech, ataxic gait, drowsiness, labile moods, antisocial behavior
250–400	Stupor, incoherent speech, vomiting
400–500	Coma
>500	Death

management of the associated complications. Hemodialysis may be helpful in severe cases. Medical complications associated with acute alcohol ingestion include:

- acute myopathy with rhabdomyolysis
- gastritis
- esophagitis
- Mallory-Weiss lesion
- thrombocytopenia
- pancreatitis
- alcoholic hepatitis
- arrhythmias, especially atrial fibrillation
- decreased myocardial contractility (synergistic with cocaine)
- peripheral vasodilation and hypotension
- alcohol withdrawal syndrome and delirium tremens
- hypoglycemia
- electrolyte disturbances, including hypokalemia, hyponatremia, hypophosphatemia, hypomagnesemia
- Wernicke's syndrome
- Lactic "acidosis"

Ethylene Glycol and Methanol Poisoning

Ethylene Glycol

Ethylene glycol is found in many deicers, antifreezes, detergents, polishes, cosmetics, paints, and lacquers. It is colorless, odorless with a slightly sweet taste. Ethylene glycol initially causes an ethanol like intoxication with little toxicity until it is metabolized in the liver to more harmful metabolites, including several aldehydes, carboxylic acids and oxalic acid. These intermediates inhibit cellular respiration, protein synthesis, and RNA replication. Ethylene glycol initially undergoes oxidation by hepatic alcohol dehydrogenase to glycoaldehyde, which is then rapidly converted by aldehyde dehydrogenase to glycolic acid. Glycolic acid is converted to

glyoxylic acid, whose most toxic metabolite is oxalic acid. Oxalic acid may crystalize as calcium oxalate in many tissues, causing hypocalcemia and tubular obstruction in the kidney. The anion gap acidosis results predominantly from elevated glycolic acid levels [10].

Classically, ethylene glycol poisoning has been divided into three stages.

- Stage 1 (30 min to 12 h) is characterized by CNS effects such as ethanol-like intoxication, stupor, coma and convulsions dominate the clinical picture.
- Stage 2 (12–24 h) is notable for cardiovascular and pulmonary effects such as tachypnea, cyanosis and pulmonary edema and progressive CNS depression.
- Stage 3 (48–72 h) is characterized by the development of acute renal failure. In addition during this stage prolonged generalized seizures may occur.

Methanol

Methanol is found in many cleaning materials, paints and varnishes, antifreeze, duplicating fluids and gasoline. It is a colorless liquid with a distinct odor. Methanol is about half as potent as ethanol in its ability to cause CNS depression. Like ethylene glycol, it must undergo metabolic transformation before toxicity occurs. Alcohol dehydrogenase catalyzes the formation of formaldehyde, which is converted to formic acid. Formic acid is an inhibitor of mitochondrial cytochrome oxidase, causes histo-cytotoxic hypoxia and is responsible for the metabolic acidosis and ocular toxicity seen with methanol. Lactic acidosis may be seen late in the course of methanol toxicity. Neurologic, ophthalmologic and gastrointestinal symptoms dominate the clinical features of methanol toxicity. Features of toxicity include blurred vision, scintillations, loss of sight, unreactive pupils, papilledema, vomiting epigastric pain, convulsions and coma. An anion gap metabolic acidosis (formate anions) is characteristic.

Management

The serum methanol and ethylene glycol levels should be measured, however they can be estimated from the osmolar gap:

- [Methanol] = 3.2 × osmol gap
- [Ethylene glycol] = 6.2 × osmol gap

It should be noted that a high osmol gap is highly suggestive of ethylene-glycol or methanol poisoning however a low osmolar gap does not exclude the diagnosis. As the primary alcohol is metabolized to its toxic intermediates the osmol gap falls [11]. Therefore this diagnosis must be considered (and often treated) in patients with an unexplained metabolic acidosis without a high osmol gap.

Syrup of ipecac should be avoided, due to the risk of aspiration. The efficacy of activated charcoal is controversial.

- If pH < 7.25 sodium bicarbonate should be given to maintain the pH above 7.25. Large doses of bicarbonate maybe required to control severe life-threatening metabolic acidosis. Unlike the metabolites in lactic acidosis and ketoacidosis, the metabolites of ethylene glycol cannot be converted back to bicarbonate.
- Ethanol. Ethanol slows down the metabolism of both methanol and ethylene glycol reducing their toxicity. Ethanol should be given to patients with ocular symptoms, acidosis, or patients with a serum methanol or ethylene glycol level greater than 20 mg/dL.
  - Loading dose: 600 mg/kg IV
  - Maintenance dose: 100–150 mg/h. The infusion should be titrated to maintain a serum ethanol level of 100–150 mg/dL
- Fomepizole. Fomepizole is a potent inhibitor of alcohol dehydrogenase and has largely replaced ethanol in the treatment of ethylene-glycol and methanol poisoning. Fomepizole has been used successfully to treat methanol, ethylene glycol and diethylene glycol poisoning in humans. The currently approved dose consists of a loading dose of 15 mg/kg IV over 30 min, followed by 10 mg/kg every 12 h for 4 doses, then 5 mg/kg every 12 h thereafter [12].
- Hemodialysis. Hemodialysis facilitates removal of methanol, ethylene glycol and their metabolites. Hemodialysis should be instituted in all patients with a serum level above 50 mg/dl, patients with ocular symptoms (methanol) and in patients with a significant metabolic acidosis.
- In methanol poisoning folic/folinic acid (50–100 mg q 4) may mitigate the toxic effects of formate. Pyridoxine (100 mg) and thiamine 100 mg should be given daily in ethylene glycol poisoning.

Isopropyl Alcohol

In general isopropyl alcohol is less toxic than either methanol or ethylene glycol. It is metabolized to acetone. Neither a metabolic acidosis nor an ion gap characteristically occurs.

Signs and Symptoms

- dizziness, confusion, slurred speech, headache, ataxia, stupor and coma
- nausea, vomiting, abdominal pain , hemorrhagic gastritis, diarrhoea
- hypotension, bradycardia, rhabdomyolysis, hemolysis

Management

Treatment is essentially supportive. Hemodialysis is recommended in severe poisoning especially when accompanied by hypotension.

Digitalis

Signs and Symptoms

Nausea, vomiting diarrhea, fatigue, malaise, headache, confusion, delusions, hallucinations, blurred vision, disorder of green yellow color perception, visualization of halos around objects and cardiac arrhythmias, including paroxysmal atrial tachycardia (PAT) with 2–1 block, junctional tachycardia, varying degrees of heart block, ventricular and ectopy, ventricular tachycardia, ventricular fibrillation.

Management

- Due to high degree of tissue binding serum drug levels do not accurately reflect tissue levels. Diagnosis of toxicity is a clinical diagnosis. The majority of patients who show signs of toxicity have a serum level above 2 ng/mL, however some patients may exhibit toxicity below this level. Similarly patients may have a level above 2 ng/mL with no signs of toxicity.
- gastric lavage and activated charcoal (acute ingestion)
- continuous ECG monitoring; evaluate old ECG's
- correction of electrolytes. Beware: K+may increase acutely with digoxin overdose
- atropine for conduction disturbances
- phenytoin or lidocaine for arrhythmias of impulse formation
- temporary pacemaker for arrhythmias that are resistant to atropine
- Digoxin specific antibodies (digoxin FAB fragment antibodies) for serious arrhythmias and severe toxicity: Digoxin FAB (Digibond) dosing:
  - Extreme caution if patient in renal failure
  - serum levels not useful once FAB given
  - dose dependent on body load; each vial contains 40 mg FAB and binds 0.6 mg digoxin
  - Body load of digoxin = (serum digoxin concentration × 5.6 × weight in kg)/1,000. Dose (vials) = body load/0.6

Phenytoin

Signs and Symptoms

Nystagmus, ataxia, slurred speech, confusion, seizures

Management

Phenytoin is highly protein bound, therefore serum levels do not correlate well with toxicity. Free levels are a better indicator of toxicity (>2 μg/ml). Treatment includes, gastric lavage and repeated activated charcoal.

Lithium

Signs and symptoms

Mild to moderate toxicity occurs when the serum concentration is between 1.5 and 2.5 meq/L and severe toxicity when the levels are between 2.5 and 3.5 meq/L. Levels above 3.5 meq/L are life threatening. Symptoms however do not necessarily correlate with lithium levels and symptoms of toxicity may occur at therapeutic levels. Neurologic symptoms dominate the clinical picture of lithium toxicity. Symptoms include: nausea, vomiting, diarrhea, polyuria, blurred vision, muscular weakness, confusion, vertigo, increased deep tendon reflexes, myoclonus, choreoathetoid movements, urinary and fecal incontinence, stupor, coma, seizures, cardiac arrhythmia, cardiovascular collapse, death.

Predisposing Factors to Lithium Toxicity

- infections
- volume depletion
- gastroenteritis
- renal insufficiency
- congestive cardiac failure
- non steroidal anti-inflammatory drugs
- diuretics
- tetracycline

Management

Gastric lavage and supportive therapy. Activated charcoal is not effective in removing lithium. Dehydrated patients should be actively rehydrated, however forced saline diuresis is not recommended. Hemodialysis is indicated with levels above 4 meq/L or in patients with signs of serious toxicity and levels above 2 meq/L. The duration of dialysis should be guided by the serum levels. It is important to bear in mind that serum levels may rebound up following dialysis and require repeat dialysis.

Opiates

Signs and Symptoms

Constricted pupils, bradycardia, hypotension, hypothermia, pulmonary edema, respiratory depression, and coma.

Management

Management of opiate toxicity includes supportive therapy and the administration of the opiate antagonist naloxone (Narcan). Naloxone should be given as an initial intravenous bolus of 0.4 mg. A bolus of between 0.4 and 2 mg can be repeated every 3–5 min up to a total dose of 10 mg. Naloxone has a duration of action of about 45–60 min, which is considerably shorter than that of all the opiate agonists. Therefore, should the patient respond to the boluses of naloxone a continuous infusion should be started, by placing 8 mg into 1,000 mL 5 % D/W and infusing at a rate of 0.4–0.8 mg/h.

Cocaine

Cocaine is a naturally occurring substance found in the leaves of the rythroxylum coca plant. The plant is endogenous to South America, Mexico, Indonesia, and the West Indies. Cocaine hydrochloride is a water-soluble powder which can be absorbed through the nasal mucosa or injected intravenously. Cocaine hydrochloride has a high melting point and decomposes when burnt; this form of cocaine is therefore not suitable for smoking. Cocaine can be effectively smoked when it has been transformed into an alkaloid form, either "freebase" or "crack". Freebase and crack are the same chemical form of cocaine but are made using different techniques.

Cocaine abuse and dependence is epidemic in the United States. More than 50 million Americans have used cocaine, and >6 million Americans of all ages use it on a regular basis. The national prevalence of cocaine use is highest among 18- to 25-year olds but is becoming quite popular in the teenage group. In New York City between 1990 and 1992, 26.7 % of fatal injury victims had cocaine metabolites in their urine or blood [13]. Death after cocaine use is one of the five leading causes of death in the 15- to 44-year-old age group. Cocaine is the most frequent drug-related cause of emergency department (ED) visits in the United States. In 2006, hospitals in the United States provided a total of 113 million ED visits; the Drug Abuse Warning Network (DAWN) estimates that 958,164 of these visits involved an illicit drug, with cocaine being involved in 548,608 cases (both cocaine and alcohol in 101,588 cases) [14].

Analysis of street samples of cocaine has found an average purity rate of 40 % [15]. Therefore, adulterants represent more than half of the composition of all cocaine sold. Local anesthetics are among the most frequent contaminants of cocaine. Local anesthetics have psychoactive and reinforcing properties similar to

cocaine and can thus potentiate these effects when combined along with cocaine. Other additives include sugars, talc, and cornstarch. Cocaine acts by promoting the release and blocking the reuptake of neurotransmitters (norepinephrine, dopamine, and serotonin) at synaptic junctions, resulting in increased neurotransmitter concentrations. This results in sympathic and central nervous stimulation. Cocaine like other amide local anesthetic agents, blocks initiation and conduction of nerve impulses by deceasing axonal membrane permeability to sodium ions. At high doses cocaine has Class 1 anti-arrhythmic effects.

Cocaine can be smoked, nasally insufflated or injected intravenously. Smoking "crack" cocaine is a popular and potentially dangerous route of administration. Due to the large absorptive surface area of the lung, very high serum levels can be achieved within seconds. Nasal insufflation produces euphoria in about 3–5 min, with peak cocaine levels being achieved in 30–60 min. The biological half-life in the blood is about 1 h. Cocaine is metabolized to benzoylecgonine and ecgonine which are excreted in the urine. Less than 5 % of cocaine is excrete unchanged in the urine. Most urinary excretion occurs within 24 h of administration. Most assays for detecting cocaine measure urinary benzoylecgonine levels. This assay will be positive for up to 6 days after a single use and as long as 21 days with high dose long-term use.

Alcohol enhances the euphoric effects of cocaine. Each year, approximately 12 million Americans use this drug combination. Cocaethylene is produced by the liver from the combination of cocaine and ethanol. Cocaethylene produces intense dopaminergic stimulation in the brain and myocardium. The risk of sudden death is 25 times greater in persons who abuse both alcohol and cocaine than in those who use only cocaine.

Chest pain is the most frequent cocaine-related symptom and accounts for up to 40 % of cocaine-related ED visits. In the COCaine Associated CHest PAin (COCHPA) study, cocaine-associated MI occurred in 6 % of patients who presented to the ED with chest pain after cocaine use [16]. Cocaine-associated chest pain may be caused by not only MI but also by aortic dissection, and this must be considered in the differential diagnosis. In the COCHPA study, the sensitivity of an ECG revealing ischemia or MI to predict a true MI was only 36 %. The specificity, positive predictive value, and negative predictive value of the ECG were 89.9 %, 17.9 %, and 95.8 %, respectively. High-risk patients with ST-segment elevation or depression >1 mm, elevated serum cardiac markers, recurrent chest pain, or hemodynamic instability should be admitted to the ICU/CCU.

Complications Associated with the Use of Cocaine

- Sudden Death, due to arrhythmias, intracerebral bleeds, respiratory arrest, seizures, hyperthermia and myocardial infarction
- Psychiatric. Cocaine use is associated with altered behavior, psychological, personality and psychomotor alterations. Patients may have an underlying depression or personality disorder
- Cardiovascular
  - Myocardial ischemia and infarction. The coronary arteries are usually normal; cocaine increases myocardial oxygen demand, induces coronary

spasm and increases platelet aggregation and has a procoagulant effect by depleting protein C and antithrombin III
  - myocarditis and cardiomyopathy
  - severe hypertension
  - dissecting aortic aneurysm (often fatal)
  - arrhythmias, including supraventricular tachycardia, ventricular tachycardia, and fibrillation
- Pulmonary
  - asthma
  - thermal airway injury
  - non-cardiogenic pulmonary edema
  - pulmonary hemorrhage
  - COP (cryptogenic organizing pneumonia)
  - pneumothorax and pneumomediastinum
  - interstitial pneumonitis
- Neurological
  - seizures
  - hemorrhagic strokes
  - cerebral infarctions
  - ruptured aneurysms
- Renal
  - Rhabdomyolysis and acute renal failure
- Other
  - intestinal ischemia
  - gastroduodenal perforations
  - DIC
  - placental abruption
  - hyperthermia

The Management of Cocaine Toxicity

- CBC, serum chemistry, Troponins and CPK's PT, PTT, ECG, CXR as well as a toxicology screen should be perform in all patients with suspected cocaine toxicity.
- Agitation is best treated with benzodiazepines.
- Seizures. Solitary seizures usually do not require therapy. Status epilepticus, however requires aggressive treatment with intravenous benzodiazepines followed by a loading dose of phenytoin.
- Hyperthermia must be treated immediately with cool-water washes and/or with cooling blankets.
- Hypertension. This is usually self limiting. However, severe or sustained hypertension should be treated. Beta- blockers (including labetalol) may cause paradoxical worsening of hypertension as a result of unopposed alpha

stimulation. Severe hypertension is best treated with a combination of benzodiazepines and calcium channel blockers (nicardipine or clevidipine).

- Myocardial ischemia/infarction
  - In cases of myocardial ischemia or impending infarction calcium channel blockers (verapamil or diltiazem), aspirin and nitroglycerin are recommended. Nitroglycerin and verapamil reverse cocaine-induced hypertension and coronary arterial vasoconstriction; therefore, they are the agents of choice in treating patients with cocaine-associated chest pain.
  - Timely percutaneous coronary intervention by experienced operators in high-volume centers is preferred over fibrinolytics in ST-segment–elevation MI and is even more desirable in the setting of cocaine use [17].
  - Thrombolytics should be avoided in patients with cocaine-related infarction because of the increased risk of bleeding in these patients as well as the unreliable electrocardiographic criteria to identify myocardial infarction [17].
  - Beta-adrenergic blocking agents (including labetalol) may exacerbate cocaine-induced coronary arterial vasoconstriction, thereby increasing the magnitude of myocardial ischemia.
  - Nifedipine should not be used as this agent may potentiate seizures and death.

Carbon Monoxide Poisoning

Carbon monoxide (CO) intoxication is the leading cause of death due to poisoning in the United States. Epidemics of CO poisoning commonly occur during winter months and sources include: smoke from fires, fumes from heating systems burning fuels and exhaust fumes from motor vehicles. CO combines preferentially with hemoglobin to produce carboxyhemoglobin (COHb), displacing oxygen and reducing systemic arterial oxygen (O_2) content. CO binds reversibly to hemoglobin with an affinity 200–230 times that of oxygen. Consequently, relatively minute concentrations of the gas in the environment can result in toxic concentrations in human blood. The history of exposure and carboxyhemoglobin levels should alert the physician to this diagnosis. In the absence of exposure history, CO poisoning should be considered when two or more patients are simultaneously sick with similar non-specific symptoms.

Many victims of CO poisoning die or suffer permanent, severe neurological injury despite treatment. In addition, as many as 50 % of those who recover consciousness and survive may experience varying degree of more subtle but disabling neuropsychiatric sequelae. The features of acute CO poisoning are more dramatic than those resulting from chronic exposure. At low COHb levels, chronic cardiopulmonary problems, such as angina and chronic obstructive pulmonary disease, may be exacerbated, since cardiac myoglobin binds with great affinity and rapidly

reduces myocardial O_2 reserve. Chest pain due to myocardial ischemia may occur, as can cardiac arrhythmias. Subacute or chronic CO poisoning presents with less severe symptoms (e.g. nausea, vomiting, headache) and patients may initially be misdiagnosed as having other illnesses.

The clinical presentation of acute CO poisoning is variable, but in general, the severity of observed symptoms correlates roughly with the observed level of COHb. However, in terms of diagnostic value, the non-specificity of these presenting symptoms makes definitive diagnosis difficult. In addition, there have several reports of levels near zero with patients showing neurologic deficits ranging from partial paralysis to coma. With levels less than 10 % the patient is usually asymptomatic. As COHb increases above 20 %, the patient may develop headache, dizziness, confusion and nausea. Coma and seizures due to cerebral edema are common with levels greater than 40 %, and death is likely above 60 %. In reality, these symptom-level guidelines tend to be unreliable because of pre-hospital delays and early oxygen therapy and with concomitant poisoning from cyanide.

The mainstay of therapy for CO poisoning is supplemental O_2, ventilatory support and monitoring for cardiac arrhythmias. There is general agreement that 100 % oxygen should be administered prior to laboratory confirmation when CO poisoning is suspected. The goal of oxygen therapy is to improve the O_2 content of the blood by maximizing the fraction dissolved in plasma (PaO_2). Once treatment begins, O_2 therapy and observation must continue long enough to prevent delayed sequelae as carboxymyoglobin unloads. Unfortunately, there are no useful guidelines as to the length of the observation period.

The role of hyperbaric oxygen in the management of carbon monoxide poisoning is controversial, although both physiological data and some randomized-trial data suggest a potential benefit. Hyperbaric-oxygen therapy elevates arterial and tissue oxygen tensions, promoting carbon monoxide elimination, and also increases adenosine triphosphate production and reduces oxidative stress and inflammation [18]. A single-center, prospective trial showed that the incidence of cognitive sequelae was lower among patients who underwent three hyperbaric-oxygen sessions (an initial session of 150 min, followed by two sessions of 120 min each, separated by an interval of 6–12 h) within 24 h after acute carbon monoxide poisoning than among patients treated with normobaric oxygen (25 % vs. 46 %, $p=0.007$ and $p=0.03$ after adjustment for cerebellar dysfunction and stratification variables). However, a Cochrane review of six trials, including two published only in abstract form, did not support the use of hyperbaric oxygen for patients with carbon monoxide poisoning [19]. The Undersea and Hyperbaric Medical Society recommends hyperbaric-oxygen therapy for patients with serious carbon monoxide poisoning—as manifested by transient or prolonged unconsciousness, abnormal neurologic signs, cardiovascular dysfunction, or severe acidosis—or patients who are 36 years of age or older, were exposed for 24 h or more (including intermittent exposures), or have a carboxyhemoglobin level of 25 % or more [20].

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Chapter 46
Alcohol Withdrawal Syndrome

Approximately 11–15 million people report heavy alcohol use or alcohol abuse and dependence in the United States; not surprisingly alcohol related medical problems are commonly encountered in critically ill and injured patients. Alcohol withdrawal syndrome (AWS) consists of symptoms and signs arising in alcohol-dependent individuals, typically within 24–48 h of consumption of their last drink. Delirium tremens (DTs) a severe and potentially fatal form of AWS typically occurs 48–96 h after withdrawal of alcohol. AWS is usually mild and self limiting however approximately 5 % of patients develop DTs with a mortality approaching 15 %. Older age, underlying disease and comorbid liver disease are associated with an increased mortality risk. Although AWS occurs intentionally in those seeking abstinence, it may arise unexpectedly in an alcohol-dependent patients after admission to hospital. This disorder usually manifests itself on hospital day 3–5 and usually lasts under 1 week although prolonged DT's has been described.

Alcohol affects many of the regulatory systems in the body including an increase in the release of endogenous opiates, activation of the gamma-amino-butyric acid type A receptor (GABA-A), inhibition of the N-methyl-D-aspartate (NMDA) receptor, and interactions with both serotonin and dopamine receptors. Chronic exposure to the inhibitory GABA-A and excitatory NMDA receptors are thought to be involved in the pathogenesis of alcohol withdrawal.

The key clinical findings in AWS include:

- Anxiety
- Tremor
- Headache
- Disorientation
- Agitation
- Delirium
- Hallucinations
- Insomnia
- Anorexia, nausea, vomiting
- Diaphoresis

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- Hyperreflexia
- Tachycardia
- Hypertension
- Seizures
- Low-grade fever
- Hyperventilation

By definition in order to make the diagnosis of AWS, the patient must have two or more of the following after cessation or reduction of alcohol use that has been heavy or prolonged:

- Autonomic hyperactivity
  - sweating
  - tachycardia
- Increased hand tremor
- Insomnia
- Nausea or vomiting
- Transient hallucinations or illusions
- Psychomotor agitation
- Anxiety
- Tonic-clonic seizures

Although AWS is usually mild and does not require treatment, if severe it may be complicated by alcohol withdrawal seizures and delirium tremens. Delirium tremens (DTs), also known as alcohol withdrawal delirium, is the most severe manifestation of alcohol withdrawal, which occurs in approximately 5–20 % of patients experiencing alcohol withdrawal. DTs are characterized by:

- A severe hyperadrenergic state with hypertension, tachycardia, diaphoresis, tremors and low grade fever.
- Disorientation and agitation
- Impaired attention and consciousness
- Visual and auditory hallucinations

DTs usually occurs 24–72 h after cessation of drinking, and the condition carries a 5 % mortality rate in uncomplicated patients and up to a 25 % mortality rate in patients with concomitant complications. Withdrawal seizures are a complication occurring within the first 48 h of cessation. They typically occur as a single generalized tonic-clonic seizure or a brief episode of multiple seizures. Prolongation or recurrence of seizure activity necessitates an infectious disease workup (e.g., complete blood count, lumbar puncture, blood cultures). Of the patients whose symptoms have progressed to withdrawal seizures, approximately 33 % will progress to DTs. Standard withdrawal therapy including benzodiazepines is indicated for the treatment of withdrawal seizures. Phenytoin has no role in the management of withdrawal seizures. Placebo controlled trials have demonstrated phenytoin to be ineffective in the secondary prevention of alcohol withdrawal seizures [1, 2].

AWS can be classified as:

- Mild—tremors and minimal sympathetic symptoms
- Moderate—hallucinations and sympathetic symptoms
- Severe—seizure activity, fever, change in mental status and significant alteration in vital signs. Severe AWS is also known as delirium tremens (DT's).

The Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar)

The CIWA-Ar is a useful assessment tool to quantitate the severity of the AWS and to guide therapy [3]. The following features are given a score ranging from 0 to 7 (except orientation which is scored from 0 to 4);

- Nausea and vomiting
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Tactile disturbances
- Auditory disturbances
- Visual disturbances
- Headache/ fullness in head
- Orientation and clouding of sensorium

Scores on the CIWA-Ar range from 0 to 67 points. A score of 0–9 is considered minimal withdrawal, 10–19 mild to moderate withdrawal and >20 severe withdrawal.

Differential Diagnosis

In hospitalized medical and surgical patients who become confused or delirious it is ESSENTIAL to exclude organic, pharmacologic or metabolic causes of altered mental state. This is particularly so in elderly patients who "have a few drinks at night". To complicate matters AWS may co-exist with many of these disorders. The differential diagnosis includes but is not limited to:

- Hypoxia
- Sepsis
- Subdural hematoma
- Stroke
- Hypertensive encephalopathy/PRESS

- Metabolic/septic encephalopathy
- Epilepsy (alcohol reduces the seizure threshold)
- electrolyte disturbances, particularly
  - Hyponatremia (common in chronic alcoholics)
  - Hypophosphatemia
  - Hypocalcemia
- Endocrine and metabolic disturbances
  - Hypothyroidism
  - Adrenal insufficiency
  - Uremia
  - Liver failure
  - Wernicke's syndrome (delirium, amnesia, ataxia and opthalmoplegia)
- Pharmacologic
  - Serotonin syndrome
  - Benzodiazepine withdrawal
  - Drug induced psychosis/drug reactions

Treatment

- Benzodiazepines
  - Benzodiazepines form the cornerstone of therapy for AWS [4, 5]. Benzodiazepines are used primarily to control agitation.
  - All the benzodiazepines have similar modes of action (bind to benzodiazepine receptors on the GABA receptor) and all are metabolized by the liver. They differ, however, in their pharmacokinetic profile and the presence of active metabolites.
  - Symptom-triggered bolus dosing of benzodiazepines as compared to a fixed-dose approach is associated with less complications and a shorter period of treatment [6, 7].
  - A continuous infusion (titrated to control agitation) should however be considered in intubated patients requiring high dosages of a benzodiazepine.
  - Lorazepam is the drug of choice for the treatment of AWS in the ICU. The dosage depends on the severity of the withdrawal syndrome; some patients requiring in excess of 20 mg/h.
  - Lorazepam is the drug of choice in patients with alcohol withdrawal seizures. Lorazepam has been shown to reduce the risk of recurrent seizures.
  - Benzodiazepines should be used with much caution in patients with significant liver dysfunction. Benzodiazepines are contraindicated in patients with hepatic encephalopathy; indeed the benzodiazepine antagonist flumazenil has been used in the treatment of hepatic encephalopathy.

- Dexmedetomidine (DEX). Case series of DEX as adjunctive therapy in AWS suggests that it is benzodiazepine sparing, minimizes oversedation, decreases autonomic hyperactivity, reduces delirium and agitation and may prevent tracheal intubation [8–11]. Mueller et al. performed a randomized placebo-controlled study investigating the use of DEX as adjustive treatment in patients with AWS [12]. In this study the addition of DEX allowed for a significant reduction in the dose of benzodiazepines while maintaining symptom control. This drug appears to be a useful agent in the treatment of AWS, particularly when used as an adjunct with benzodiazepines.
- Haloperidol is an alternative agent for control of delirium and hallucinations [13]. Contrary to popular belief haloperidol DOES NOT reduce the seizure threshold and is not contraindicated in AWS [14, 15].
- Oral baclofen. Chronic alcohol use leads to downregulation of the GABA-A receptor subunits rendering the receptor less sensitive to benzodiazepines. The GABA-B receptor is more resistant to downregulation with chronic alcohol exposure. Baclofen is a pure GABA-B receptor agonist that has potential utility in patients with AWS. In a placebo controlled RCT, Lyon et al. demonstrated that baclofen 10 mg PO TID significantly reduced the dosage of benzodiazepines required for the management of patients with AWS [16]. Considering the ease of administration and its safety profile, baclofen would appear to be a very useful adjunctive agent for the management of AWS.
- Divalproex sodium (Depakote) and valproic acid have demonstrated benefit as adjective agents in AWS [17, 18]. It should hover be noted that these agents interfere with NH3 metabolism and should therefore be avoided in patients with hepatic dysfunction.
- Beta blockers and clonidine have been shown to be useful as adjunctive therapy. A β-blocker (metoprolol) and/or clonidine should be added in patients showing marked autonomic instability i.e. tachycardia and hypertension [19].
- In cases of AWS refractory to standard therapy propofol is very effective [20]. It is recommended that propofol be added to lorazepam once the dose of lorazepam exceeds 20–30 mg/h (in intubated patients) [20]. Propofol's mechanism of action is thought to be similar to the action of alcohol on the central nervous system. Propofol directly activates the GABA-A receptor increasing chloride conductance and inhibits the NMDA subtype of glutamate receptor. Propofol is associated with less cross tolerance than the benzodiazepines, is easily titratable, and has a rapid metabolic clearance.
- Chlorpromazine should be avoided as it is epileptogenic

Other Treatment Considerations

- Hypomagnesemia, hypokalemia and hypophosphatemia are particularly common in chronic alcoholic patients; these electrolyte disorders may become life threatening after the initiation of nutrition (refeeding syndrome). These electrolytes should be routinely supplemented and closely monitored.

- Alcoholic ketoacidosis may be seen in malnourished, non-diabetic alcoholic patients. Restoration of normal fluid balance with glucose-containing saline solution (with added thiamine) usually reverses this syndrome.
- Hypoglycemia may occur in the withdrawing alcoholic, since malnutrition and liver disease impair the storage of glycogen. This mandates monitoring the serum glucose in the withdrawing alcoholic.
- Patients who abuse alcohol are at risk of developing acute pancreatitis, erosive gastritis and acute alcoholic hepatitis. Hence, a serum amylase/lipase and liver function tests should be performed in all acutely ill alcoholic patients.
- Due to the increase sympathetic activity patients with coronary artery disease are at risk of myocardial ischemia

Prevention of Post-operative DT's

- The best way to prevent postoperative AWS and its complications is to screen for high-risk patients preoperatively.
- A scheduled low dose benzodiazepine regimen supplemented by symptom-triggered dosing is recommended in high risk patients.
- Intravenous ethanol has no role in the prevention of AWS [21].

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Chapter 47
Pregnancy Related Disorders

Critical illness is an uncommon but potentially devastating complication of pregnancy. In Western nations about 1 % of obstetric patients will require admission to an ICU. Mortality of critically ill obstetric patients ranges from 12 to 20 % [1]. The most common cause of maternal death in the ICU is ARDS [1].

The majority of pregnancy related critical care admissions occur postpartum. Antenatally, the pregnant patient is more likely to be admitted with diseases non-specific to pregnancy, such as pneumonia. Pregnancy-specific diseases resulting in ICU admission include obstetric hemorrhage, pre-eclampsia/eclampsia, HELLP syndrome, amniotic fluid embolus syndrome, acute fatty liver of pregnancy, and peripartum cardiomyopathy [2]. Physiologic changes associated with pregnancy may result in strain on organ systems with limited reserve and result in deterioration of pre-existing medical conditions (see Table 47.1). Hemorrhage, particularly post-partum, and hypertensive disorders of pregnancy remain the most frequent indications for ICU admission [2].

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Table 47.1 Cardio-respiratory changes during pregnancy

System	Changes
Respiratory	Increased alveolar ventilation
	Relative hypocarbia (P_aCO_2 25–32 mmHg)
	Reduced functional residual capacity
	Increased oxygen consumption
Cardiovascular	Increased cardiac output (40 %); increased SV 25 % increased HR 25 %
	Reduced total peripheral resistance
	Increased blood volume
	Increased plasma volume
	Physiologic anemia

Obstetrical Hemorrhage

Major obstetric hemorrhage is the leading cause of maternal mortality worldwide and is the most frequent indication for ICU admission. It may occur antepartum or postpartum [2].

Antepartum Hemorrhage

Antepartum hemorrhage occurs in 1 in 20 pregnant women; in the majority of cases, there is no risk to the mother or fetus. Causes include abruptio placentae, placenta previa, placenta accreta/increta/percreta, and uterine rupture [2]. The patient may present with pain, vaginal bleeding, uterine tenderness, and increased uterine activity. Depending on the location of bleeding, considerable blood loss may occur prior to diagnosis. Significant hemorrhage is associated with coagulopathy.

Postpartum Hemorrhage

Postpartum hemorrhage (PPH) involves blood loss of greater than 500 mL within 24 h regardless of the mode of birth. In 60–70 % of cases, the cause of PPH is failure of uterine contraction following delivery [2]. Uterine atony results in continuous bleeding that is often painless. Placental retention is the second most common cause of PPH (20–30 % of cases).

Management

An aggressive coordinated multidisciplinary approach is required. Initial management depends on the cause of the hemorrhage and whether delivery of the fetus has occurred. Where the hemorrhage occurs postpartum, uterine atony with or without

retained products should be suspected. Oxytocin should be administered, the bladder should be emptied, and the uterus massaged. The obstetrician should examine the genital tract for evidence of trauma. If bleeding persists, prostaglandin therapy – either intravenous prostaglandin E2 or 15-methyl prostaglandin F2α—is administered [2]. Patients should be volume resuscitated with crystalloids, blood and blood products. Surgical intervention should be considered with ongoing bleeding: arterial ligation, Cesarean hysterectomy, or uterine artery embolization.

Hypertension

Hypertension is one of the most common medical disorders affecting pregnancy. It complicates 12 % of pregnancies and is responsible for 18 % of maternal deaths in the United States [3]. The presentation of a patient with gestational hypertension may range from a mild to a life threatening disease process. In 2000, the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy defined four categories of hypertension in pregnancy, namely [4];

- chronic hypertension
- gestational hypertension
- preeclampsia
- preeclampsia superimposed on chronic hypertension.

Pre-eclampsia

Pre-eclampsia is a multiorgan disease process of unknown etiology characterized by the development of hypertension and proteinuria after 20 weeks of gestation. It is characterized by abnormal vascular response to placentation that is associated with increased systematic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial dysfunction [4]. Pre-eclampsia is a heterogeneous syndrome with a spectrum of maternal and fetal manifestations with probable multiple causative factors. Clinically pre-eclampsia can manifest as a maternal syndrome with hypertension and proteinuria with/without other multisystem abnormalities and/or a fetal syndrome characterized by fetal growth retardation, reduced amniotic fluid and abnormal oxygenation. In general, maternal and perinatal outcomes are usually favorable in women with mild pre-eclampsia developing beyond 34 weeks gestation. In contrast, maternal and perinatal morbidities and mortalities are increased in women who develop the disorder before 33 weeks gestation, in those with pre-existing medical disorders and in those from developing countries.

Several factors have been identified which increase the risk of pre-eclampsia, including:

- Primagravida
- Extremes of age
- Pre-eclampsia in previous pregnancy
- Family history of pre-eclampsia
- Obesity
- Preexistent thrombophilia
- Chronic hypertension
- Renal disease
- Men who have previously fathered a pre-eclamptic pregnancy

Generally, pre-eclampsia is regarded as a disease of first pregnancy. Eclampsia, the occurrence of seizures superimposed on the syndrome of pre-eclampsia, complicates 1 in 2,000 pregnancies in Western nations. In developing countries it is more common, being a common cause of maternal death. It is not clear what percentages of patients with eclampsia have the posterior reversible encephalopathy syndrome (PRES; see Chap. 28).

Diagnosis of Pre-eclampsia

Pre-eclampsia is defined as the presence of hypertension with a blood pressure of at least 140/90 mmHg on at least two occasion 4–6 h apart and proteinuria of 300 mg or more in 24 h. If a 24-h urine sample is not available, proteinuria is defined as a protein concentration of 300 mg/L or more in at least two random samples taken at least 4–6 h apart. However a quantitative 24 h urine protein should be measured in all patients with suspected pre-eclampsia. The signs and symptoms of pre-eclampsia include:

Symptoms

- Severe headache
- Fatigue
- Epigastric/RUQ pain
- Vomiting
- Visual disturbances
- Swelling of hands, face and feet

Signs

- Hypertension (>140/90 mmHg)
- Proteinuria (>300 mg/day)

- Hyperreflexia
- Oliguria
- Seizures
- Focal neurological signs
- Increased serum creatinine (>0.7 mg/dL)
- Increased serum uric acid (>5.8 mg/dL)
- Intrauterine growth retardation
- Oligohydramnios
- HELLP
  - Reduced platelet count (<100,000/μl)
  - Elevated liver enzymes (AST > 70 IU/L)
  - Evidence of microangiopathic hemolytic anemia
    LDH > 600 IU/L
    Bilirubin > 1.2 mg/dL
    Decreased haptoglobin
    Schizocytes on peripheral smear

Patients are considered to have severe pre-eclampsia when the systolic blood pressure is at least 160 mmHg, the diastolic ≥110 mmHg or in patients with severe proteinuria (≥5 g/day). Furthermore, patients with pulmonary edema, oliguria, severe central nervous system symptoms or the HELLP (hemolysis, elevated liver enzymes and thrombocytopenia) or posterior reversible encephalopathy (PRES) syndromes are considered to have severe pre-eclampsia. It should be recognized that hypertension or proteinuria may be absent in 10–15 % of women who develop the HELLP syndrome and in up to 35 % of those who develop eclampsia. Women with systemic lupus erythematosus (SLE) may develop lupus nephritis during pregnancy which may be confused with pre-eclampsia, which is itself more common in women with SLE. An auto-immune workup should be considered in women with severe proteinuria, oliguria and/or progressive renal dysfunction. As the treatment of these two disorders is quite different, a renal biopsy may be required to confirm the diagnosis. The complications of pre-eclampsia include:

Central Nervous System

- Eclampsia (seizures)
- Cerebral hemorrhage
- Central venous thrombosis
- Hypertensive encephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES); see Chap. 63
- Seizures/status epilepticus
- Altered mental status
- Cortical blindness

Hepatic

- Jaundice
- Subcapsular/intrahepatic hematoma
- Hepatic rupture

HELLP Syndrome

- Thrombocytopenia
- Hepatic dysfunction
- Microangiopathic hemolytic anemia

Coagulation System

- Disseminated intravascular coagulation
- Microangiopathic hemolysis
- Hematoma
- Hematuria
- Pulmonary embolism

Other

- Acute renal failure
- Cardiogenic/noncardiogenic pulmonary edema
- Infection/sepsis
- Placenta infarction
- Placenta abruption

Fetal

- Death
- Preterm birth
- Intrauterine growth retardation

HELLP Syndrome

The acronym HELLP describes a variant of severe pre-eclampsia characterized by hemolysis, elevated liver enzymes, right upper quadrant pain and thrombocytopenia. The development of HELLP syndrome places the pregnant patient at increased

risk for morbidity and death. The HELLP syndrome usually develops suddenly during pregnancy (27–37 weeks gestation) or in the immediate puerperium. The HELLP syndrome occurs in up to 20 % of pregnancies complicated by severe pre-eclampsia. The clinical presentation of the HELLP syndrome is variable; 12–18 % of affected women are normotensive and 13 % do not have proteinuria [5, 6]. Hepatic injury appears to play a central role in the HELLP syndrome and it has been proposed that placenta-derived proteins damage hepatocytes. Indeed, Strand et al. demonstrated apoptosis in the liver of HELLP patients and cytotoxicity of human hepatocytes exposed to the serum of patients with HELLP [7]. In many respects the HELLP syndrome mimics many of the features of the systemic inflammatory response syndrome (SIRS) which are superimposed on pre-eclampsia.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a clinico-neuro-radiological entity characterized by headache, vomiting, altered mental status, blurred vision and seizures with neuroimaging studies demonstrating white-gray matter edema involving predominantly the posterior region of the brain (see Chap. 28) [8]. Pre-eclampsia is the commonest cause of PRES. Patients may present with PRES post-partum without the classic pre-eclamptic signs. Furthermore, status epilepticus has been reported to occur in these patients. It is unclear what percentage of patients previously diagnosed with eclampsia or patients with severe-eclampsia and neurological signs/symptoms in actuality met the diagnostic criteria for PRES. This distinction is important as patients with PRES may require aggressive management of raised intracranial pressure.

Treatment of Pre-eclampsia

Initial therapy of pre-eclampsia includes cautious volume expansion, magnesium sulfate for seizure prophylaxis and blood pressure control. Delivery is the definitive treatment for pre-eclampsia and eclampsia. The decision to deliver involves balancing the risks of worsening pre-eclampsia against those of prematurity. Delivery is generally not indicated for women with mild preeclampsia until 37–38 weeks gestation and should occur by 40 weeks.

Magnesium sulphate prophylaxis reduces the risk of eclampsia and its complications, particularly in women with severe pre-eclampsia [9, 10]. In addition, magnesium sulphate reduces the rate of progression of disease in those with mild pre-eclampsia without substantive harmful effects on either mother or child. Magnesium sulphate is clearly the anticonvulsant of choice for treating eclampsia, with substantial reduction in the risk of further seizures compared with diazepam or phenytoin. It is also better at preventing maternal death than diazepam. Magnesium sulfate is usually given as a loading dose of 4–6 g in 100 cc 5 % dextrose 1/4 NS

over 15–20 min followed by a constant infusion at a rate of 1–2 g/h. Magnesium may be given for a total of 24 h or for up to 24 h postpartum. Magnesium is a membrane stabilizer and muscle relaxant. Side effects include, flushing, hypotension, muscle weakness, respiratory depression and confusion. As magnesium is renally excreted, the urine output should be closely monitored and adjustment of the infusion dose is required in patients with impaired renal function [9]. Reduction or loss of tendon reflexes precedes respiratory depression. Tendon reflexes and the respiratory rate should therefore be checked on an hourly basis and magnesium sulphate administration adjusted as appropriate to prevent toxicity [9]. While monitoring of magnesium serum levels is not usually required [9, 11], the serum level should be checked in women with suspected toxicity (usual upper limit of therapy is 7.0 mg/ dL).

The next step in the management of pre-eclampsia is to reduce the blood pressure to a safe range being diligent to avoid significant hypotension. The objective of treating severe hypertension is to prevent intracerebral hemorrhage and cardiac failure without compromising cerebral perfusion or jeopardizing uteroplacental blood flow which is already reduced in many women with pre-eclampsia [12]. Studies of women with mild pre-eclampsia have shown no benefit with the use of antihypertensive therapy (labetalol or calcium channel blockers). Anti-hypertensive therapy is therefore given primarily to prevent complications in the mother. The Working Group Report on High Blood Pressure in Pregnancy recommends initiation of antihypertensive therapy for a diastolic blood pressure of 105 mmHg or greater [4]. Furthermore, most authorities and the current guidelines from the American College of Obstetricians and Gynecologists recommend keeping the systolic blood pressure between 140 and 160 mmHg and the DBP between 90 and 105 mmHg [4, 12, 13]. This recommendation is supported by a recent study which demonstrated that a systolic blood pressure greater than 160 mmHg was the most important factor associated with a cerebrovascular accident in patients with severe pre-eclampsia and eclampsia [14]. This would suggest that a systolic blood pressure between 155 and 160 mmHg should be the primary trigger to initiate antihypertensive therapy in a patient with severe pre-eclampsia or eclampsia [14, 15]. It should be noted that patients with pre-eclampsia/eclampsia may have a very labile blood pressure; this fact together with the narrow target blood pressure range dictate that these patients be closely monitored in an ICU preferably with an arterial catheter. Intracerebral hemorrhage is a devastating complication in these patients which can be avoided by scrupulous attention to blood pressure control.

Anti-hypertensive Agents for the Treatment of Pre-eclampsia

Hydralazine has been recommended as the drug of choice to treat severe pre-eclampsia and eclampsia since the early 1970s [16]. However, hydralazine has a number of properties that make it “unsuitable” for this indication. Its side effects

(such as headache, nausea and vomiting) are common and mimic symptoms of deteriorating pre-eclampsia. Most importantly, however, it has a delayed onset of action, an unpredictable hypotensive effect and a prolonged duration of action. These properties may result in a precipitous hypotensive overshoot compromising both maternal cerebral blood flow and uteroplacental blood flow. Indeed, in a meta-analysis published by Magee and colleagues hydralazine was associated with an increased risk of maternal hypotension which was associated with an excess of cesarean sections, placental abruptions and low Apgar scores [17]. Based on the available data hydralazine should not be used as first line treatment of severe hypertension in pregnancy.

Parenteral labetalol is rapidly replacing hydralazine as the most commonly used antihypertensive agent in the treatment of severe pre-eclampsia (see Chap. 18). Nicardipine, a dihydropyridine calcium channel blockers appears to be a safe and effective alternative agent for the control of blood pressure in patients with severe pre-eclampsia. Nitroglycerin, nitroprusside ACE and ARB's are contraindicated in patients with pre-eclampsia.

Corticosteroids and Plasmapheresis as Adjunctive Treatment of HELLP

The developed of a SIRS-like condition with increased levels of pro-inflammatory cytokines in patients with HELLP led to the consideration of the use of corticosteroids to treat this disease [18]. A number of retrospective cohort studies have been published which suggest improved maternal and fetal outcome with the use of corticosteroids. In addition, four small randomized controlled studies (RCT) have been conducted which randomized participants to standard therapy or dexamethasone. A meta-analysis of these RCT's demonstrated no significant difference in maternal mortality or morbidity or fetal outcome, however hospital stay was significantly shorter in the women allocated to dexamethasone [19]. Furthermore, taken together most of the studies demonstrate that corticosteroids produce a significant improvement in the hematologic abnormalities associated with the HELLP syndrome together with a more rapid improvement of the clinical features such as mean arterial pressure and urine output. Most of the studies to-date used dexamethasone in a dose of 10 mg (equivalent to 200 mg hydrocortisone) every 12 h for 24–36 h. In should be noted that the placenta has a high concentration of the enzyme 11 β-hydroxysteroid dehydrogenase (11 β–HSD) type 2, which converts cortisol to the inactive metabolite cortisone and prednisolone to prednisone [20]. Inactivation, of the synthetic corticosteroid dexamethasone and betamethasone by the placenta is negligible [21]. With our increased understanding of the role of corticosteroids in SIRS, dexamethasone in a dose of 10 mg every 12 h appears appropriate. However, we would recommend treatment for at least 5 days followed by a slow taper (see Chap. 39).

Due to the presence of circulating pro-inflammatory mediators and hepatotoxic factors in the serum of patients with the HELLP syndrome, plasmapheresis would appear to be a logical treatment strategy. Indeed, a number of cases have been reported in which plasmapheresis appeared to be associated with improved patient outcome [22, 23]. This treatment modality should be considered in patients with severe HELLP syndrome who have failed traditional treatment measures.

Acute Fatty Liver of Pregnancy

Acute fatty liver disease of pregnancy (AFLP) occurs in about 1 per 10,000 pregnancies characterized by hepatic microvesicular steatosis and manifests in the third trimester. Without early diagnosis and treatment (fetal delivery), the patient may develop acute liver failure and hepatic encephalopathy [2]. AFLP is a mitochondrial disorder related to inherited mutations that cause a deficiency of the long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD), a fatty acid beta-oxidation enzyme.

Amniotic Fluid Embolus Syndrome

Amniotic fluid embolus syndrome is a devastating complication that usually occurs within 24 h of delivery. It manifests with acute severe hypoxic respiratory failure, associated with shock, disseminated intravascular coagulopathy (DIC), confusion and seizures. The pathophysiology of amniotic fluid embolus syndrome is unclear. There is no specific therapy and management is largely supportive.

Sepsis in Pregnancy

Pregnancy predisposes women to four specific infectious complications, namely pyelonephritis, chorioamnionitis (including septic abortion), endometritis (often following Cesarean delivery) and pneumonia. Acute pyelonephritis is the most common severe medical complication of pregnancy and is the leading cause of septic shock in the pregnant patient. The disease most commonly presents after the first trimester with fever, lumbar pain, shaking chills, nausea, and vomiting. The majority of infectious are caused by *E. coli*. 'Puerperal sepsis' or 'puerperal fever' is an umbrella term for a variety of infections that occur in the puerperium. The leading risk factor for puerperal sepsis is Cesarean delivery. Endometritis is most commonly associated with group A streptococcal infection, although Staphylococcus, coliform, and anaerobes may also be present. Hand washing and disinfectants dramatically decreased the incidence of puerperal fever. Pre-emptive

antibiotics are administered if prolonged rupture of the membranes has occurred, to treat amnionitis, or if the woman has a fever and a foul-smelling vaginal discharge. The principles of the management of the septic pregnant patient does not differ from that of non-pregnant patients (see Chap. 12). Mechanical ventilation in the pregnant patient is discussed below.

Respiratory Failure in Pregnancy

In the pre-H_1N_1 influenza era, ARDS was reported to account for as many as 19 % of obstetrical ICU admissions with a maternal mortality as high as 44 % [24–27]. The commonest causes of ARDS included community acquired pneumonia (especially in HIV positive patients), aspiration pneumonitis, septic abortion and eclampsia/pre-eclampsia [24–27]. H_1N_1 influenza has a predilection to cause severe ARDS in pregnant patients [28]. Consequently, the number of pregnant patients admitted to the ICU with severe respiratory failure increased dramatically during the H_1N_1 pandemic of 2009.

The clinical criteria for intubating a pregnant patient are similar to those in non-pregnant patients and include increased work of breathing, mental status deterioration, hemodynamic instability, and inability to protect the airway or manage secretions [29]. Blood gas criteria for intubation may vary depending on the gestational age of the pregnancy, but later in pregnancy, which is when most cases of ARDS in pregnancy occur, a normal P_aCO_2 should be interpreted as a sign of impending respiratory failure. Inability to maintain a P_aO_2 of > 70 mmHg or an S_pO_2 of > 95 %, with conservative therapy should also be interpreted as a sign of respiratory compromise requiring intubation [29].

The physiologic changes of pregnancy have a significant impact on the pathophysiology of ARDS. The mechanical effect of pregnancy causes a decrease in chest wall compliance particularly in late pregnancy [30]. This compounds the decrease in lung compliance associated with ARDS, causing a significant fall in total compliance. The functional residual capacity and the residual volume decrease with advancing pregnancy [30]. These changes increase the risk of alveolar collapse, particularly in the dependent areas of the lung. Although a P_aO_2 of 55 mmHg (7.5 kPa) and a S_aO_2 of 88 % is well tolerated in non-pregnant patients with ARDS, "classic teaching" states that fetal oxygenation requires a P_aO_2 of >70 mmHg which corresponds to a maternal S_pO_2 of about 95 % [29, 31].

There are no published studies which have investigated a low V_T ventilatory strategy in pregnant women with ARDS. A low V_T strategy in these patients may result in severe lung derecruitment. Furthermore, due to increased oxygen demands a low V_T ventilatory strategy may be unable to maintain adequate arterial oxygenation. Permissive hypercapnia has not been studied in pregnancy. Theoretically, maternal respiratory acidosis could lead to fetal acidosis, shift of the fetal oxyhemoglobin dissociation curve to the right and consequently impaired oxygenation of fetal hemoglobin. An animal model suggested that maternal hypercapnia (P_aCO_2

greater than 60 mmHg) may lead to increased uterine vascular resistance and decreased uteroplacental blood flow [32]. However, good pregnancy outcomes have been reported with the use of permissive hypercapnia in a few pregnant patients with status asthmaticus [33]. Observational data on the higher V_T ventilation technique that predated the current standard suggest that pregnant women with ARDS are even more susceptible to barotrauma than the non-pregnant population [25, 27]. This may have been due to the higher airway pressures required to deliver a set tidal volume because of the decreased extra-thoracic compliance. These data suggest that in pregnant patients undergoing a low V_T ventilatory strategy, esophageal manometry may be essential to optimize PEEP and tidal volume. In patients who have "failed" a low-tidal-volume ventilatory strategy, APRV should be considered. APRV may be an ideal ventilatory mode in pregnant patients with severe ARDS, as the increased mean alveolar pressure with short release time will recruit collapsed dependent lung while preventing over-distension of ventilated alveoli. We have previously reported two pregnant patients with life threatening ARDS who were successfully managed with APRV [34]. We believe that APRV should be considered as an alternative ventilatory strategy in pregnant patients with severe ARDS. During the H_1N_1 outbreak many patients failed "conventional" modes of ventilation and required inhaled nitric oxide (NO), high-frequency oscillatory ventilation and/or extra-corporal membrane oxygenation (ECMO) [28, 35, 36].

Shortly after beginning care for a pregnant woman with ARDS, fetal assessment should take place and plans for possible delivery should be made. These plans are influenced by the gestational age of the fetus, fetal status, maternal status, and the gestational age at which the treating institution can support a preterm infant, which is often 24–26 weeks for larger centers [29]. As is often the case in the management of critically ill pregnant women, difficult decisions have to be taken in circumstances when optimal management of the mother may reduce the chance of a good fetal outcome

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Chapter 48
The Geriatric ICU Patient

Population aging is accelerating rapidly worldwide, from 461 million people older than 65 years in 2004 to an estimated 2 billion people by 2050 [1]. Age is associated with an increasing prevalence of multiple diseases and disabilities. Age is also associated with a decline of the functional reserve of multiple organ systems and a progressive restriction in personal and social resources. It is therefore not surprising that elderly patients will utilize a disproportionate share of health care resources. By virtue of having lived longer, increasing numbers of elderly patients (age >65 years) are being admitted to ICU's and this trend is only likely to escalate in the years to come. In the US elderly patients currently account for 42–52 % of ICU admissions and for almost 60 % of all ICU days [2–5]. However, a disproportionate number of these ICU days are spent by elderly patients before their death. Thirty percent of Medicare expenditures are attributable to the 5 percent of beneficiaries who die each year, resulting in per-capita spending on decedents that is six times as great as for non-decedents [6]. Clearly ICU utilization by the elderly will increase exponentially over the next decades. The reality of our aging society dictates that we must focus on how to best care for the elderly who develop critical illness and how to more appropriately utilize critical care services.

The Physiology of Aging

Aging is a process of gradual and spontaneous change that places healthy adults at risk for decline with diminished reserves in most physiologic systems and with an exponentially increasing vulnerability to most diseases and to death. The process of aging is a continuum progressing throughout the individual's life. Unlike pathologic conditions, the aging process affects all individuals. It is a process that is genetically programmed but modified by environmental influences, so the rate of aging can vary widely among people. At the cellular level, aging can be defined as a progressive deterioration of structure and function that occurs over time [7]. Cellular aging

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is believed to result from the lifelong accumulation of molecular and cellular damage caused by many mechanisms that are regulated by a complex system of maintenance and repair. The factors that lead to primary aging are poorly understood, however, the interplay between genetics and oxidant damage is believed to play a major role [7, 8].

The changes in cardio-pulmonary, renal, immune and musculoskeletal systems with aging have important implications for the critical care physician and will be briefly reviewed.

Cardiovascular Changes

Cardiovascular performance impacts on critical illness in the elderly in two ways. First, age is a major risk factor for cardiovascular disease, which accounts for over 40 % of deaths in those aged 65 years and above [9]. Second, the effect of aging on cardiovascular structure and function has implications for hemodynamic support of the elderly. A substantial lack of cardiac reserve is noted by the age of 70. This lack of reserve may not affect the daily functioning of a "well" older individual, but when this same older person experiences physiological stress such as blood loss, hypoxia, sepsis or volume depletion, the lack of reserve becomes apparent through cardiac dysfunction

Aging results in an increase in arterial and myocardial stiffness. Increased arterial stiffness is manifested by an increased systolic arterial pressure, pulse pressure and pulse wave velocity whereas increased myocardial stiffness is manifested by impaired left ventricular diastolic filling [10, 11]. Increased arterial stiffness increases cardiac workload, further aggravating already existing adverse changes in left ventricular structure and function. With aging there is a progressive decrease in the number of myocytes and an increase in myocardial collagen content. Increased cardiovascular stiffness is usually attributed to the development of fibrosis. Ventricular relaxation which is more energy dependent than ventricular contraction, and therefore more oxygen dependant also becomes impaired with aging. Diastolic dysfunction is therefore common in the elderly, particularly in those patients with systemic hypertension [11–14]. Indeed, diastolic dysfunction is responsible for up to 50 % of cases of heart failure in patients over the age of 80 years. These cardiovascular changes result in a decrease in left ventricular ejection fraction with compensatory myocyte hypertrophy; consequently left ventricular mass index increases with aging [11, 13]. Resting cardiac output is maintained despite the increased afterload imposed by the stiffening of the outflow tract. However maximal heart rate, ejection fraction and cardiac output decrease with aging. There is decreased responsiveness to β-adrenergic receptor stimulation and decreased reactivity to baroreceptors and chemoreceptors with aging. Fibrosis and calcification of the fibrous skeleton of the heart, composed of the annular rings and fibrous trigones, together with calcification of the bases of the aortic cusps develops. These changes contribute to the high incidence of sick sinus syndrome, atrial arrhythmias and bundle branch blocks.

In younger persons, cardiac output is increased predominantly by increasing heart rate in response to β-adrenergic stimulation. With aging there is a relative "hyposympathetic state" in which the heart becomes less responsive to sympathetic stimulation, possible secondary to declining receptor function. The aging heart, therefore increases cardiac output predominantly by increasing ventricular filling (preload) and stroke volume rather by an increase in heart rate. Because of the dependence of preload, even minor hypovolemia can result in significant cardiac compromise. The dependence on preload to maintain cardiac output is made even more important by the diastolic dysfunction associated with aging. However, due to decreased ventricular compliance overzealous fluid resuscitation is likely to cause pulmonary edema. These changes dictate scrupulous management of the elderly patient's volume status. The contribution of left atrial systole to left ventricular filling increases with age [15]. Atrial fibrillation is therefore poorly handed by elderly patients particularly those with marked diastolic dysfunction.

Changes in Respiratory Function

Declining respiratory function in the elderly is the result of changes in both the chest wall and the lung [16, 17]. There is a progressive decrease in chest wall compliance caused by structural changes of kyphosis and vertebral collapse. In the lung there is a loss of elasticity with collapse of the small airways and uneven alveolar ventilation with air trapping. Uneven alveolar ventilation leads to ventilation perfusion mismatch, which in turn causes a decline in arterial oxygen tension of approximately 0.3 mmHg/year from the age of 30 years. There is a progressive decline in respiratory muscle and diaphragmatic strength resulting in a decline in maximal inspiratory and expiratory force by as much as 50 % (see below). The control of ventilation is also affected by aging. Ventilatory response to hypoxia and hypercapnia fall by 50 % and 40 % respectively.

Changes in Renal Function

There is a marked decline in renal function with aging. Between the ages of 25 and 85 years, approximately 40 % of the nephrons become sclerotic. The remaining functional units hypertrophy in a compensatory manner. Sclerosis of the glomeruli is accompanied by atrophy of the afferent and efferent arterioles and a decrease in renal tubular cell number. Renal blood flow falls by approximately 50 %. Functionally, there is a decline in glomerular filtration rate of approximately 45 % by age 80 years. Serum creatinine, however, remains unchanged because there is a concomitant decrease in lean body mass and, thus a decrease in creatinine production. Estimates of GFR in the healthy aged can be made from the serum creatinine by using the formula derived by Cockroft and Gault [18]. This formula must be used

with caution in critically ill patients as the serum creatine may be altered by factors other than the GFR including numerous medications and increased muscle breakdown due to sepsis, trauma, protein catabolism and immobility.

Immune System Changes

A progressive decline in the integrity of the immune system occurs with aging [19–22]. The age related changes are most evident in the peripheral T cell pool, which show signs of decreased reactivation to challenge with antigens [21–23]. The age related changes in the immune system, together with the increased burden of chronic disease may explain the increased incidence of infections in the elderly.

Body Composition and Muscle Mass

Body composition changes dramatically with aging. There is an increase in body fat and a decrease in lean muscle mass by up to 40 % at age 80 years [24]. The rate of loss of lean body mass accelerates after the age of 60 years. The loss of muscle mass or "sarcopenia" in the elderly is strongly associated with impaired mobility, increased risk of falls, lower quality of life and increased morbidity and mortality.

Generally loss of lean body mass is paralleled by changes in diaphragmatic mass; sarcopenia of the elderly is therefore associated with reduced diaphragmatic function. Critical illness is associated with loss of lean body mass. Elderly patients demonstrate greater muscle catabolism during critical illness than their younger counterparts. This is compounded by mechanical ventilation which results in rapid diaphragmatic atrophy. Decreased diaphragmatic mass is strongly implicated in the failure to wean from mechanical ventilation. Consequently, elderly patients are at a greater risk of weaning failure, with ongoing ventilation resulting in further diaphragmatic weakness. This sets up a vicious cycle whereby it may become increasing difficult to wean elderly patients from mechanical ventilation. This may explain the poor outcome of elderly patient's requiring mechanical ventilation (see below).

The Outcome of Elderly Patients Admitted to the ICU

With the projected exponential increase in the number of elderly patients and the increasing burden of chronic disease how best should we select which patients are likely to derive the most benefit from admission to the ICU? The current guidelines of the Society of Critical Care Medicine state that "*in general ICU's should be reserved for those patients with reversible medical conditions who have a reasonable prospect of substantial recovery*." [25] Despite this recommendation,

almost all patients with serious and life-threatening illnesses in the USA regardless of their prognosis or prospect of recovery are admitted to an ICU, unless the patient or his/her surrogate specifically declines ICU admission. It is therefore exceeding uncommon for intensivists in the USA to refuse ICU admission; if a bed is not immediately available, one is "made." This contrasts to the situation in most Western nations in which not all requests for an ICU bed are honored. Indeed, refusal of ICU admission is common, with a rate that varies from 24–46 % [26–30]. Advanced age and poor functional status are reported to be the commonest reasons for ICU refusal [26, 27, 30, 31].

In general severity of illness, co-morbidities, pre-morbid functional status and age appear to be the most important factors determining ICU and hospital survival [32–35]. While the ICU and hospital mortality of older patients is greater than that of younger patients, in multivariate analyses the contribution of age to ICU mortality is generally smaller than that for disease severity [36]. However, the requirement for mechanical ventilation appears to be an important determinant of both short and long-term outcome in elderly patients. Ely and colleagues reported that the 28-day survival of patients with acute lung injury decreased significantly with increasing age (74.6 % vs. 50.3 % for those older and younger than 70 years respectively) [37]. Using data from the Nationwide Inpatient Sample, Behrendt demonstrated that both the incidence and mortality from acute respiratory failure increased significantly with aging [38]. Nava and colleagues compared the use of non-invasive venation (NIV) with standard care in a cohort of patients >75 years [39]. In this study the requirement for mechanical ventilation and hospital mortality were significantly lower in the NIV group. In light of these findings non-invasive ventilation should be considered as an alternative to mechanical ventilation in elderly patients particularly those with poor functional status.

ICU survival may not be the most appropriate end-point when evaluating the role of critical care, particularly in the elderly. The goal of critical care medicine is to restore patients to a level of functioning similar to that of their pre-admission status and to return patients back into the community from which they came. Not infrequently, ICU patients are discharged to subacute facilities with persistent organ failure, where they linger for months before ultimately dying. Therefore, post-discharge disposition and long term survival (1–3 years) may be more important than hospital survival in evaluating the role of ICU admission. Wunsch and colleagues studied the 3 year outcomes of Medicare beneficiaries who survived their ICU stay [40]. In this study the 3 year mortality was 39.5 % for ICU survivors, 34.5 % for matched hospital controls and 14.9 % for general controls. However, those receiving mechanical ventilation had a substantially increased mortality compared to the hospital controls (57.6 % vs. 32.8 %). Kaarlolo and colleagues assessed the long term survival and quality of life of 882 elderly patients (>64 years of age) as compared to 1,827 controls (<65 years of age) admitted to a medical-surgical ICU [41]. The cumulative 3-year mortality rate among the elderly patients were 57 % as compared to 40 % in the control group ($p < 0.05$). The majority (88 %) of the elderly survivors assessed their present health status as good or satisfactory.

An analysis of the available data suggests that functional elderly patients have a favorable long-term outcome following ICU admission. This suggests that age

alone should not be used in making ICU triage decisions. The decision to admit an elderly patient to an ICU should be based upon the patient's comorbidities, acuity of illness and pre-hospital functional status which includes "quality of life" and whether the patient was living independently or was admitted from a subacute/chronic health care facility. However, elderly patients' who may require prolonged mechanical ventilation appear to do poorly. A time limited trial in the ICU may be appropriate in such patients. Furthermore, the 1 year survival of the oldest of the old is particularly poor and this factor should be considered in these patients. The patients preferences (or surrogates best estimate of the patient's wishes) with regards to mechanical ventilation and other forms of life sustaining treatment should be considered in all triage decisions. For dying patients with irreversible disease admission to the ICU is frequently inappropriate and the care of these patients should be primarily focused on a palliative approach allowing a dignified death.

Trauma and the Elderly Patient

Geriatric patients are at high risk of traumatic injuries, particularly those patients with diminished functional status. Falls are the most common mechanism of injury in the elderly population and are responsible for significant morbidity, mortality and medical costs [42–44]. Pedestrian- motor vehicle injuries affect the elderly disproportionately and result in a higher mortality as compared with other age groups. Perdue and colleagues reported that trauma patients older than 65 years were 4.6 times likely to die than younger patients [45]. A number of factors contribute to the increased mortality of elderly patients after traumatic injuries, most notably their limited physiologic reserve together with the presence of comorbid cardio-pulmonary disease. Elderly patients compensate poorly following blood loss due to limited chronotropic and inotropic reserve (hypo-adrenergic state), diastolic dysfunction, and the inability of the kidney to conserve fluid. Many elderly patients are prescribed beta-blockers; these drugs further reduce the ability of the patient to compensate for decreased intravascular volume. In addition, elderly patients are frequently treated with Coumadin and/or anti-platelet drugs which increase the propensity for uncontrolled hemorrhage.

Evidence suggests that many injured elderly patients are under-triaged despite the increased risk of death and complications. One possible cause of under-triage is the late presentation of physical findings indicating hypovolemia. Elderly patients who have severe injuries are best treated in trauma centers where the outcome is reported to be improved [46].

Surgery and the Elderly

The operative mortality and incidence of postoperative complications are increased in elderly patients undergoing elective surgery [47]. It is not uncommon for elderly patients who appear fit and healthy (physiologic age less than chronologic age) to

do poorly following elective surgery (the "knife" is the great equalizer). The decreased physiologic reserve and increased incidence of comorbidities probably accounts for this finding. Liu et al. reported an operative mortality of 4.6 % and a postoperative complication rate of 25 % in a cohort of octogenarians undergoing non-cardiac surgery [48]. Elderly patients have a high incidence of protracted disabilities following major surgery. Lawrence and coworkers reported a high incidence of functional disabilities at 6 months following major abdominal surgery in a cohort of elderly patients [49]. In patients undergoing thoracic surgery dependence for the performance of activities of daily living and impaired cognition were predictors of postoperative complications [50]. Postoperative delirium is common following surgery and is associated with increased length of stay, morbidity and mortality. The operative mortality and rate of postoperative complication are even higher in elderly patients undergoing emergency surgery, being reported in up to 49 % and 68 % of cases respectively [47, 51–53].

Elective surgery must be considered very carefully in the elderly. Most randomized controlled trial comparing surgical to a more conservative approach are performed in patients less than 65 years of age. It is probably not appropriate to extrapolate the results of these trials to the elderly population. Coronary artery bypass surgery is frequently performed in the elderly with no evidence to support the benefit in this population of patients. Rady and Johnson compared the outcome from cardiac surgery in octogenarians compared to younger patients [54]. The octogenarians had a significantly higher incidence of postoperative complications and a significantly higher hospital mortality (13.5 % vs. 1.3 %, $p<0.001$) than the cohort of younger patients. Furthermore, significantly more octogenarians were discharge to a subacute/chronic health care facility than their younger counterparts (39.5 % vs. 13 %, $p<0.001$). This study demonstrated that only 47 % of the octogenarians (all who were living at home and independent prior to surgery) were discharged to home after surgery and therefore potentially benefited from undergoing coronary revascularization.

Over the last few years, geriatricians have developed an approach to care for the elderly called comprehensive geriatric assessment (CGA). CGA evaluates the comorbid illnesses, mental status, nutritional status, living circumstances, social support systems and polypharmacy [50, 55]. The goal of CGA is to provide information to the surgeon which will allow more accurate risk assessment for surgery. CGA will also allow for a pro-active team-based approach to interventions which will limit complications in those patients who undergo surgery.

Delirium in the Elderly

Delirium is common in elderly hospitalized patients and is cause of significant morbidity [56, 57]. Using CAM-ICU, McNicoll et al. reported that 70.3 % of elderly ICU patients developed delirium at some time during their hospitalization [58, 59]. A systematic review which included six observational studies evaluated risk factors for delirium by multivariate analysis. Twenty five risk factors were significantly

associated with delirium and among those four were recognized as predisposing to delirium: respiratory disease, older age, alcohol abuse, and dementia [60]. Medications are an important risk factor for delirium, especially in the elderly. Classes of medications commonly associated with delirium include anticholinergic agents, antihistaminics, benzodiazepines, and opiates (see Beers Criteria below) [61]. Delirium is common following major surgery in elderly patients. Postoperative delirium has an onset of approximately 24 h after surgery and generally resolves within a week. Delirium was reported to occur in 33 % of elderly patients undergoing coronary artery bypass surgery (CABG) [62]. Due to their advanced age, delirium is common following hip fracture repair, occurring in 28–65 % of patients [63–66]. Pre-operative cognitive dysfunction (dementia) is a strong predictor of postoperative delirium [67]. Postoperative delirium is associated with an increased mortality, a more frequent incidence of medical complications and a prolonged hospital stay [68]. In addition, postoperative delirium is associated with a poor long term functional outcome [63, 64, 69]. Furthermore, some patents may progress into a long term confusional state. Marcantonio et al. reported that 6 % of patients remained delirious 6 months after hip fracture surgery [64]. The assessment and management of delirium are disused in Chap. 15.

Drug Dosing and Polypharmacy in the Elderly

Adverse drug reactions (ADRs) are common causes of complications in hospitalized elderly patients. Age has been shown to be an independent risk factor for ADRs [70–72]. Polypharmacy is an independent predictor of ADR's . Aging is associated with decreased renal and hepatic reserve with delayed renal and hepatic clearance of drugs. Renal function can be readily estimated from the serum creatinine level, however, this estimate is unreliable in the elderly because of the frequent loss of muscle mass secondary to age itself and aging related conditions. Hypertension and type 2 diabetes mellitus are common in the elderly, and these patients are more likely to have concealed renal insufficiency, that is, renal insufficiency (decreased GFR) despite a normal serum creatinine. Digitalis, angiotensin-converting enzyme inhibitors, anticoagulants, sedatives and hypoglycemic drugs are common causes of ADR's in elderly patients. ACE inhibitor should be used cautiously in elderly patients, particularly those with deranged renal function. Excessive bleeding with the use of low molecular weight heparins (LMWH) is associates with a decreased GFR [73–75]. The dose of LMWH should be reduced in patients with mild renal insufficiency (CrCl 50–70 mL/min) and unfractionated heparin used in patients with a more marked decline in renal function (CrCl <50 mL/min) [73–75]. Aminoglycoside antibiotics should be avoided in elderly patients with renal dysfunction, as both age and preexisting renal dysfunction are predictors of nephrotoxicity. Age, diabetes and preexistent renal dysfunction are risk factors for the development of contrast induced nephrotoxicity. As contrast studies are frequently performed in elderly ICU patients preventative

measures should always be undertaken i.e. prehydration, N-acetyl-cysteine and avoidance of concomitant nephrotoxic drugs. Magnetic resonance imaging (MRI) and contrast MRI should be considered as an alternative to contrast CT scans in high risk patients. On discharge from the ICU any unnecessary medications started in the ICU should be discontinued (eg. PPIs, sedatives, antiarrhythmic agents, etc.). Furthermore, due to the myriad of possible drug interactions, the medication list of all elderly patients should be "trimmed" as much as possible. As a general rule the patients should be discharged on as short a list of medications as possible, and preferably less than 5 drugs.

American Geriatric Society Beers Criteria

T*he AGS 2012 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* (*AGS 2012 Beers Criteria*), has been developed to assist healthcare providers in improving medication safety in older adults [76]. Originally conceived in 1991 by the late Mark Beers, MD, a geriatrician, the *Beers Criteria* catalogues medications that cause adverse drug events in older adults due to their pharmacologic properties and the physiologic changes of aging. Each criterion is rated (quality of evidence and strength of evidence) using the American College of Physicians' Guideline Grading System, which is based on the GRADE scheme. The full document together with accompanying resources can be viewed online at www.americangeriatrics.org. An abbreviated list of drugs that should be avoided in elderly ICU patients is listed below:

Drugs to Avoid in the Elderly

- Tricyclic antidepressants alone or in combination:
- Barbiturates
- Benzodiazepines
- Diphenhydramine
- Promethazine
- Sulfonylureas, long-duration
  - Chlorpropamide
  - Glyburide
- Meperidine
- NSAIDS
- Clonidine
- Antiarrhythmic drugs (Class Ia, Ic, III)
  - Amiodarone
  - Dofetilide

  - Dronedarone
  - Flecainide
  - Ibutilide
  - Procainamide
  - Propafenone
  - Quinidine
  - Sotalol
- Digoxin >0.125 mg/day
- Aminoglycosides
- Vasodilators
  - Nitrates
  - Nifedipine
- Anticoagulants
  - Dabigatran
  - Prasugrel
- Alpha-blockers
  - Doxazosin
  - Prazosin
  - Terazosin
- H2 receptor antagonists

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Chapter 49
Obesity in the ICU

We are in the midst of a worldwide obesity pandemic with the USA being the epicenter [1, 2]. According to the 2009–2010 National Health and Nutrition Examination Survey 35 % of adults in the USA are obese with 4.4 % of men and 8.2 % of women having a BMI ≥40 [3]. Obesity is an independent predictor for the development of type 2 diabetes, hypertension, cardiac disease, the metabolic syndrome, obstructive sleep apnea (OSA), malignancy as well as cerebrovascular, liver and kidney disease [4–6]. The risk of death from all causes increases throughout the range of moderate and severe overweight for both men and women in all age groups [4–6]. With the increasing prevalence of obesity in the general population and the association of obesity with many disease states, it is not surprising that a significant proportion of ICU patients are obese. Obesity alters the function of many organ systems and these changes impact on the management of the critically ill obese patient. Almost every organ systems is negatively affected by obesity furthermore, patients with extreme obesity frequently develop hypercapnic respiratory failure which may be the primary reason for admission to the ICU. This latter condition known as the Malignant Obesity Hypoventilation Syndrome is frequently misdiagnosed and mismanaged (see below) [7].

Effect of Obesity on Critical Care Outcomes

The risk of death from all causes increases throughout the range of moderate and severe overweight for both men and women in all age groups [4, 8]. The graphed relationship between body mass index (BMI) and mortality is "J-shaped" with increased death rates with malnutrition and with increasing BMI [4, 9]. Obesity is associated with an increased risk of death in hospitalized patients. The association between BMI and mortality is altered in the critically ill. Paradoxically, patients who are overweight (BMI 26–30; class I obesity) and moderately obese (BMI 30–40; class II obesity) have a lower mortality than patients of normal body weight [10, 11].

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Meta-analyses have indicated that survival in obese ICU patients may be better or at least unchanged when compared to non-obese critically ill patients [12, 13]. In a recent Italian epidemiological cohort study the highest risk of death in the ICU was reported in underweight or morbidly obese patients, while overweight and obesity of class I/II were associated with a lower ICU mortality [14]. While some studies have suggested that morbidly obese patients (BMI >40) are at an increased risk of dying this observation has not been demonstrated by other studies [15]. Obesity is however associated with a prolonged duration of mechanical ventilation and increased ICU length of stay [12, 15]. The increased production of anti-inflammatory mediators by adipose tissue and the increased energy reserve has been postulated to account for the protective effect of moderate obesity during critical illness.

Respiratory Effects of Obesity

The effects of obesity on respiratory function are complex and influenced by the degree of obesity, age and body fat distribution (central or peripheral). The expiratory reserve volume (ERV) is consistently decreased in obese patients while the FEV1 to FVC ratio is increased [16]. The vital capacity (VC), total lung capacity (TLC) and functional residual volume (FRV) are generally maintained in otherwise normal individuals with mild to moderate obesity but are reduced by up to 30 % in morbidly obese patients.

Obese patients have an increased work of breathing due to abnormal chest elasticity, increased chest wall resistance, increased airway resistance (Raw), abnormal diaphragmatic position and upper airway resistance, as well as the need to eliminate a higher daily production of carbon dioxide. Patients with morbid obesity are generally hypoxemic, with a widened alveolar-arterial oxygen gradient caused by ventilation-perfusion mismatching The FRC falls when assuming a supine position, further increasing ventilation-perfusion mismatching. Abnormalities in the control of ventilation are common in obese patients with a high percentage of patients having obstructive sleep apnea and daytime hypoventilation. Patients with severe obesity (BMI generally greater than 40) may develop chronic hypoventilation with hypercapnic respiratory failure (MOHS). Presumably the increased work of breathing results in resetting of the respiratory control centers. Patients who present to the ICU with MOHS are best managed by non-invasive ventilation; mechanical ventilation may result in severe adverse sequelae in these patients (see Management of MOHS).

Particular attention to ventilator settings is required in obese patients who require mechanical ventilation. Lung volumes are determined by height and sex and not by weight. Lung volumes do not increase (grow) with increasing body weight. Tidal volumes MUST therefore be set according to ideal body weight and NOT actual body weight. Using actual body weight will result in severe barotrauma. The initial tidal volume should be based on IBW and adjusted according to inflation pressures and blood gases. In patients with chronic CO_2 retention, minute ventilation should be titrated to normalize pH and not pCO_2. Positive expiratory pressure (PEEP) is

required to prevent end-expiratory airway closure and atelectasis. A PEEP of 8–10 cm H_2o is generally recommended. However in patients with severe obesity PEEP is best determined by measuring intrapleural pressures using an esophageal balloon (see Chaps. 19 and 23). We have previously reported a mean end-expiratory pressure of 17.0 ± 2.9 cm H_2O in patients with MOHS [11]. Bilevel/APRV may be a particularly useful mode of ventilation in the morbidly obese patient [17].

Ideal Body Weight

Male: 50 + 0.91 (height in cm −152.4)
Female: 45.5 + 0.91 (height in cm—152.4)

Weaning the obese patient from mechanical ventilation is frequently a difficult and challenging task. Burns and colleagues have demonstrated that in obese patients the reverse Trendelenburg position at 45° resulted in a larger tidal volume and lower respiratory rate than the 0, or 90° position, and they postulated that this position may facilitate the weaning process [18].

Obese patients are at particular risk for aspiration pneumonia, especially in the postoperative period. This risk is increased due to several factors, including a higher volume of gastric fluid, a lower than normal pH of gastric fluid in fasting obese patients, increased intra-abdominal pressure and a higher incidence of gastroesophageal reflux. This is another important reason to nurse the obese patient in the semi-upright position. Obesity is an important risk factor for pulmonary embolism. The high risk of thromboembolic disease in obese ICU patients, warrants an aggressive approach to deep venous thrombosis prophylaxis.

Endotracheal intubation can be a challenging in the morbidly obese patient. In the Australian Incident Monitoring Study, obesity with limited neck mobility and mouth opening accounted for the majority of cases of difficult intubation [19]. Physicians caring for these patients must be well versed in intubation techniques as well as the use of adjuncts for intubation.

Cardiovascular Effects of Obesity

The alterations of cardiac function in patients with severe obesity are complex due to the frequent presence of comorbid conditions including systemic hypertension, diabetes, and hyperlipidemia [20]. Patients with morbid obesity have an increase in total blood volume and resting cardiac output. Both increase in direct proportion to the amount the patient weighs over the IBW. The cardiac index and stroke index are normal in otherwise healthy obese patients. Obesity is an independent risk factor for left ventricular hypertrophy [21–24]. Left ventricular hypertrophy is related to the increased cardiac output associated with obesity as well as the effect of adipokines

(leptin, adiponectin, cardiotrophin-1) on myocyte function [24–26]. Left ventricular hypertrophy results in an increased incidence of diastolic dysfunction. Although the resting cardiac output is increased, obese patients have been demonstrated to have impaired left ventricular contractility and a depressed ejection fraction.

The left ventricular filling pressure is elevated in obese patients due to the combination of increased preload and reduced ventricular distensibility. Consequently, fluid loading is poorly tolerated in these patients.

Hepatic and Renal Effects of Obesity

Obesity is associated with fatty infiltration of the liver. This may be asymptomatic or result in non-alcoholic steatohepatitis (NASH) and cirrhosis. NASH may be evident by increased transaminases, increased NH3 and increased serum ferritin and triglyceride concentrations [27, 28]. Chronic renal insufficiency is common in patients with obesity. This is related to the increased incidence of hypertension and diabetes; however obesity is associated with a focal segmental glomerulosclerosis which is known as obesity-related glomerulopathy [29, 30].

Drug Dosing in Obese Patients

Drug distribution, metabolism, protein binding, and clearance is altered by the physiological changes associated with excessive weight Some of these pharmacokinetic changes may, however, negate the consequences of others and the pharmacokinetic alterations may differ in the morbidly obese compared to the mildly or moderately obese. However, a number of drugs used in the ICU, most notably digoxin, aminoglycosides and cyclosporin, can cause drug toxicity if the obese patients are dosed based on their actual body weight.

In obese patients with renal dysfunction, the creatinine clearance, as calculated using standard formulae, correlates very poorly with the measured creatinine clearance [31]. Therefore, in the obese patient with renal dysfunction, the dosing regimen of renally excreted drugs should be based on the measured creatinine clearance [32].

Nutritional Requirements

Nutrition should not be withheld from the obese patients in the mistaken belief that weight reduction is beneficial during critical illness. Sarcopenia is the loss of lean body mass (muscle mass) that occurs with aging. Sarcopenic obesity is a body composition category in which obesity is accompanied by low skeletal muscle mass [33]. In Western societies, the age group of the population with the highest prevalence of obesity ranges from 55 and 75 years [34, 35]. Sarcopenic obesity is therefore

especially prevalent in the elderly [36]. Patients with sarcopenic obesity are likely to develop severe protein energy malnutrition in response to metabolic stress.

Obese patients should generally receive between 20 and 25 Kcal/Kg of IBW/ day (see Chap. 32). Most of the calories should be given as carbohydrates with fats given to prevent essential fatty acid deficiency. It has been suggested that critically ill obese patients receive nutritional support with a hypocaloric high-protein formulation [37, 38]. It has been postulated that if adequate protein is supplied and obligatory glucose requirements are met, endogenous fat stores will be used for energy [39]. Current consensus recommends a level of 1.5–2.0 g/kg of IBW to achieve nitrogen equilibrium [40].

Gaining Vascular Access

One of the most challenging features of the morbidly obese patient is venous and arterial access. Poor peripheral venous sites in these patients necessitate more frequent use of central venous access. A short stubby neck, loss of physical landmarks and a greater skin-blood vessel distance make internal-jugular and subclavian vein cannulation technically difficult.

Obese patients have a higher incidence of catheter malpositions and local puncture complications, with catheter related infections and thromboses. Femoral venous access may not be possible as these patients usually have severe intertrigo and morbid obesity is a major risk factor for catheter associated blood stream infection (CRBI) when the femoral site is used [41]. The use of Doppler ultrasound-guided techniques for obtaining central venous access is recommended in these patients. Furthermore, early placement of a PICC should be considered.

Radiological Procedures

Bedside radiographs are of a very poor quality in the morbidly obese patient, limiting their diagnostic value. Abdominal and pelvic ultrasonography is limited by extensive abdominal wall and intra-abdominal fat. Percutaneous aspiration and drainage of intraperitoneal and retroperitoneal collections may be hindered by the obese body habitus. Many computed tomography tables have weight restrictions (about 350 lbs.) that prohibit imaging of morbidly obese patient.

Malignant Obesity Hypoventilation Syndrome (MOHS)

MOHS is a systemic illness involving many organ systems related to extreme obesity [7]. The organ systems associated with MOHS include hypercapnic respiratory failure, systemic hypertension, left ventricular hypertrophy with diastolic dysfunction,

pulmonary hypertension, right ventricular volume overload, chronic renal insufficiency and NASH. The pathophysiology of MOHS is related to the complex interactions and feed-back loops. The defining feature of MOHS is chronic hypercapnic respiratory failure. Lung function tests in demonstrate a restrictive pattern. Remarkably, however the majority of these patients have been diagnosed and treated for chronic obstructive lung disease. The diagnostic features of MOHs are listed below[1]:

Major Criteria

a) Morbid Obesity (BMI >40 kg/m^2)
b) Chronic daytime hypoventilation with $PaCO_2$ >45 and increased baseline HCO_3 >28 meq/L
c) Restrictive Lung Disease/exclusion of COPD or musculoskeletal disease
d) Metabolic syndrome/ Type 2 Diabetes

Minor Criteria

a) Multiple hospital admission for type II respiratory failure
b) Sleep disordered breathing (OSA)
c) Eccentric left ventricular hypertrophy (LV Mass >47 g/m 2.7)
d) Diastolic left ventricular dysfunction
e) Pulmonary Hypertension
f) Right ventricular volume overload
g) Systemic hypertension
h) Chronic renal insufficiency
i) Non-alcoholic steatohepatitis
j) Vitamin D deficiency
k) Elevated C-reactive protein

Treatment of MOHS

The management of patients with MOHS includes short term measures to improve the patients' medical condition and long term measures to achieve enduring weight loss. Non-invasive ventilation (NIV) should be considered in all patients with MOHS. NIV is likely to improve gas exchange and clinical symptoms [42–44], and it may improve insulin resistance and hypertension.

[1] Patients require all 4 major criteria and at least 2 minor criteria.

Due to the high intrapleural pressure, high levels of expiratory positive airway pressure (ePAP) may be required. While MOHS patients are morbidly obese they are usually "malnourished" and should undergo dietary counselling, encouraging a high protein low caloric diet. Hypertension, hyperlipidemia and diabetes should be aggressively treated. Sildenafil may be particularly useful in patients with MOHS. This drug is an effective pulmonary vasodilator that is emerging as the treatment of choice for diastolic dysfunction and cor pulmonale [45–48]. Weight loss is the most important element in the management of MOHS and treating MOHS without achieving significant weight loss is unlikely to reduce the significant morbidity and mortality associated with this syndrome. A number of studies have demonstrated that bariatric surgery is much more effective in achieving weight loss and reversing the organ dysfunctions associated with severe obesity [49, 50]. Bariatric surgery would therefore appear to be the treatment of choice for patients with MOHS.

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Chapter 50
Radiology

The Chest Radiograph

Interpretation of the bedside (antero-posterior, supine) chest radiograph (CXR) is fraught by numerous pitfalls. These include:

- On the AP view, the heart and mediastinum appear about 15 % wider than on an upright PA chest radiograph (false impression of cardiomegaly and mediastinal widening)
- Portable chest radiographs may be difficult to interpret due to poor positioning
- Pleural effusions and pneumothoraces are frequently "missed" because the patient is in the supine position
- The pulmonary vasculature is distorted on supine radiographs because blood no longer flows preferentially to the lower lobes
- Because lateral chest films cannot be obtained, abnormalities in the posterior costophrenic angles (retrocardiac), within the mediastinum and adjacent to the spine can easily be missed.
- Interstitial infiltrates may be poorly seen on the CXR

It should be appreciated that the CXR is a 2-dimensional image of a complex 3-dimensional structure and that even on the "best" bedside CXR significant pulmonary pathology may be missed; e.g., pneumothorax, air-space consolidation, abscesses and interstitial lung disease [1]. The intensivist should therefore have a low threshold for performing a chest CT scan; however the risks of moving a patient to the radiology suite must be weighed against the possible benefits. Chest CT scans provides a more comprehensive evaluation of the lung parenchyma providing a much better assessment of the nature and extent of lung pathology than the CXR. It is likely that in the future portable CT scans will be performed routinely in the ICU [2].

Despite its inherent limitation, a careful review of the bedside AP CXR provides useful information in the management of critically ill patients. In previous years, the standard practice was to obtain daily CXR's in all ICU patients. Recently however,

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a number of well conducted studies indicate that this is not a cost-effective practice and that CXR's should only be performed on "demand", i.e. as clinical circumstances dictate [3, 4]. These studies have demonstrated that it is rare that such an approach leads to findings that would have been missed had daily CXR been performed. A meta-analysis by Oba and Zaza which included 8 trials and 7,078 ICU patients demonstrated eliminating routine daily CXR did not affect mortality, length of stay in the hospital or ICU, or ventilator days in either group [5]. However, all patients require a CXR on admission to the ICU, after endotracheal intubation and after insertion of a subclavian or internal jugular central venous catheter [6].

The chest radiograph should be studied systematically; firstly the position of all the tubes and catheters should be evaluated, followed by an evaluation of the lung parenchyma, pleura, mediastinum and diaphragm followed by a search for signs of extra-alveolar air.

Position of Tubes and Catheters

- Endotracheal tube. With the head in a neutral position the tip of the tube should be 4–6 cm from the carina. It should be noted that with movement of the head, from a flexed to an extended position, the tube can move by as much as 4 cm. A useful landmark for the tip of the ET tube is the superior border of the aortic notch (Marik's sign) or the upper border of T4 (see Fig. 50.1). The aortic arch is the "center of an imaginary sphere" so even if the CXR is rotated, Marik's sign can still be used to determine the position of the ET tube.
- Central venous catheters. The tip of the catheter should be located beyond the venous valves of the subclavian or internal jugular vein but proximal to the right atrium (i.e. above the superior vena cava-right atrial junction). Placement in the right atrium may result in atrial perforation. Two useful radiographic landmarks for the position of the tip of the catheter are:
  - the first costochondral junction
  - a point 2 cm inferior to a line joining inferior margins of the clavicular heads (see Fig. 50.1).
- The position of other tubes and catheters, such as the nasogastric tube, feeding tube, chest tubes, intra-aortic balloon catheter and pacing wires should be noted.

Lung Parenchyma, Pleura and Mediastinum

The presence of pulmonary infiltrates should be noted. It should be noted whether the infiltrate is interstitial or alveolar (or both), unilateral or bilateral, and patchy or diffuse. An infiltrate may be caused by water (cardiogenic or non-cardiogenic pulmonary edema), cells (infection) and/or blood (pulmonary hematoma, intra-alveolar

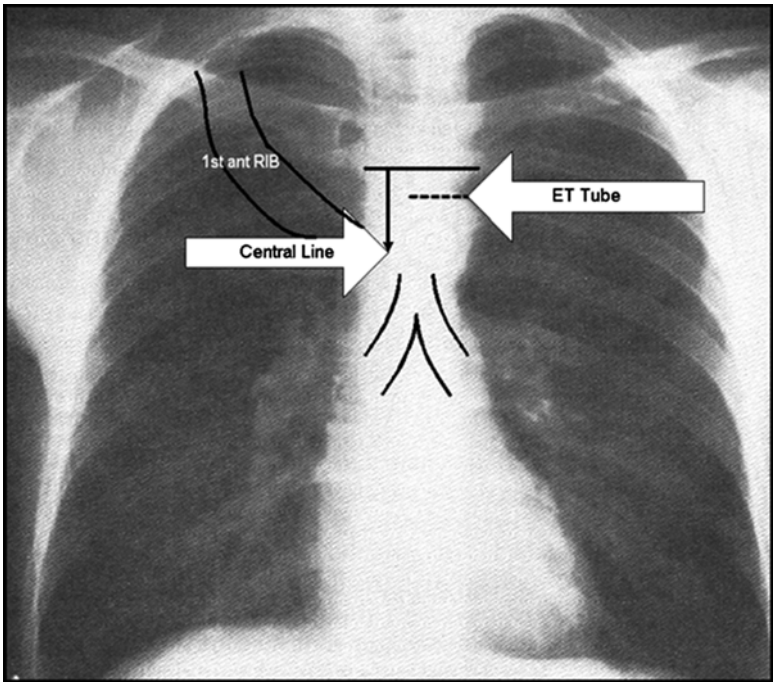

Fig. 50.1 Idealized CXR with optimal position of endotracheal tube and central line

bleed). It should be appreciated that it may not be possible to distinguish between these entities by examination of the chest film alone. The following radiographic findings may help distinguish cardiac and non-cardiac pulmonary edema:

- Non-cardiac pulmonary edema (acute lung injury)
  - normal heart shape
  - absence of septal lines
  - no peribronchial cuffing
  - frequent air bronchograms
  - patchy increased lung density
  - peripheral increased lung density
- Cardiogenic pulmonary edema
  - base-to-apex blood flow inversion
  - even distribution of increased lung density
  - septal lines
  - peribronchial cuffing

It is however critically important to appreciate that the CXR is a very poor indicator of volume status. A number of studies in diverse patient populations have demonstrated a poor relationship between CXR assessment of volume status and measurement of lung water (EVLW) even when interpreted by expert chest radiologists [7–11].

In the supine position fluid tracks posteriorly resulting in a diffuse haziness of the lung fields. It is therefore very easy to miss a significant pleural collection. Fluid collections can be confirmed by ultrasonography. The width of the mediastinum should be noted (normal; <10 cm) as well as the presence of mediastinal nodes or masses.

The traditional apico-lateral collection of air may not be present on a portable CXR in patients with pneumothoraces. Free air will often be located in the anterior costophrenic sulcus as this is the most superior portion of the pleural space in the supine patient. Other radiographic signs of a pneumothorax in the supine position include; a relative hyperlucency over the upper abdominal quadrants and a deep costophrenic angle (the deep sulcus sign). It should be noted that the sensitivity of the supine AP chest radiograph for the diagnosis of pneumothorax averages 50 % [12]. This compares to a sensitivity of >95 % for ultrasonography [13].

The portable chest radiograph is not ideal for evaluating the hilum and lung parenchyma. Conventional and high resolution computed tomography (HRCT) may be useful for evaluating aortic dissection, pleural disease, the lung parenchyma (especially in immunocompromised patients with pulmonary infiltrates), characterization of diffuse infiltrative pulmonary disease and evaluation of suspected masses in the mediastinum or hilum. Routine CT evaluation of the chest can be done with or without intravenous administration of contrast media. Contrast is reserved for those cases in which mediastinal or hilar pathology are suspected. HRCT differs from conventional CT not only in the use of a thinner X-ray beam (e.g. 1.5 mm vs 1 cm), but also the use of digitized X-ray construction which allows for better spatial resolution and for more detailed images of the lung parenchyma. HRCT is therefore useful in the evaluation of patients with diffuse infiltrative lung diseases. Spiral CT differs from conventional CT primarily in that it allows continuous scanning of the patients. In spiral CT, the X-ray tube makes continuous 360-degree revolutions without interruption. The patient is moved through the circulating beam at a predetermined speed, and imaging information is then obtained as a solid cylinder, instead of one slice at a time. Spiral CT is most helpful in evaluating lesions at or near the diaphragm (less motion artifact), evaluating vascular structures (main pulmonary arteries in suspected pulmonary embolism) and small pulmonary nodules.

While CT scanning has revolutionized imaging in critically ill patients it comes at the expense of increased radiation exposure. Recent publications have emphasized the potential future cancer risk from radiation exposure due to CT examinations [14]. It is estimated that 1 individual in 1,000 will develop cancer from an exposure to 10 milliSieverts (mSv) of low-dose radiation [15]. Lutterman et al. estimated the cumulative radiation exposure of hospitalized patients from radiological imaging [16]. The mean dose estimate per ICU patient was 17.9 mSv with CT scans accounting for 82 % of the radiation dose. The estimated radion exposure by radiographic study is listed in Table 50.1 [16]. This data is somewhat alarming and suggests that patients' cumulative radiation exposure should be monitored during their hospitalization.

Table 50.1 Average radiation exposure for common radiologic studies

Examination	mSv
PA chest	0.02
Abdomen radiograph	0.7
Ventilation/perfusion lung scan	2.0
Cardiac perfusion isotope scan	15
CT head	2.6
CT chest	11.2
CT abdomen	19.1

Plain Abdominal Radiography

Plain abdominal radiographs are commonly requested for patients with non-specific abdominal symptoms and signs, yet this test has limited diagnostic and clinical utility [17, 18]. This is particularly true in ICU patients in whom plain abdominal radiographs rarely impact management decisions. This diagnostic test should therefore only be obtained in specific clinical circumstances. The most useful diagnostic findings include free air under the diaphragm (indicative of bowel perforation) and features suggestive of bowel obstruction such as dilated loops of bowel, lack of rectal gas and fecal impaction. Plain films may also be useful in the evaluation of suspected bowel ischemia because certain findings (e.g. pneumatosis intestinalis and portal venous gas) are pathognomonic for this condition. In addition, plain abdominal films (or a half/half film) are required to confirm the position of NG and feeding tubes. Beyond these clinical indications plain abdominal radiographs have limited diagnostic utility. Andrews and colleagues evaluated the role of plain abdominal films in patients admitted to the ICU with GI bleeding [19]. In this study, abdominal radiography failed to reveal a single abnormality that changed management or outcome. It has been suggested that a normal or negative study is implicitly valuable because of the reassurance provided to the requesting physician. However, the sensitivity of this test is too low to exclude significant abdominal pathology with any degree of certainty and "abnormal" findings lack diagnostic specificity.

Computed Tomography (CT)

While portable computed tomographic (CT) scanners are becoming available [2, 20], in most hospitals ICU patients must be transported to the radiology department. Transporting patients out of the ICU carriers a risk of serious physiologic changes and life threatening complications. Therefore only those patients whose treatment is likely to be changed by the test should undergo CT scanning. With advances in portable CT technology it is likely that portable scanners will become ubiquitous. Additional concerns with CT scanning include radiocontrast agent induced renal dysfunction, allergic reactions and radiation exposure (especially with repeated tests).

Ahvenjari et al. evaluated the role of abdominal and thoracic CT scanning in 64 ICU patients who underwent 82 CT examinations [21]. Seventy-one percent of the examinations (58/82) were made to identify a possible focus of infection. Fifty of the 82 (61 %) examinations resulted in a new treatment intervention directly or after additional examinations. Similarly, Barkhausen and colleagues demonstrated the utility of thoracic and abdominal CT scans in the evaluation of patients with fever or sepsis without a known source [22]. In this study a septic focus was detected by CT in 19 % of the patients which directly altered patient management with changes in the antibiotic regimen, percutaneous drainage and/or surgery. These studies demonstrate the utility of "Body CT scanning" in patients with sepsis and an unclear focus of infection. In addition, CT scans have specific indications in patients with suspected pulmonary embolism, pulmonary infiltrates of unclear cause, suspected sinusitis, as well as patients with severe pancreatitis, mesenteric ischemia and colitis, to name but a few.

Neurological dysfunction is common in patients admitted to the ICU. Clinically these patients present with a spectrum of neurological findings including depressed consciousness, delirium, seizures as well as focal neurological signs. The use of sedative drugs (especially benzodiazepines and opiates), the systemic inflammatory response as well as metabolic and endocrine disturbances may lead to reversible neurological syndromes (depressed consciousness, confusion, and delirium). However, due to hemodynamic instability and coagulation abnormities this group of patients is at high risk of cerebrovascular accidents which have important therapeutic and prognostic implications. Salerno et al. reviewed the utility of head CT scans performed in 123 MICU patients [23]. A new finding was present in 26 (21.1 %) patients. In the patients with a new CT finding, there was a change in diagnosis in 11 patients and a change in treatment in 6 patients. The presence of an acute brain abnormality detected by head CT scanning could not be reliably predicted by patient characteristics or other clinical variables. Rafanan and colleagues reviewed the medical records of 230 MICU patients who underwent head CT scanning [24]. These authors reported that 31 % of their patients had new findings on their CT scans with ischemic stokes (49 %) being the commonest lesion. While a focal neurologic deficit was more common in the patients with a positive scan, the patients' clinical characteristics were poorly predictive of new CT findings. These studies suggest that all patients with unexplained acute neurological findings should undergo CT scanning. Head imaging is not usually considered in the diagnostic workup of ICU patients who develop confusion/delirium [25–27]. However, it is likely that with widespread head CT scanning many of these patients may be determined to have ischemic strokes. The identification of new findings on head imaging has important prognostic and therapeutic implications.

Indium Labeled Leukocye Scans

ICU patients frequently develop a sepsis like syndrome with the source of the infection being unclear. Indium labeled leukocyte scans are frequently performed to localize the source of infection and/or in the evaluation of patients with suspected

osteomyelitis. A wide range of sensitivities and specificities has been reported for indium-labelled leucocyte studies in patients with febrile illness. Syrjala et al. studied 68 patients with fever of unknown origin (FUO) and found a sensitivity of 86.4 % and a specificity of 87.8 % [28]. More recently, Seshadri et al. studied the diagnostic accuracy of WBC scans in patients with a FUO [29]. The overall sensitivity of scintigraphy was 60 %, specificity 71 %, positive predictive value 55 %, and negative predictive value 75 %. In this study 83 % of patients with abnormal radiological examinations had positive findings on scintigraphy and 87 % of patients with negative findings on radiology had normal scintigraphy. Wanahita et al. evaluated 145 indium scans done for possible skeletal infection [30]. Infection was judged to be present in 52 cases with a sensitivity of 83 %, a specificity of 90 %, with a diagnostic accuracy of 88 %. While none of these studies were done in ICU patients this data suggests that indium labelled white scans may have adjunctive diagnostic utility in ICU patients with undiagnosed fever.

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Chapter 51
End-of-Life Issues

To cure sometimes, to relieve often, to comfort always

—Hippocrates, Greek Physician, Father of Western Medicine (460–370 BC)

The prime goal of the intensive care unit is to provide temporary physiologic support for patients with potentially reversible organ failure allowing their acute illness to resolve and enabling the patient to return their previous level of functioning. The guidelines of the Society of Critical Care Medicine state that "*in general ICU's should be reserved for those patents with reversible medical conditions who have a reasonable prospect of substantial recovery*" [1]. Despite this recommendation, almost all patients with serious and life-threatening illnesses in the USA regardless of their prognosis or prospect of recovery are admitted to an ICU, unless the patient or his/her surrogate specifically declines ICU admission. Consequently, with increasing frequency patients with end-stage and terminal illnesses are admitted to the ICU. In the USA it is exceeding uncommon for intensivists to refuse ICU admission; if a bed is not immediately available, one is "made." This contrasts to the situation in most Western nations in which not all requests for an ICU bed are honored. Indeed, refusal of ICU admission is common, with a rate that varies from 24 to 88 % [2–8]. Wunsch and colleagues compared the use of ICU services during terminal hospitalization in England and the US [9]. While the overall population mortality statistics were similar between England and the US, 5.1 % of all deaths in England involved the ICU compared to 17.2 % in the US, representing 10.1 % of hospital deaths in England versus 47 % in the United States. ICU care was used for 31.5 % of medical deaths and 61.0 % of surgical deaths in the US versus 1.9 and 8.5 % of deaths respectively in England. These data suggest that in the USA end-of-life issues and realistic goals of care are not adequately addressed in patients with chronic and life threatening illnesses.

Americans appear to be unaccepting of death and frequently want "everything to be done" in the face of certain death. This may be due to unrealistic expectations that patients and their families have with regards to what modern medicine can actually achieve. These unrealistic expectations are perpetuated by misinformation provided by the lay press, television and the Internet. It is likely that in many instances physicians contribute to these unrealistic expectations by failing to provide honest information regarding the likelihood of a prolonged hospital course, the need for prolonged

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rehabilitation in a long term acute care facility and about expected 1-year survival, functional status, cognitive status and alternatives to continuing aggressive life supportive measures [10]. Azoulay and colleagues interviewed family members of ICU patients after meeting with a treating physician [11]. In 54 % of cases the family representative failed to understand the diagnosis, prognosis or treatment plan of the patient.

Admission of a dying patient with irreversible disease to the ICU serves only to transform death into a prolonged and painful experience. It should be appreciated that death is the only certainty of life, and that the ICU is not a halfway station between life on earth and the hereafter. The function of the ICU should not be to prolong death. In terminal or incurable illnesses, our aim should not be to preserve biological life, but to make the life that remains as comfortable and as meaningful as possible. The culture of our current health care system is highly invested in "aggressive" treatment of terminal disease with the notion that death represents medical failure. However, the ethical principles of patient autonomy dictates that patients have the right to determine the use of medical technologies and the use of medications to control pain near the end of life. In addition, policy statements of national organizations recognize the right of competent patients to forgo treatment, even if refusal may lead to death [12–14]. Withholding and withdrawing life supportive measures, a practice which was once considered controversial is now widely accepted. As a general principle, when the goals of cure cannot be achieved with aggressive life-sustaining treatments such as mechanical ventilation, it is appropriate to withdraw these treatments and to allow death to occur naturally [13–16].

Because most critically ill patients are unable to participate in end-of-life treatment decisions, family members are generally asked to speak for the patients, and to varying degrees, to participle in decision making. Yet shared decision making about end-of-life treatment choices is often incomplete, with family's having a poor understanding of the ultimate decisions that are made [17]. Patients and relatives faced with end of life issues identify poor communication with the treating physicians as the greatest source of frustration and anxiety [18, 19].

Palliative Care

Palliative care originated as end-of-life care in the 1960s. Since then the scope of practice of palliative care has expanded far beyond its roots. The goal of palliative care is to maintain and improve the quality of life of all patients and their families during any stage of illness, whether acute, chronic, or terminal [14]. According to the World Health Organization (WHO), palliative care aims to prevent and relieve suffering by early identification, assessment, and treatment of pain and other types of physical, psychological, emotional, and spiritual distress [20]. Ideally, all patients should receive palliative care concurrently with medical care, the elements and intensity of which are individualized to meet the patient's and family's needs and preferences. Palliative care should not be restricted to end-of life care but rather involves determining of the goals of care along the continuum of the patients illness.

The primary goal of palliative care is to achieve the best possible quality of life for patients' for as long as they are alive and to support the patient's family while the patient is alive and after death. Clearly, palliative care should be available near the end of life. However, it should also be available at any point during the course of a progressive or chronic disease or critical illness when the patient becomes symptomatic. An important concept is that, in general, palliative care should be available when curative/restorative care begins, while curative/restorative care continues, after life-prolonging treatments are withheld or withdrawn, and, for the patient's family, after the patient's death.

"Principles" of Palliative Care [14]

- Palliative care is foremost centered on the patient and the patient's family (with the patient defining his/her family constellation). It recognizes the right of competent adult patients to determine their goals of care both before and after they face disabling symptoms and approach their end of life
- Palliative care includes identification of, and respect for, the preferences of patients and families. This should be done through careful assessment of their values, goals, and priorities, as well as their cultural context and spiritual needs.
- Palliative care encourages and supports family involvement in planning and providing care to the extent desired by the patient.
- Palliative care should begin at ICU admission and then be adjusted, analogous to curative/restorative care, to meet the needs of the patient and family in accord with their preferences
- All patients with symptomatic or life-threatening diseases, particularly those with chronic or advanced respiratory diseases or critical illnesses, regardless of age or social circumstances, should have access to palliative care.
- Health care providers should strive to develop a comprehensive, interdisciplinary approach that provides palliative care sensitive to the patient's and family's needs and respectful of their cultural and spiritual values
- Bereavement care for families is an integral part of palliative care.
- Health care providers should have an appropriate level of competence in palliative care. Their training and educational experiences should help them to acquire the core competencies necessary to provide compassionate and individualized palliative care. They should appreciate the limits of their knowledge and skills and know when to seek consultation from palliative care experts.

There is evidence that palliative care programs in the ICU play a key role in improving communication with patients' families regarding diagnosis, prognosis, goals of care, management of pain and anxiety and provision of spiritual and emotional support [21–23]. Palliative Care programs that include structured family meetings to discuss patient-specific goals and advance care planning and which

address the emotional and spiritual well-being of patients and families have led to improvement in quality of care, effective use of resources and enhanced staff satisfaction [24]. A study done by Nelson and colleagues suggest that an ICU "palliative care bundle" improves patient comfort, family communication and end-of-life decision making [25]. This bundle of Palliative Care measures includes:

- the identification of a medical decision maker
- advance directives
- resuscitation status
- pain assessment and optimal pain management
- spiritual support
- Multidisciplinary family meetings.

Family meetings are considered to have a central role in providing families with information concerning their loved one's diagnosis, prognosis and treatment options. Such meetings allow families to make decisions based on the patient's wishes and current prognosis. Not only do these meetings address the patient's medical condition and quality of life, but they also provide emotional and spiritual support for the patient and family at a time of significant stress [24]. Lautrette and colleagues randomized family members of 126 patients dying in the ICU to a proactive communication strategy or to a customary end-of-life conference [19]. In this study the family members who participated in the proactive communication meetings suffered less anxiety, depression and post-traumatic stress after the death of the patient.

Informal dialogue between each patient's family and the treating ICU team should occur on a daily basis, however "pro-active" multidisciplinary family meetings are recommended in patients who are at imminent risk of death and patients who have required 5 or more days of mechanical ventilation. While the prognosis of patients on admission to the ICU is often uncertain, studies suggest that after five days of supportive care the outcome is easier to predict [26]. The family meeting should follow a structured format to ensure that all the elements of the "palliative care bundle" are addressed. Family meetings should include the key physicians involved in the patients' care, the patient's bed-side nurse, representatives from pastoral and palliative care with participation by all the patients' close relatives. The meetings should be held in a quiet room outside of the ICU, with adequate and comfortable seating and appropriate furnishings. Furthermore, the meeting should be planned at a time that allows for uninterrupted discussions with ample time for the family to voice their feelings and concerns and have all their questions answered.

Adequate preparation is a key component to the success of a family meeting. This includes ensuring participation by key family members and physicians involved in the patients care. Clinicians should review the patient's medical history as well as what is known about the patients disease, including treatment options and likely outcomes. Any disagreements among health care providers must be resolved prior to meeting with the family. Staff-staff conflict will only increase the family's anxiety and lead to mistrust. The pre-meeting for clinicians is a good strategy to resolve any conflict and clarify goals of the family meeting. The pre-meeting can be brief, but is an important step in preparation for a successful family meeting. A knowledge of family dynamics and their religious background and beliefs aids in the preparation of the meeting.

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Chapter 52
Words of Wisdom

- Failure is success if you learn from it
- Common sense occurs uncommonly [1]
- Common things occur commonly [1]
  - If it looks like a horse, whines like a horse and smells like a horse, don't expect a zebra to appear
- We only see what we know (or look for)
- Respect your fellow health care workers: they are your most important clinical asset [2]
- It is a privilege to practice medicine; don't abuse the privilege [2]
- When you don't know what to do, do nothing.
- Corollary: Doing something harmful is not better than doing nothing
- Don't assume the obvious and don't make assumptions
- The less a procedure is indicated the more likely that it will be accompanied by a complication [1]
- If a patient is reluctant to undergo a procedure, don't force the issue; that's the patient who will have a complication
- When doing a procedure remember nature always sides with the hidden flaw
- Never open a can of worms unless you plan to go fishing
- The Law of Sub-specialization
  - If you are a hammer the world looks like a nail.
- An acute surgical abdomen is when a good surgeon says it's an acute surgical abdomen. There is no test for it.
- Before ordering a test decide what you will do if it is (a) positive, or (b) negative. If both answers are the same, don't do the test.
- Never ignore an abnormal lab value; if it seems "wrong" repeat it "stat"
- Hyperkalemia, hypokalemia and hypophosphatemia should always be treated emergently
- There is no manifestation that cannot be caused by a given drug
- If a drug is not working, stop it
- Any order that can be misunderstood, will be misunderstood

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- Lasix® (furosemide) is not a volume expander
- Never ignore an ICU nurse's observation
- Be kind to nurses, and they will be kind to you. Be unkind to nurses, and they will make your life miserable.
- Be respectful and attentive to your patients and their family [3]
- Always introduce yourself to the patient and his/her family and explain your role in the health care team [3]
- Good manners are key to an effective relationship with your patients, their families and your colleagues
- Don't dress like a slob (no jeans and track shoes). Wear a white coat and name badge [4, 5]. Look and act like a professional, this inspires confidence in your patients and their relatives.

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Index

A
Abdel-Wahab, O.I., 602
Abdominal surgery, 13, 47, 100, 188, 293, 314, 779
Aberda, 498
ABG. *See* Arterial blood gas (ABG)
Abid, O., 125
Acetyl-para-aminophenol (APAP), 735
Activated charcoal
  digitalis, 743
  dose, 732–733
  lithium, 744
  phenytoin, 743–744
  serum salicylate, 738–739
  syrup of ipecac, 742
  tricyclic antidepressants, 738
Acute acalculous cholecystitis (AAC), 282–283
Acute coronary syndromes (ACS)
  STEMI
    acute pericarditis, 477
    atrial fibrillation, 478
    class I and II recommendation, 475–476
    ischemia, 477
    left ventricular failure, 478
    low output states, 478
    mitral regurgitation, 477
    right ventricular infarction, 478
  unstable angina/NSTEMI
    Canadian cardiovascular classification, 472
    class I recommendation, 474–475
    class II recommendation, 475
    differential diagnosis, 472
    electrocardiography, 472–473
    GRACE risk model, 474
    risk stratification, 473
    TIMI risk score, 473–474
    tropinins, 473
    types, 472
Acute decompensated heart failure (ADHF)
  BNP, 447
  diagnosis, 446–447
  echocardiography, 448
  invasive hemodynamic monitoring, 448
  laboratory testing, 448
  long-term management, 456–457
  NT-proBNP, 447
  precipitating factors, 449
  treatment
    anemia, 456
    anticoagulation, 455
    atrial fibrillation, management, 455
    beta-blockers, 453
    diuretics, 450–452
    dobutamine, 454
    hypertension management, 455
    milrinone, 454
    morphine, 450
    oxygen, 449
    ultrafiltration, 454–455
    vasodilators, 452–453
    vasopressin, 454
Acute ethanol intoxication, 739–740
Acute fatty liver, 768
Acute ischemic stroke (AIS)
  aneurysmal SAH, 670
  cerebellar hemorrhage, 671
  cerebellar ischemic infarction, 671
  classification, 671
  endovascular interventions

P.E. Marik, *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-11020-2

Acute ischemic stroke (AIS) (*cont.*)
antiplatelet therapy and anti-coagulation, 676
cardio-embolic stroke, 676–677
decompressive surgery, 677
fever, 678
hyperglycemia, 678
post stroke hypertension, 678–680
supportive medical therapy, 680–681
trials, 675
ganglionic intracerebral hemorrhage, 670
hemispheric ischemic infarction, 671
lobar intracerebral hemorrhage, 670
NECT, 671–672
pontine hemorrhage, 671
prevalence, 669
stroke intensive care units, 670
thrombolytic therapy, 672–674
treatment, 674–675
Acute kidney injury (AKI), 14, 173, 175
contrast-induced nephropathy, 655
diuretics, 654
fluid and electrolyte management, 657
fluid resuscitation, 653–654
nephrotoxic agents, 656–657
pathophysiology, 653
pre-renal azotemia, 654–655
prevention, 655–656
rhabdomyolysis (*see* Rhabdomyolysis)
RIFLE criteria, 653, 654
RRT (*see* Renal replacement therapy (RRT)
Acute lung injury, 13
Acute myocardial infarction with ST elevation (STEMI)
acute pericarditis, 477
atrial fibrillation, 478
class I and II recommendation, 475–476
ischemia, 477
left ventricular failure, 478
low output states, 478
mitral regurgitation, 477
right ventricular infarction, 478
Acute on chronic liver disease (ACLF), 537
Acute pancreatitis. *See* Pancreatitis
Acute postoperative hypertension (APH), 439–440
Acute renal failure. *See* Acute kidney injury (AKI)
Acute respiratory distress syndrome, 13
Acute severe asthma
ICU admission, 382
initial settings, 387–388
intubation indication, 385
mechanical ventilation, 386–387
NFA, 381
NPPV, 384–385
phenotypes, 381–382
respiratory rate, 381
sedation post-intubation, 386
treatment, 382–384
Adams, R.C., 585
ADAMTS13 deficiency, 613
ADHF. *See* Acute decompensated heart failure (ADHF)
Adrenal insufficiency
causes of, 622–623
clinical features of, 623–624
corticosteroid treatment
acute rebound, 627
adverse effects, 630
dose and dosing strategy, 626–627
genetic polymorphisms, 627–628
glucocorticoid receptor abnormalities, 628
hydrocortisone, 630
immune status, host, 625–626
timing of, 626
cortisol, 621
diagnosis of, 624–625
glucocorticoids, 629
randomized controlled trials (RCTs), 629–630
Adult respiratory distress syndrome (ARDS)
ALI, 349
American European Consensus, 349
APRV, 357–359
berlin definition, 350
causes, 351
DAD, 350
ECMO
β2-agonist, 365
corticosteroids, 363
glucocorticoid treatment, 364
H1N1 infection, 363
nitric oxide, 365
omega-3 fatty acids, 366
prostacyclin, 365
surfactant dysfunction, 365
EVLW, 350–351
non-ventilatory adjuncts
NMBA, 362
prone positioning, 361
PCV, 354–357
PEEP, 359–360
permissive hypercapnia, 359
recruitment maneuvers, 361
refractory hypoxemia, 366
ventilatory strategy

APRV, 354
ARDSNet protocol, 353
chest radiographs, 352
HFOV, 354–355
low-tidal-volume ventilation, 353
mortality and plateau pressure, 353–354
MSOF, 353
total tidal volume, 352
Advanced trauma life support (ATLS) strategy, 57
Adverse drug reactions (ADRs), 780–781
AF. *See* Atrial fibrillation/flutter (AF)
Agency for Health Care Quality and Improvement (AHQI), 214, 237
Age of Blood Evaluation trial (ABLE) study, 592
Age of Blood in Children in Pediatric Intensive Care Units (ABC PICU) study, 592
Aging. *See* Geriatric
Ahvenjarvi, L.K., 802
Airway pressure release ventilation (APRV), 296, 301–303, 354, 357–359
AIS. *See* Acute ischemic stroke (AIS)
AKI. *See* Acute kidney injury (AKI)
Al-Aama, T., 205
Alcohol withdrawal syndrome (AWS)
CIWA-Ar, 753
classification, 753
clinical findings, 751–752
delirium tremens, 752
diagnosis, 752
differential diagnosis, 753–754
GABA-A, 751
NMDA receptors, 751
treatment
alcoholic ketoacidosis, 756
benzodiazepines, 754
beta blockers and clonidine, 755
chlorpromazine, 755
DEX, 755
divalproex sodium, 755
haloperidol, 755
hypoglycemia, 756
hypokalemia, 755
hypomagnesemia, 755
hypophosphatemia, 755
post-operative DT's, 756
standard therapy propofol, 755
Alelectasis
bilevel/APRV, 395
bronchoscopy, 395
mucolytics, 394
respiratory therapy, 394
Alhazzani, W., 517
Ali, M., 535
Allen, S.J., 245
American College of Chest Physicians (ACCP), 107, 401, 404, 406, 417, 606, 611–612
American Geriatric Society (AGS) Beers Criteria, 781–782
Amiodarone, 455, 483, 484, 489
Amitrano, L., 536
Amniotic fluid embolus syndrome, 768
Andrews, A.H., 567, 801
Angiotensin converting enzyme (ACE), 269
Annane, D., 16, 482, 626
Antepartum hemorrhage, 760
Antibiotic Associated Diarrhea (AAD), 576
Antidotes, 731, 732
Antigen presenting cells (APC), 589
Antihypertensive treatment of acute cerebral hemorrhage (ATACH), 689
Apical ballooning syndrome (ABS). *See* Takotsubo cardiomyopathy
ARDS. *See* Adult respiratory distress syndrome (ARDS)
Arginine vasopressin (AVP), 639
Aronson, D., 598
Aronson, S., 175
Arrhythmias
accelerated idioventricular rhythm, 487
acute atrial fibrillation/flutter
acute management components, 482–483
anticoagulation, 484–485
dopamine, 483
electrical cardioversion, 483
etiology and management strategies, 482
pharmacologic cardioversion, 484
pulmonary hypertension, 482
rate control, 483
bigeminy, 487
hypokalemia, 482
intravenous magnesium, 481–482
MAT, 485
PSVT
accessory pathways, 486–487
atrioventricular nodal reentrant tachycardia, 485
management, 486
sick-sinus syndrome, 487
sinus bradycardia, 487
ventricular premature complexes, 487
ventricular tachycardia
nonsustained, 488
PVT (*see* Polymorphic ventricular tachycardia (PVT))
sustained, 488–489

Arterial blood gas (ABG), 306–307
acid-base balance, 334–335
acid-base disorders
anion gap, 336–337
clinical states, 335–336
compensatory response, 336–337
normal values, 336
osmolar gap, 337–338
physical examination, 335
primary disturbance, 336–337
alveolar ventilation, 331
anion gap, 335
indications, 329–330
metabolic acidosis
bicarbonate, 340
causes, 338–339
lactic acidosis, 340–341
myocardial depression, 338
metabolic alkalosis, 341–342
oxygenation, 332–334
$PaCO_2$, 329
PaO_2, 329
$SmvO_2$ and $ScvO_2$, 343–344
specimens, 330–331
VBGs, 342–343
Arterial catheters, 34–35, 226
Asfar, P., 15
Aspiration pneumonia (AP), 262
Asthma/acute lung injury (ALI), 291
Asymptomatic vasospasm, 701
Atrial fibrillation/flutter (AF)
acute management components, 482–483
anticoagulation, 484–485
cardioversion
electrical, 483
pharmacologic, 484
dopamine, 483
etiology and management strategies, 482
pulmonary hypertension, 482
rate control, 483
Australian Incident Monitoring Study, 789
Automated implantable cardioverter-defibrillator (AICD), 459
AWS. *See* Alcohol withdrawal syndrome (AWS)
Azoulay, E., 806

B
Bacterial pneumonia. *See* Pneumonia
Badawi, O., 155
Bahrani-Mougeeot, F.K., 230
Baka, 174
Barber, R.E., 185
Bare below the elbows (BBE), 217
Bariatric surgery, 793
Barkhausen, J., 802
Barkun, A.N., 555
Basal ganglia bleeds, 685
Baxi, S.M., 221
Beers Criteria, 781–782
Beers, Mark 781
Behavioral Pain Scale (BPS), 200
Behrendt, C.E., 777
Bellomo, R., 192
Benbadis, S.R., 717
Ben-Joseph, R., 517
Bigeminy, 487
Bilevel positive airway pressure (BiPAP), 311
Blajchman, M.A., 14
Blatchford risk severity score, 552, 553
Bleck, T.P., 720
Bleyer, A.J., 190
Blood urea nitrogen (BUN), 80
Blumberg, N., 593
Boekstegers, P., 134
Bohe, J., 505
Bolton, C.F., 49
Bonten, M.J., 515
Boomer, J.S., 625
Bouchard, J., 121
Boyd, J.H., 121, 132
Brain natriuretic peptide (BNP), 447
Brain Trauma Foundation guidelines, 705
Brandstrup, B., 100
Brogly, N., 607
Brooks, J.P., 602
Brown, C.B., 665
Brown, R.B., 266
Burns, S.M., 789
Burtin, P., 670

C
Calcium homeostasis, 645
Calderwood, M.S., 215
Cameron, L., 185
CAP. *See* Community-acquired pneumonia (CAP)
CAP multi-sensitive organism (CAP-MSO), 263
Carbapenem Resistant Enterobacteriaceae (CRE), 216
Carbon monoxide poisoning, 748–749
Cardiac function, 89–90
Cardiac output
bioreactance, 94
esophageal Doppler, 93
fluid and inotrope responsiveness, 94
pulmonary artery catheter, 90–91

pulse contour analysis, 92
supranormal hemodynamic approach, 94–95
transpulmonary thermodilution, 91–92
USCOM, 93
Cardiac resynchronization therapy (CRT), 459–460
Cardiogenic pulmonary edema, 799
Cardiovascular changes, 774–775
Carson, J.L., 596
Casaer, M.P., 50, 499, 502, 505
Catheter associated blood stream infection (CRBI), 791
Catheter associated urinary tract infections (CAUTI)
annual costs, 213
asymptomatic bacteriuria, 227
Foley catheters, 228
mortality, 214
National Anti-Foley Obsession, 229
symptomatic CAUTI, 227–228
CCL. *See* Chronic critical illness (CCL)
CDI. *See Clostridium difficile* infection (CDI)
Cellular aging, 773–774
Centers for Disease Control (CDC), 233
Centers for Medicare and Medicaid Services (CMS), 214
Central line associated blood stream infection (CLABSI)
annual costs, 213
bundles of care, 220
causes, 220
CNS, 222, 223
culture-negative, 223, 224
CVC
arterial lines, 221
cuffed, 220
femoral site, 222
incidence of, 221
internal jugular site, 222
non-tunneled, 221
peripheral venous site, 224
subclavian site, 221, 222
tunneled, 220, 221
diagnosis, 222–223
estimation, US, 220
factors, 221
management, 224–225
mandatory report, 214–215
meta-analysis, 221–222
PICC catheters, 221
prevention, 225–226
risk of, 221
tunneled hemodialysis catheters, 220–221
Central nervous system, 26, 40, 42, 284, 518, 763
Central venous access/Central venous catheter (CVC)
arterial lines, 221
complications, 34
cuffed, 220
femoral site, 222
femoral vein catheterization, 33
incidence of, 221
internal jugular site, 222
internal jugular vein catheterization, 32–33
non-tunneled, 221
peripheral venous site, 224
subclavian site, 221, 222
subclavian vein catheterization, 31–32
tunneled, 220, 221
Central venous oxygen saturation ($ScvO_2$), 343–344
Cerebral blood flow (CBF), 698–699, 703
Cerebral perfusion pressure (CPP), 700
Cerebral salt wasting syndrome, 637, 638, 680
Cerebral vasospasm
CBF, 698–699
computed angiography (CTA), 698
CPP, 700
DIND, 699
ETAs, 700
goal, 699
hypervolemia, 699
MAP, 700
prevalence, 698
transcranial Doppler (TCD)
asymptomatic vasospasm, 701
diagnosis, 700–701
symptomatic vasospasm, 701
Triple-H therapy, 699
Chanques, G., 200
Charpentier, C., 16
Charron, T., 643
Chatterjee, S., 597
Chest radiograph (CXR)
antero-posterior position, 797
cardiogenic pulmonary edema, 799
mediastinum, 800
non-cardiac pulmonary edema, 799
pleural collection, 800
pulmonary pathology, 797
radion exposure, 800, 801
supine, 797
tubes and catheters position, 798, 799
Child- Turcotte-Pugh (CTP) scoring system, 523, 524
Cho, Y.S., 75

Chronic critical illness (CCL)
anabolic steroids, 54
brain dysfunction, 51
definition, 47
exercise program, 54
general management, 53
ICU admission, 47
LTAC hospital, 47
metabolic bone disease, 48, 53
neuromuscular abnormalities (*see* Neuromuscular abnormalities)
pathophysiology, 48
patients prognosis, 48
prevention, 51–52
stress hyperglycemia, 53
testing, 52
trauma and burn patients, 47
vitamin D deficiency, 48
Chronic liver failure (CLF)
ACLF, 537
alcoholic hepatitis
clinical syndrome, 538
differential diagnosis, 539
laboratory studies, 538
management, 539–540
mDF and GAHS, 538–539
bacterial infection, 532–533
causes of, 524–525
coagulopathy, 534–535
CTP scoring system, 523, 524
FHF (*see* Fulminant hepatic failure (FHF))
HE (*see* Hepatic encephalopathy (HE))
hepato-adrenal syndrome, 532
HRS (*see* Hepatorenal syndrome (HRS))
MELD, 523
metabolic/hematologic deran, 525
POPH, 532
prevalence, 523
PVT, 535–537
SBP, 525–527
Chronic obstructive pulmonary disease (COPD), 291
endotracheal intubation, 377
hospitalization, 375
hospital mortality, 373
ICU admission, 375
initial settings, 378
mechanical ventilation, 373, 377–378
NPPV, 377
precipitating factors, 374–375
pro-BNP, 373
risk factors, 373
treatment, 375–377
Chronic renal insufficiency, 790
Cirrhosis. *See* Chronic liver failure (CLF)
CLABSI. *See* Central line associated blood stream infection (CLABSI)
Clevidipine monotherapy, 690
CLF. *See* Chronic liver failure (CLF)
Climo, M.W., 214, 216
Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar), 753
Clinical pulmonary infection score (CPIS), 232
Clopidogrel, 474, 476, 518
Clostridium difficile infection (CDI), 516, 517
acid-suppressive therapy, 239–240
annual costs, 213, 239
annual incidence, US, 239
cardinal symptom, 240
laboratory diagnosis, 241–242
mode of action, 239
morphology, 240
probiotics, 245
sigmoidoscopy, 242
surgical intervention, 245
toxin A & B, 240
treatment
adjunctive treatment options, 244
antibiotic therapy, 243
antimicrobial therapy, 243
antimotility agents, 243
fidaxomicin, 244
metronidazole, 243–244
vancomycin, 243–244
Coagulase-negative staphylococci (CNS), 222, 223
Coagulation disorders, 598
Cocaine
chest pain, 746
complications, 746–747
freebase and crack, 745
management, 747–748
prevalence, 745
Coca, S.G., 653
Cockcroft, D.W., 775
Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) pneumonia, 266–267
Community-acquired pneumonia (CAP), 261
atypical pathogens, 265
CAP-DRP
antimicrobial de-escalation, 263
low and acuity of illness, 263–264
monotherapy, 263
percentage, 262
risk factors, 262–264
classic CAP, 266
dual coverage, 266
macrolides, 266

Comprehensive geriatric assessment (CGA), 779
Compression ultrasonography (CUS), 408–409
Computed tomographic (CT), 801–802
Confusion Assessment Method for the ICU (CAM-ICU), 203
Conivaptan, 639
Connors, A.F., 14
Constantin, D., 500
Constantin, J.M., 13
Constipation, 579
Continuous mandatory ventilation (CMV), 300
Continuous positive airway pressure (CPAP), 295, 311, 395
Continuous renal replacement therapies (CRRT), 658–659
Continuous spontaneous ventilation (CSV), 295
Cook, D.J., 513, 514
COPD. *See* Chronic obstructive pulmonary disease (COPD)
Corona, G., 635
Corticosteroid Therapy of Septic Shock Study (CORTICUS) study, 625
Corticotropin-releasing hormone (CRH), 149
Cortisol, 621
Creatinine phosphokinase (CPK), 499
Cremer, O.L., 705
Critical care medicine
  generic treatment orders, 20–21
  ICU organizational models, 19
  patients admission, ICU, 20
Critical-Care Pain Observation Tool (CPOT), 200
Critical Illness Myopathy (CIM), 499
Critical Illness Related Corticosteroid Insufficiency (CIRCI). *See* Adrenal insufficiency
Cronberg, T., 17
Cryprecipitate, 614
CTP scoring system. *See* Child- Turcotte-Pugh (CTP) scoring system
CT pulmonary angiography (CTPA), 410
Cuff leak test, 323, 326
Cushing, H., 170
CXR. *See* Chest radiograph (CXR)

D
Dabbagh, O., 535
Daneman, N., 219
Davis, D.P., 186
Dawson, N.V., 14
de jonge, E., 186
Delayed ischemic neurological deficit (DIND), 699, 700, 702
Delirium
  benzodiazepines, 203
  CAM-ICU, 203, 204
  Delirium Rating Scales scores, 205
  dexmedetomidine, 205
  elderly, 779–780
  haloperidol, 204
  hyperactive, 203
  hypoactive, 203
  ICDSC, 203
  incidence, 203
  melatonin, 205
  mortality, 203
  non-pharmacological approaches, 204
  opiates, 199
  risk factors, 203
  symptoms, 203
Delirium tremens (DTs), 752
DeLorenzo, R.J., 726
de-Madaria, E., 569
de Mulder, M., 156
Derde, L.P., 217
Devlin, J.W., 204
Dial, S., 516
Diarrhea
  definition, 575
  infectious, 575
  non-infectious
    AAD, 576
    enteral feeding-associated diarrhoea, 576
    management of, 576–577
    risk factors, 575
  probiotics and prebiotics, 577–579
Diastolic blood pressure (DBP), 171
Diastolic dysfunction, 774
Diffuse alveolar damage (DAD), 350
Diffusion-weighted MRI imaging (DWI), 672
Diltiazem, 483
Direct Fick method, 90, 94
Disseminated intravascular coagulation (DIC), 598–600, 660, 768
Dobutamine, 126, 454, 478, 700, 702
Doppler ultrasound-guided techniques, 791
Drakulovic, M.B., 237
Drug-induced thrombocytopenia (DIT), 608
Duning, T., 154
Dutch Acute Pancreatitis Study, 578
Dysphagia, 267–269

E
Early goal directed therapy (EGDT), 15, 57, 115–117, 122–123, 126
Early Ventilator Associated Pneumonia (E-VAP), 262

Early warning scoring systems (EWS), 191
Eclampsia, 764. *See also* Pre-eclampsia
ECMO. *See* Extracorporeal membrane oxygenation (ECMO)
Egi, M., 154
Ekelund, 699
Electrolyte disturbances
  calcium homeostasis disorders, 645
  hypercalcemia, 648–650
  hypernatremia, 640–641
  hypocalcemia
    cause of, 646
    definition, 646
    intracellular calcium, 646–647
    treatment, 647–648
    vitamin D deficiency, 646
  hypokalemia, 641–642
  hypomagnesemia, 643–645
  hyponatremia
    AVP, 639
    cerebral/renal salt wasting syndrome, 637, 638
    conivaptan, 639
    definition, 635
    diagnostic approach and management, 636
    FEurate, 637–638
    optimal rate of correction, 639–640
    plasma Na+ concentration, 640
    SIADH, 637–639
  hypophosphatemia, 642–643
  sodium and water, 635
El-Sohl, A.A., 268
Elwany, S., 246, 248
End-of-life issues
  dying patient admission, 806
  palliative care
    goal, 806–807
    principles, 807–808
    scope of, 806
  prevalance, 805
  terminal/incurable illnesses, 806
  unrealistic expectations, 805
Endometritis, 768
Endothelin, 700
Epidural hematoma, 703
Erstad, B.L., 514
Etomidate, 622, 629
European Cooperative Acute Stroke Study (ECASS), 672
European Society for Clinical Nutrition and Metabolism (ESPEN), 529
Evidence based critical care
  clinical outcomes, 3
  clinical practice guidelines, 5
  iatrogenic complications, 7
  randomized controlled clinical trials, 3
  scientific evidence, 4
  treatment effect, 3
Expiratory positive airway pressure (EPAP), 311, 792–793
External ventricular drain (EVD), 692
Extracorporeal membrane oxygenation (ECMO)
  ARDS, 363
  β2-agonist, 365
  corticosteroids, 363
  glucocorticoid treatment, 364
  H1N1 infection, 363
  nitric oxide, 365
  omega-3 fatty acids, 366
  prostacyclin, 365
  surfactant dysfunction, 365
Extra vascular lung water (EVLW), 59, 320, 350–351

F

Fann, F.A., 625
Febrile non-hemolytic transfusion reactions (FNHTR), 589, 593
Feeding tubes, 36, 519, 801
Fegler, G., 90
Feissel, M., 66
Fever
  acute ischemic stroke, 678
  antibiotics, impact on, 275
  axillary measurements, 276
  blood cultures, impact on, 275
  body temperature, 275
  C. difficile toxin, 288
  chest radiograph, 286
  CT scan, 288
  cytokines, 276
  health care costs, 275
  infectious causes, 279
  infrared ear thermometry, 276
  intravascular thermistor, 276
  management algorithm, 286–287
  mechanisms and etiology, 275
  non-infections causes, 282–283
    alcohol and drug withdrawal, 281
    blood transfusions, 282
    drug fever, 279–281
    malignant hyperthermia, 279, 283
    neuroleptic malignant syndrome, 279, 283–284
    postoperative period, 281–282

serotonin syndrome, 279, 284–286
thromboembolic disease, 282
patients' status re-evaluation, 288
physical examination, 286
procalcitonin and lactate levels, 286
pro-inflammatory cytokines, 278
radiologic imaging, impact on, 275
rectal temperatures, 276
subarachnoid hemorrhage, 694
treatment, 276–278
ultrasound examination, 288
venous Doppler's, 288
Fever of unknown origin (FUO), 803
FFP. *See* Fresh frozen plasma (FFP)
FHF. *See* Fulminant hepatic failure (FHF)
Fick, A., 90
Fisher, N.C., 603
Fluid and catheter treatment trial (FACTT) trial, 121
Fluid boluses, 70–71
Fluid expansion as supportive therapy (FEAST), 122
Forel, J.M., 16
Forkhead box O (FOXO), 500
Forrest, E.H., 540
Foster, P.F., 603
Fractional excretion of sodium (FENa), 654–655
Fractional excretion of urate (FEurate), 637–638
Francoz, C., 536, 537
Fresh frozen plasma (FFP)
indications, 601
invasive procedure
central venous catheterization, 602–603
coagulation tests, 601–602
coagulopathy, 601–603
thoracentesis and chest tube placement, 604
paracentesis, 604–606
risks, 600
stable clotting factors, 600
TRALI, 601
Fuchs, B.D., 14
Fuid responsiveness and resuscitation
aggressive fluid strategy, 58
albumin, 76–77
burns, 80
conservative fluid srategy, 57
crystalloid bolus, 58
CVP, 63, 64
definition, 59
dehydration, 79
echocardiographic assessment, 67
dynamic echocardiographic parameters, 66–67
dynamic techniques, 67
static echocardiographic parameters, 66
static pressure and volume parameters, 67
elective non-cardiac surgery, 57
endothelial glycocalyx, 60, 61
EVLW curves, 59
fluid boluses, 70–71
fluid challenge, 69–70
Frank-Starling principle, 59
heart lung interaction, 64
hemodynamic instability, 57
hemodynamic management, 58
hemorrhage, 78–79
hetastarches, 77–78
hypoperfusion, 58
hypovolemia, 58
iatrogenic salt water drowning, 57
lactated Ringers (LR) solution
coagulopathy, 75
HCO_3, 73–74
hyperchloremic metabolic acidosis, 73
and kidney disease, 74–75
and liver disease, 75
metabolic fuel, 75–76
vs. NaCl, 72–73
renal failure, 73
Marik-Phillips curves, 60
morbidity and mortality, 57
oliguria, 80–81
passive leg raising maneuver
echocardiographic/Doppler techniques, 69
heart-lung interactions, 68
hemodynamic effects, 68
reversible auto-transfusion, 68
PPV, 65
sepsis and SIRS, 80
stroke volume, 59
SV, 62
traumatic brain injury, 79
Fulminant hepatic failure (FHF), 540
causes of, 541
cerebral edema, 542–543
clinical picture of, 541
ICP management, 543–544
intra-cranial pressure management, 543–545
Kings criteria, 546
liver transplantation, 545
patients presenting, 541–542
supportive measures, 545
Functional Risk Stratification Score (FUNC), 685
Furosemide, 437, 451–452, 654, 664, 703
Futier, E., 13

G
Gacouin, A., 16
Gallstone-induced pancreatitis, 565, 570
Gamma-amino-butyric acid type A receptor (GABA-A), 751
Gandhi, G.Y., 157
Ganz, W., 63
Garcia-Pagan, J.C., 555
Gastric residual volume, 497, 507
Gastrointestinal bleeding (GIB), 514–515
  Blatchford risk severity score, 552, 553
  bleeding peptic ulcers, 557–559
  esophageal varices, 559–560
  hemodynamic assessment, 551, 552
  history and examination, 551–552
  laboratory tests, 552
  lower GI bleeding, 560–562
  nasogastric aspiration, 552
  rate of bleeding, 551
  rebleeding, 555
  resuscitation, 553–555
  UGIB, 555
Gault, M.H., 775
Gazzaneo, M.C., 504
Geriatric
  AGS, 781–782
  body composition and muscle mass
    diaphragmatic function, 776
    elderly patient outcomes, 776–778
  cardiovascular changes, 774–775
  delirium, 779–780
  immune system changes, 776
  physiology, 773–774
  renal function, 775–776
  respiratory function, 775
  surgery
    ADRs, 780–781
    CGA, 779
    coronary artery bypass, 779
    delirium, 779–780
    elective, 778–779
  traumatic injuries, 778
Girard, T.D., 14, 202, 204
Glasgow alcoholic hepatitis score (GAHS), 538
Glasgow Coma Scale (GCS), 201
Global registry of acute coronary events (GRACE) risk model, 474
Glomerulosclerosis, 790
Goldfarb, G., 603
Golestanian, E., 670
Graduated compression stockings (GCS), 403
Grap, M.J., 237
Greif, R., 188
Grief, 188
Guerin, C., 16
Guerrero, J., 628
Guglielmi, G., 698
Gulley, D., 535
Guly, H.R., 189
Gusmao-Flores, D., 203
Gu, W.J., 578
Guyton, A.C., 131

H
HAI. *See* Hospital acquired infection (HAI)
Hall, J.E., 131
Haloperidol, 197, 204–205, 208, 755
Hamel, J.F., 15
Hamzaoui, O., 125
Harris, A.D., 217, 218
Havstad, S. E., 15
Healthcare associated pneumonia (HCAP), 261
Heart failure (HF)
  ADHF (*see* Acute decompensated heart failure (ADHF))
  systolic heart failure
    ACE inhibitors, 457
    AICD, 459
    aldactone, 458
    beta-blocker therapy, 457–458
    calcium channel blocking drugs, 459
    CRT, 459–460
    digoxin, 459
    HFpEF, 461–462
    hydralazine/isosorbide dinitrate, 458–459
    LVAD, 460–461
    revascularization, 460
    surgical options, 460
  Takotsubo cardiomyopathy
    ACE inhibitors, 464–465
    β-blockers, 464–465
    clinical symptoms, 463
    diffuse T wave inversion, 463–464
    emotional stress, 462–463
    features, 463
    octopus trapping pot, 462
    physical stress, 463
    post-menopausal women, 463
    QT interval prolongation, 463–464
Heart failure with preserved ejection fraction (HFpEF), 461–462
Hebert, C.A, 589
Hebert, P.C., 14
Helicobacter pylori, 556
Heme oxygenase-1 (HO-1), 591

Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
clinical presentation, 765
hepatic dysfunction, 764
hepatic injury, 765
microangiopathic hemolytic anemia, 764
SIRS, 765, 767
thrombocytopenia, 764
Hemolytic-uremic syndrome (HUS), 612
Hemorrhage, 78–79
Heparin-induced thrombocytopenia (HIT), 610–612
Hepatic encephalopathy (HE)
aggressive protein restriction, 529
colonic bacteria, 528
MARS, 529
neuropsychiatric syndrome, 527
nonabsorbable antibiotics, 528–529
West Haven criteria, 527–528
Hepato-adrenal syndrome, 532
Hepatorenal syndrome (HRS)
diagnostic approach, 529–531
diagnostic criteria, 529–530
pathophysiological, 529
treatment, 531
Herridge, M.S., 48, 499
Herzig, S.J., 516
Hetastarches (HES), 77–78
HF. *See* Heart failure (HF)
Hibbert, R.M., 604
Hickey, M., 605
Hickson, M., 577
High-frequency oscillatory ventilation (HFOV), 354–355
High resolution computed tomography (HRCT), 800
Hilbert, G., 246
Hillary, 182
Hill, G.E., 592
Histamine-2 receptor blockers (H2RB), 517
Holland, L.L., 602
Homsi, E., 665
Horvath, K.A., 593
Hospital acquired infection (HAI)
CAUTI (*see* Catheter Associated Urinary Tract Infections (CAUTI))
CDI (*see Clostridium difficile* infection (CDI))
CLABSI (*see* Central Line Associated Blood Stream Infection (CLABSI))
control measures
chlorhexidine bathing, 216–217
gloves and gowns, 217
hand antisepsis, 216
healthcare provider apparel, 217
oropharyngeal and gastrointestinal decolonization, 218–219
private rooms and environmental control, 219–220
counter-productive approach, 214
ICU death, 214
MDR
colonization, 215–216
MRSA isolation, 217–218
risk factors, 231
mediastinitis infection rates, 215
nosocomial rhinosinusitis, 246–248
in US, 213, 214
VAP (*see* Ventilator associated pneumonia (VAP))
Hospital acquired pneumonia (HAP), 214, 261
Hotchkiss, R.S., 134
H2 Receptor Antagonists (H2RA), 517–518
HRS. *See* Hepatorenal syndrome (HRS)
Huang, S.S., 218
Hughes, R.E., 62
Hu, H., 205
Hunt and Hess Classification system, 693
Hunt, W.E., 699
Huskins, W.C., 217
Hydrocortisone, 16, 627–628, 630
Hypercalcemia, 648–650
Hypernatremia, 640–641
Hypertensive crises
blood pressure management
ACE inhibitors, 436
antihypertensive agents, 435
APH, 439–440
autoregulatory range, 433, 434
clevidipine, 438, 439
clonidine, 436
esmolol, 438, 439
furosemide, 437
hydralazine, 436
labetalol, 437, 438
management principles, 436
nicardipine, 438, 439
nitroglycerin, 437
preoperative hypertension, 440–441
resident/hospitalist, 434–435
sodium nitroprusside, 437
sublingual and intranasal nifedipine, 436
definitions, 429–430
medical history, 432
objective evaluation, 433
pathophysiology, 430–431
physical examination, 432

Hypertensive crises (*cont.*)
PRES
characteristics, 441
clinico-neuro-radiological entity, 441
CT and MRI, 441
drugs, 442
pathogenetic theory, 441
pregnancy-induced PRES, 441
signs and symptoms, 431–432
Hypertonic saline, 706, 707
Hypervolemia, 699
Hypokalemia, 641–642
Hypomagnesemia, 643–645
Hyponatremia
AVP, 639
cerebral/renal salt wasting syndrome, 637, 638
conivaptan, 639
definition, 635
diagnostic approach and management, 636
FEurate, 637–638
optimal rate of correction, 639–640
plasma Na+ concentration, 640
SIADH, 637–639
Hypophosphatemia, 642–643
Hypothermia, 102

I
Ibrahim, G.M., 699
Ibsen, B., 7
Increased intracranial pressure (ICP)
CBF, 703
corticosteroids, 707
FHF patient, 543
hyperosmotic agents, 706–707
hyperventilation, 706
indications for, 704–705
management of, 543–545
measurement of, 704
mechanical ventilation, 708
narcotics, 705
prophylactic hypothermia, 707
TBI, 703
volume resuscitation, 706
Infection related ventilator associated complication (IVAC), 233
Infectious Diseases Society of America (IDSA), 243–244, 275
Inhaled nitric oxide (iNO), 365, 418
Inspiratory positive airway pressure (IPAP), 311
Inspiratory to expiratory (I:E) ratio, 298–299, 305, 378
Institute for Healthcare Improvement (IHI), 214, 236, 237
Intensive Care Delirium Screening Checklist (ICDSC), 203
Intensive care unit (ICU)
admission criteria, 39–40
admission history and physical examination, 23
cardiovascular system, 41–42
clinical pearls, 28
daily examination
abdomen, 25
additional observations, 24
chest, 25
CNS, 26
daily neurological examination, 26
heart, 25
ventilator, 25
vital signs, 24
discharge criteria, 44–45
drug ingestion and drug overdose, 42
endocrine, 43
follow up patients, 28
gastrointestinal disorders, 43
imaging, 27
laboratory tests, 26–27
neurological disorders, 42
new admissions, 27–28
patient's status, 27
physiologic indication, 44
postoperative care, 44
prioritization, 40–41
pulmonary system, 42
renal disorders, 43
INTERACT2 trial, 689
Intermittent hemodialysis (IHD), 14, 658
International Ascites Club, 529, 530
International Cooperative Pulmonary Embolism Registry (ICOPER), 399
International Stroke Trial (IST), 672, 676
Intracerebral hemorrhage (ICH)
blood pressure control, 689–690
Clot volume, 685
common sites of, 685, 686
incidence, 685
medical management, 687–689
prognostic score, 685, 686
risk factors, 685–686
STITCH trail randomized, 690–692
warfarin-associated, 685
Intravenous Nimodipine West European Trial, 679
Intraventricular hemorrhage (IVH), 685, 691–692

J
Janda, S., 271
Janz, D.R., 186, 591
Jawaheer, G., 505
Jehovah Witness literature, 596
Jepson, M.M., 134
Johnson, D.J., 779
Joseph, 699
Juffermans, N.P., 593
Juttler, E., 677

K
Kaarlola, A., 777
Kaasch, A.J., 224
Kalisvaart, K.J., 205
Kanji, S., 484
Kansagara, D., 597
Kantorova, I., 515
Karl, I.E., 134
Katsanos, C.S., 503, 626
Kcentra, 605
Keh, D., 16
Khan, H., 601
Khuri, S.F., 99
Kiguli, S., 16
Kilgannon, J.H., 186
Koo, H.L., 243
Kosnik, E.J., 699
Krag, M., 517
Kress, J.P., 13, 14

L
Lactate. *See* Stress hyperlactemia
Lactated ringers (LR) solution
  coagulopathy, 75
  HCO_3, 73–74
  hyperchloremic metabolic acidosis, 73
  and kidney disease, 74–75
  and liver disease, 75
  metabolic fuel, 75–76
  vs. NaCl, 72–73
  renal failure, 73
Lambert, M.L., 213
Lansdorp, B., 65
Late Ventilator Associated Pneumonia (L-VAP), 262
Latta, Thomas, 71
Lautrette, A., 808
Lawrence, V.A., 779
Lee, P., 646
Lees, K.R., 673
Left ven-tricular assist device (LVAD), 460–461
Left ventricular stroke work index, 120
Legrand, M., 131
Lehman, L.W., 175
Leppick, I.E. , 726
Levetiracetam, 72, 726, 727
Levine, S., 50, 500
Liberation
  classic weaning method, 319
  cuff leak test, 326
  EVLW, 320–321
  extubation failure, 325
  factors, 319–320
  failure causes, 324
  NIV, 324–325
  noradrenaline group, 321
  oxygen consumption and cardiac function, 320
  process, 322
  readiness testing, 322–323
  SBT, 323–324
  standard care, 319
  vasoactive drug treatment, 321
Lim, H.Y., 627
Lin, P.C., 517
Liu, L.L., 779
Liu, L.Y., 628
Long term acute care associated pneumonia (LTAC-P), 262
Long term acute care (LTAC) hospital, 47
Lorazepam, 205–206
Lowenstein, D.H., 720
Lowey, 244
Low molecular weight heparin (LMWH), 401, 403, 676, 780
Luca, A., 536
Lundy, J.S., 585
Lung parenchyma, 798–800
Lutterman, A.C., 800
Lyon, J.E., 755

M
Maas, M.B., 691
Macdonald, R.L., 720
MacLaren, R., 517
Maddrey's discriminant function (mDF), 538, 539
Maesaka, J.K., 637
Magee, L.A., 767
Magovern, G.J., 62
Mahjoub, Y., 65
Maitland, K., 16
Maki, D.G., 221, 227, 228
Malcolm, D.S., 647

Malignant obesity hypoventilation syndrome (MOHS)
chronic hypercapnic respiratory failure, 792
criteria, 792
pathophysiology, 792
treatment of, 792–793
Mannitol, 705–707
Mannucci, P.M., 534
Marcantonio, E.R., 780
Marik, P.E., 221
Martini, R.P., 699
Masko, 505
Matevosyan, K., 602
Maurya, I., 507
McNicoll, L., 779
McVay, P.A., 604
Mean arterial pressure (MAP), 700
Mean perfusion pressure (MPP), 175
Mechanical ventilation
ABG analysis, 306–307
acute cardiogenic pulmonary edema, 291
acute severe asthma, 386–387
ALI, 291
ALI/ARDS, 293
APRV, 296, 301–303
auto-PEEP, 305–306
clinical judgment, 291
CMV, 300
COPD, 291, 377–378
CPAP breaths, 295
hypercarbic respiratory failure, 291
IMV and SIMV, 299–300
indications, 291–292
initial settings, 293, 295
liberation (*see* Liberation)
NIV, 291
PBW, 292
PC-CMV, 299
PC-CSV, 300
PEEP, 303–305
phase variables, 293, 295
PSV and CPAP, 295, 296
SIMV, 295, 296
standard ventilator terminology and variables, 293–294
tracheostomy, 307–308
variables
cycling method, 297
I:E ratio, 298–299
inspiratory flow patterns, 297–298
trigger variables, 298
VC-CMV mode, 299
Meduri, G.U., 628
Melsen, W.G., 230
Meperidine, 208
Messori, A., 514
Methicillin resistant staphylococcus aureus (MRSA), 216
Methylprednisolone, 613, 629, 630
Metlay, J.P., 227
Meziani, F., 15
Micek, S.C., 121
Midazolam, 206
Mixed venous oxygen saturation ($SmvO_2$), 343–344
Model for end-stage liver disease (MELD), 523
Molecular adsorbent recirculating system (MARS), 529
Moller, J.T., 179
Morphine, 197, 208
Mueller, S.W., 755
Muench, E., 699
Muizelaar, J.P., 706
Mullens, W., 131
Muller, L., 69
Multidrug resistant organisms (MDR)
colonization, 215–216
MRSA isolation, 217–218
risk factors, 231
Multifocal atrial tachycardia (MAT), 485
Multi-sensitive organisms (MSO), 262
Multi-system organ failure (MSOF), 353
Mumtaz, H., 603
Murphy's laws of procedures, 29–30
Murphy, T., 639
Mutoh, T., 702
Myocardial infarction without ST-segment elevation (NSTEMI). *See* Unstable angina (UA)

N

Naloxone, 745
National Early Warning Score (NEWS), 191
National Health and Nutrition Examination Survey, 787
National Healthcare Safety Network (NHSN), 227
National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 761
National Institute of Neurological Disorders and Stroke (NINDS), 672
Nava, S., 777
Near-fatal asthma (NFA), 381
Needham, D.M., 500
Nelson, J.E., 808
Nesiritide, 453

Neuroleptic malignant syndrome, 279, 283–284
Neuromuscular abnormalities
  critical illness myopathy
    body composition, 51
    definition, 49
    diaphragm, 49
    diaphragmatic atrophy, 51
    implications, 51
    respiration, 49
    respiratory muscles, 50
    ventilatory support, 50
  critical illness polyneuropathy, 49
Neuromuscular blockers, 16
Neuromuscular blocking agents (NMBA), 362
Ng, T., 595
Nguile-Makao, M., 230
Nguyen, B., 15
Nguyen, H.B., 158
Nielsen, N., 17
Nieuwenhoven, C.A., 237
Nimodopine, 693–694
Nitroglycerin, 452–453
N-methyl- D-aspartate (NMDA) receptor, 751
Nohria, A., 132
Non-alcoholic steatohepatitis (NASH), 790
Non-cardiac pulmonary edema, 799
Non-contrast enhanced CT scans (NECT), 671–672
Nonconvulsive status epilepticus, 727–728
Noninvasive positive pressure ventilation (NPPV), 384–385
Non-invasive ventilation (NIV), 291, 792
  BiPAP ventilators, 311–312
  COPD, 312
  CPAP, 311
  EPAP cycle, 311–312
  face-mask, 311
  hypercapnic respiratory failure, 315
  hypoxemic respiratory failure, 315
  indications
    acute cardiogenic pulmonary edema, 313
    COPD exacerbations, 313
    facilitating extubation, 313
    immunocompromised patients, 314
    post-operative patients, 314
  initial settings, 312
  NIPPV, 315–316
Norfloxacin, 526–527
Nosocomial rhinosinusitis (NS), 246–248
Nosotti, M., 595
Novel oral anti-coagulants (NOAC's), 412–414
N-terminal pro-brain natriuretic peptide (NT-proBNP), 447
Nursing-home acquired pneumonia (NHP), 262
Nussenblatt, V., 229
Nutrition
  bolus *vs.* continuous feeding, 504–506
  composition, 493–494
  digest, 495–497
  EDEN trial, 498
  enteral nutrition (EN), 493
  feed critically ill patients, 506–507
  mTOR Pathway, 502–504
  muscle wasting
    anabolic and catabolic pathways, 500, 501
    CIM, 499
    CPK levels, 499
    FOXO, 500, 502
    myostatin, 500
    protein synthesis, 501
    proteolysis, 500
    steroids, 502
  myths of, 494
  obese patient, 507
  quantity, 493
  refeeding syndrome, 507–508
  starvation, 498–499
  time intervals, 493
  TPN, 494–495

O
Oba, Y., 798
Obesity
  cardiovascular effects, 789–790
  critical care outcomes, 787–788
  drug toxicity, 790
  hepatic and renal effects, 790
  ideal body weight, 789
  MOHS
    chronic hypercapnic respiratory failure, 792
    criteria, 792
    pathophysiology, 792
    treatment of, 792–793
  nutritional requirements, 790–791
  prevalence, 787
  radiological procedures, 791
  respiratory effects, 788–789
  vascular access, 791
Obstetrical hemorrhage, 760–761
O'Connor, M.F., 13
Octogenarians, 779
Oliguria, 80–81
O'Malley, C.M., 75
Ong, J.P., 527
Oostdijk, E.A., 219

Opelz, G., 588
Opoka, R.O., 16
Orogastrictube, 35
Osler, W., 3, 261, 269
Oxytocin, 761

P
Pabinger, I., 605
Page, V.J., 204
Pain, agitation and delirium pathway (PAD), 199
Pain management
  anxiety, 197
  BPS, 200
  CPOT, 200
  delirium (*see* Delirium)
  GCS, 201
  neuromuscular blockade, 209–210
  non-pharmacologic interventions, 202
  sedation
    ABC trial, 202
    analgesia protocol, 197–199
    bolus doses, lorazepam, 199
    complications, 199–200
    daily awakening trial, 202
    dexmedetomidine infusion, 199, 207
    fentanyl, 208
    haloperidol, 208
    lorazepam, 205–206
    meperidine, 208
    midazolam, 206
    morphine, 197, 208
    nonbenzodiazepine, 199
    propofol, 199, 206–207
    Ramsey Sedation Scale, 201
    RASS, 201–202
    treatable causes, 200
Palliative care, 806–808
Pancreatitis
  abdominal pain, 565–566
  causes of, 565
  complications, 568–569
  diagnosis, 566–567
  patient management, 569–571
  prevalence, 565
  risk stratification, 567–568
Pandharipande, P., 199
Panwar, R., 175
Papazian, L., 16, 209
Paracentesis, 36
Paradoxical vocal cord motion disorder (PVCM), 388
Pareznik, R., 134
Parienti, J.J., 222
Park, H.Y., 626
Paroxysmal supraventricular tachycardia (PSVT), 485–487
Partial pressures of carbon dioxide ($PaCO_2$), 329
Partial pressures of oxygen (PaO_2), 329
Passive leg raising maneuver (PLR), 67
Patanwala, A.E., 579
Paugam-Burtz, C., 13
Pedestrian- motor vehicle injuries, 778
Perfusion Index (PI), 189
Peri-operative fluid optimization
  goal-directed hemodynamic therapy, 99–100
  hypothermia, 102
  interventions, 99
  intraoperative oxygen debt theory, 101
  long-term survival, 99
  and postoperative complications, 101
  postoperative morbidity and mortality, 99
  $SmvO_2/ScvO_2$, 103
  technologies and treatment algorithms, 100
  traditional fluid management, 99
Petrov, M.S., 578
Phelan, H.A., 592
Phillips, R.A., 91
Plain abdominal radiography, 801
Platelet transfusion. *See* Thrombocytopenia
Platelet Transfusion in Cerebral Hemorrhage trial, 609, 689
Platt, R., 227
Pleth Variability Index (PVI), 189
Pleural effusions
  hepatic hydrothorax, 393
  pathophysiology, 391–392
Pneumonia
  appropriate initial antimicrobial therapy, 261
  aspiration
    ACE, 269
    antimicrobial therapy, 268–269
    diagnosis, 268
    dysphagia, 267
    NG tube, 269
    risk factors, 267–268
    SLP, 269
  CA-MRSA, 266–267
  CAP (*see* Community-acquired pneumonia (CAP))
  classification, 261–262
  co-existent/influenza pneumonia, 264
  complicated pleural effusion/empyema, 271
  C. pneumoniae, 265
  criterias, 264–265
  diagnostic testing, 265

DRP, 261, 262
HAP, 261, 262
HCAP, 261, 262
inappropriate initial antimicrobial therapy, 261
non-infectious diseases masquerade, 265
nursing home-acquired pneumonia, 269
persistent temperature/failure, 269–270
unusual pathogens, 270
Pohlman, A.S., 13
Polymorphic ventricular tachycardia (PVT), 489
management, 489–490
normal QT interval, 489
prolonged QT interval, 489
QRS morphology, 489
Polypharmacy, 780
Pongruangporn, M., 221
Portal vein thrombosis (PVT), 535–537
Portopulmonary hypertension (POPH), 532
Positive end-expiratory pressure (PEEP), 359–360, 788–789
Posterior reversible encephalopathy syndrome (PRES), 765
characteristics, 441
clinico-neuro-radiological entity, 441
CT and MRI, 441
drugs, 442
pathogenetic theory, 441
pregnancy-induced PRES, 441
Postpartum hemorrhage (PPH), 760
Predicted body weight (PBW), 23, 292
Pre-eclampsia
diagnosis
central nervous system, 763
coagulation system, 764
fetal, 764
HELLP syndrome, 764–765
hepatic, 764
PRES, 765
signs, 762–763
symptoms, 762
hepatic, 763
multiorgan disease process, 761
risk of, 762
treatment
anti-hypertensive agents, 766–767
corticosteroids and plasmapheresis, 767–768
hypertension, 765–766
Pregnancy, 339–340, 441
acute fatty liver, 768
amniotic fluid embolus syndrome, 768
cardio-respiratory changes, 759, 760
hypertension, 761
obstetrical hemorrhage
antepartum, 760
patient management, 760–761
postpartum, 760
pre-eclampsia (*see* Pre-eclampsia)
respiratory failure, 769–770
sepsis, 768–769
Pre-renal azotemia, 654–655
Press, M.J., 227
Pressure controlled intermittent mandatory ventilation (PC-IMV), 299–300
Pressure controlled ventilation (PCV), 354–357
Pressure support ventilation (PSV), 295
Propofol, 199, 206–207
Proton pump inhibitors (PPIs), 518
PROXI trial, 188
Pryor, K.O., 188
Puerperal sepsis, 768
Pulmonary artery catheter (PAC), 7, 343–344
Pulmonary artery occlusion pressure (PAOP), 63
Pulmonary embolism
absolute contraindications, 419
catheter directed clot fragmentation and aspiration, 418
diagnosis of
algorithm, 410, 411
CTPA, 410
CUS, 408–409
DD-US-CT strategy, 410
revised Geneva score, 408, 409
scoring systems, 408
V/Q scan, 410
Wells score, 408, 409
hypoxemic respiratory failure, 408
iNO, 418
thrombolytic therapy, 413, 415–416
treatment
NOAC's, 412–414
pulmonary embolism severity index, 411–412
vena caval interruption, 419
Puthucheary, Z.A., 50, 500, 502, 505

R

Raad, I., 224
Radiology
chest radiograph
antero-posterior, 797
cardiogenic pulmonary edema, 799
diaphragm, 800
non-cardiac pulmonary edema, 799
pneumothoraces., 800
pulmonary pathology, 797

Radiology (*cont.*)
radion exposure, 800, 801
supine, 797
tubes and catheters position, 798, 799
computed tomographic (CT), 801–802
indium labeled leukocye scans, 802–803
plain abdominal radiography, 801
Rady, M.Y., 779
Rafanan, A.L., 802
Raff, T., 515
Rahman, N.M., 271
Ramsey, M.A., 201
Ramsey Sedation Scale, 201
Ranson's Criteria, 567
Rao, S.V., 598
Rapid response team (RRT), 191–192
Reactive oxygen species (ROS), 185, 186, 188
Red blood cell transfusions
anemia, 585, 596
benefit/harm of, 596
complications, 588
FNHTR, 593
infectious, 587
noninfectious, 588
oxygen delivery equation, 586
packed red blood cells, 586, 587
postoperative and nosocomial infections, 592–593
randomized clinical trial, 597–598
storage lesion, 590–591
TACO, 594
TRALI, 594
transfusion-associated thrombosis, 594–595
10/30 transfusion trigger, 585
TRIM, 588–589
tumor recurrence, 595
Red Cell Storage Duration Study (RECESS), 592
Refeeding syndrome, 507–508
Refractory status epilepticus, 720–721, 726–727
Regueira, T., 134
Reignier, J., 16
Renal replacement therapy (RRT), AKI
criteria for, 657–658
CRRT, 658–659
dosing of, 659
recommendations for, 659
Renal salt wasting syndrome, 637, 638
Reperfusion therapy, 475–476
Respiratory function, 775
Rhabdomyolysis
acute renal failure mechanisms, 663
clinical manifestations, 663–664
creatine kinase, 659–660
dialysis, 665–666
epidemiology, 660
laboratory findings, 664
muscular trauma, 660
non physical causes, 661–662
pathophysiology, 663
physical causes, 660–661
risk factors, 662
treatment of, 664–665
Rice, T.W., 498
Richard, J.C., 16
Richmond Agitation-Sedation Scale (RASS), 201–202
Rifaximin, 528
Right ventricular infarction (RVI), 478
Rincon, F., 186, 708
Rivers, E., 15, 57, 58
Rodriguez, A., 266
Rohde, J.M., 593
Ronco, J.J., 134, 176
Rose, L., 237

S

Saccharomyces boulardii, 578
Safar, P., 7
Safdar, N., 221
SAH. *See* Subarachnoid Hemorrhage (SAH)
Salerno, D., 802
Salerno, F., 526
Salgado, C.D., 219
Salicylates, 738–739
Saline-adenine-glucose- mannitol (SAG-M), 590
Saline versus Albumin Fluid Evaluation (SAFE) study, 77
Salman, S.S., 609
Sarcopenia, 776, 790
Schuetz, P., 223
Schmidt, J.M., 700
Schmidt, M.G., 219
Schreiber, M.P., 630
Schweickert, W.D., 202
Sebille, V., 16
Segal, R., 602
Seizures
complication, 718
hypoglycemia, 717
management, 719
primary neurological disease, 719
therapy, 719–720
tonic-clonic convulsions, 717
Selective decolonization of the digestive tract (SDD), 218–219

Selinger, C.P., 577
Semmelweis, I., 216
Sepsis, 80
  antibiotic therapy, 118
  bacteriologic data, 108
  B-blockers and phenylephrine, 128–129
  blood-pressure, 15
  CVP, 117
    detrimental effect, 131
    ESCAPE trial, 132
    lung protective strategy, 133
    mean capillary pressure, 132
    mean systemic filling pressure, 131
    microcirculatory flow and organ function, 131
    natriuretic peptides, 132
    normal venous pressures, 130
    renal replacement therapy, 132
  definition, 107
  diagnosis, 115
  EGDT, 116
  epidemiological data, 107
  fluid therapy
    aggressive fluid resuscitation, 119
    EGDT, 122–123
    endothelial injury, 120
    endotoxin, 119
    FACTT trial, 121
    FEAST study, 122
    fluids and vasopressor, 123
    Frank-Starling curve, 119–120
    iatrogenic injury, 119
    iatrogenic salt water drowning, 119
    left ventricular stroke work index, 120
    mean arterial pressure, 123
    myocardial edema, 120
    natriuretic peptides, 119
    pneumonia, 121
    tissue edema, 120
    vasodilatation, 119
    vasopressin in septic shock trial, 121
    vasopressor agent, 123
  ICU, 107
  incidence, 107
  mortality, 108
  organ dysfunction
    blood cultures, 113
    manifestation, 113
    polymerase chain reaction, 113
    procalcitonin, 113–114
    systemic inflammation, 113
  pathophysiology
    cardiomyopathy, 109–111
    complications, 111
    resuscitation end-points, 129–130
    and septic shock, 15, 107
    tissue hypoxia and mitochondrial dysfunction
      animal models and patients, 134
      in animal models and patients, 134
      blood transfusion, 135
      corticosteroids, 135–136
      hemodynamic profile over time, 137
      hypoxic hypoxia, 134
      nitric oxide and glutathione, 135
      oxygen delivery, 134
      source control, 136
      tissue oxygen saturation, 134
    vasopressors and inotropic agents
      central venous catheterization, 126
      dobutamine, 126
      extravasation injuries, 127
      global biventricular dysfunction, 126
      mean perfusion pressure, 125
      mortality and organ failures, 125
      norepinephrine, 125
      SEPSISPAM, 124
      terlipressin, 127
      VASST trial, 127
      ventricular function, 126
SEPSISPAM trial, 175
Sequential compression devices (SCDs), 401, 676
Serotonin syndrome, 279, 284–286
Seshadri, N., 803
Severe acute respiratory distress syndrome, 16
Severe Community Acquired Pneumonia (S-CAP), 261
Sharma, B.C., 528
Shehabi, Y., 199
Shindo, Y., 262
Shoemaker, W.C., 100, 102, 103
Shulman, R.J., 505
Sick-sinus syndrome, 487
Siebig, S., 628
Sildenafil, 793
Sinus bradycardia, 487
3-SITES Multicenter Randomized Controlled Trial, 222
Skillman, J.J., 513
Skippen, P., 706
Sleeswijk, M.E, 484
Sligl, W.I., 266
Smith, D.T., 268
Smith, G.I., 503
Smith, I.J., 500
Society for Healthcare Epidemiology (SHEA) of America, 217, 243–244

Society of Critical Care Medicine, 805
Society of Critical Care Medicine, 275
Sort, P., 526
Stoutenbeek, C.P., 219, 514
Speech and language pathologist (SLP), 269
Speroff, T., 14
Spontaneous bacterial empyema (SBEM), 393
Spontaneous bacterial peritonitis (SBP), 525–527
Spontaneous breathing trials (SBT), 319, 323–324
Sprung, C.L., 16
Stark, R.P., 227
Status asthmaticus. *See* Acute severe asthma
Status epilepticus
  causes of, 721
  complications, 722
  definition, 720
  diagnosis, 722–723
  epilepticus, 728
  etiology, 721
  general measures, 723–724
  nonconvulsive, 727–728
  pathophysiology, 722
  pharmacotherapy, 724–726
  prevalence, 720
  refractory
    classification, 721
    definition, 720–721
    management of, 726–727
  treatment, 723
Stoll, B., 505
Strand, S., 765
Stress hyperglycemia
  acute hyperglycemia, 154, 155
  chronic hyperglycemia, 155
  clinical outcomes, 154
  epinephrine and norepinephrine, 153
  glucose, 153
  glucose control and steroids, 158
  iatrogenic normalization, 154
  insulin, 153
  observational data, 154
  skeletal muscles, 153
  thermal injury and sepsis, 153
  treatment, 155–157
Stress hyperlactemia
  brain metabolism, 163–164
  heart metabolism, 163
  illness severity, 160
  metabolic fuel, 162
  metabolic stress, 161–162
Stress response
  activation, 150
  cardiovascular effects, 152
  chronic stress syndrome, 152
  dysfunction, 151
  immune effects, 152–153
  metabolic effects, 153
  modulators, 151–152
Stress ulcer prophylaxis (SUP)
  acid suppressive therapy, 516
  complications
    H2RA, 517–518
    PPIs, 518
    sucralfate, 518–519
  enteral nutrition, 515–516
  GIB, 514–515
  H2RB's, 517
  pathogenesis, 514
  "ventilator bundles", 513
Stroke intensive care units, 670
Strom, T., 197
Study of Prevention of Postoperative Atrial Fibrillation (SPPAF), 482
Subarachnoid Hemorrhage (SAH)
  antifibrinolytic therapy, 698
  cerebral vasospasm management (*see* Cerebral vasospasm)
  diagnosis and evaluation, 693
  initial management
    agitation/delirium, 694
    anemia, 696
    bed rest, 693
    blood pressure control, 696
    brain tissue oxygen monitoring, 697
    cerebral microdialysis, 697
    corticosteroids, 697
    DVT prophylaxis, 696–697
    ECHO and ECG screening, 697
    fluid management, 694–695
    glucose control, 695–696
    laxatives, 696
    magnesium, 695
    mechanical ventilation, 697
    mild sedation/anxiolysis, 694
    nimodopine, 693–694
    nutrition, 697
    pain, 694
    sodium, 695
    statins, 697
    stress ulcer prophylaxis, 697
    temperature/fever, 694
  surgical and endovascular methods, treatment, 698
  TPTD, 701–702
Subdural hematoma (SDH), 702–703
Sucralfate, 518–519

SUP. *See* Stress ulcer prophylaxis (SUP)
Supraventricular tachycardia (SVT), 486
Surgical site infection (SSI), 187–188
Swan. H.J., 7, 63
Swiston, J., 271
Sympathoadrenal system (SAS), 149
Symptomatic vasospasm, 701
Synchronized intermittent mandatory ventilation (SIMV), 295, 296, 387
Syrjala, M.T., 803
Systemic inflammatory response syndrome (SIRS), 765
Systemic lupus erythematosus (SLE), 763
Systolic blood pressure (SBP), 171
Systolic heart failure
  ACE inhibitors, 457
  AICD, 459
  aldactone, 458
  beta-blocker therapy, 457–458
  calcium channel blocking drugs, 459
  CRT, 459–460
  digoxin, 459
  HFpEF, 461–462
  hydralazine/isosorbide dinitrate, 458–459
  LVAD, 460–461
  revascularization, 460
  surgical options, 460

T
Tachycardia-bradycardia syndrome, 487
Takotsubo cardiomyopathy
  ACE inhibitors, 464–465
  β-blockers, 464–465
  clinical symptoms, 463
  diffuse T wave inversion, 463–464
  emotional stress, 462–463
  features, 463
  octopus trapping pot, 462
  physical stress, 463
  post-menopausal women, 463
  QT interval prolongation, 463–464
Tambyah, P.A., 228
Tavernier, B., 66
Technetium-labeled red blood cell (Tc-RBC), 561
Teltsch, D.Y., 219
Tenzing, 182
Thoracentesis, 36
Thrombocytopenia
  anticonvulsants, 607
  antimicrobials, 607
  causes, 607
  complications, 608
  definition, 606
  DIT, 608
  diuretics, 608
  etiology, 607
  HITT, 610–612
  indications of, 608, 609
  platelet product contents, 608, 609
  TTP, 612–613
Thromboembolic disease (TED)
  DVT
    diagnosis, 405–406
    diagnostic algorithm, 410–411
    distal lower extremity, 406
    pregnancy, 399–400
    prophylaxis protocols, 405
    UEDVT, 406–408
    venous thrombosis (*see* Venous thrombosis)
    Wells score, 409
  pulmonary embolism (*see* Pulmonary embolism)
Thrombolysis in myocardial infarction (TIMI) risk score, 473–474
Thrombotic thrombocytopenic purpura (TTP), 612–613
Timset, J.F, 222, 226
Torsades De Pointes, 489–490
Total parenteral nutrition (TPN), 494–495
Towne, A.R., 723
Toxicology
  activated charcoal, 732–733
  anticholinergic syndrome, 735
  cholinergic syndrome, 735
  depressed level of consciousness, 734
  ethylene glycol and methanol poisoning
    cocaine (*see* Cocaine)
    digitalis, 743
    isopropyl alcohol, 742–743
    lithium, 744
    opiates, 745
    osmolar gap, 741
    phenytoin, 743–744
  extrapyramidal, 735
  flumazenil, 731
  gastric lavage, 731–732
  hallucinations, 735
  hemodialysis, 733–734
  hemoperfusion, 733
  intoxications
    acetaminophen, 735–738
    acute ethanol, 739–740
    antidotes, 731, 732
    carbon monoxide poisoning, 748–749

Toxicology (*cont.*)
salicylates, 738
tricyclic antidepressants, 738–739
ipecac, 731
isopropyl alcohol, 742–743
methanol poisoning, 741–742
nystagmus, 735
seizures, 734–735
serotonin syndrome, 735
sympathetic syndrome, 735
toxidromes, 734
Toxidromes, 734
Transcranial Doppler (TCD) technology, 700–701
Transfusion associated circulatory overload (TACO), 594
Transfusion associated graft-versus-host disease (TA-GvHD), 589
Transfusion related acute lung injury (TRALI), 594
Transfusion related immunomodulation (TRIM), 588–589
Transpulmonary thermodilution, 91–92
Trauma, 778
Traumatic brain injury (TBI), 79, 703
Treggiari-Venzi, M., 197
Tricyclic antidepressants, 738–739
Tripodi, A., 534Tsai, M.H., 530, 532

U
Undersea and Hyperbaric Medical Society, 749
Unfractionated heparin (UFH), 401
Unstable angina (UA)
Canadian cardiovascular classification, 472
class II recommendation, 475
class I recommendation, 474–475
differential diagnosis, 472
electrocardiography, 472–473
GRACE risk model, 474
risk stratification, 473
TIMI risk score, 473–474
tropinins, 473
types, 472
Upper extremity deep venous thrombosis (UEDVT), 406–408
Upper gastrointestinal bleeding (UGIB)
causes of, 556
definition, 555
endoscopy, 556–558
peptic ulcer disease, 555

V
Vancomycin, 224, 243–244
Vancomycin resistant enterococci (VRE), 216
van den Akker, 628
van den Berghe, G., 15, 155, 157
Van Santvoort, H.C., 571
Vargas, F., 246
Varpula, M., 124, 175
Venous blood gas analysis (VBGs), 342–343
Venous thrombosis
bleeding risk score, 403–404
Caprini DVT risk assessment score, 401, 403
distal lower limb leg, 400
GCS, 403
IVC filter, 401
LMWH, 401, 403
lower leg, 401, 402
SCDs, 401, 403
UFH, 401, 402
Ventilation/perfusion scanning (V/Q), 410
Ventilator associated condition (VAC), 233
Ventilator associated pneumonia (VAP), 516
annual costs, 213
APACHE II Score, 230
clinical signs, 229
diagnosis, 229, 232–233
empiric antibiotic choice, 235
incidence rate, 229
individual patient data, 230
mortality, 214
pathogenesis, 230–232
prevention
acid suppressive therapy, 238
chlorhexidine mouth wash, 237–238
endotracheal tube remove, 235
head of bed elevation, 237
probiotics, 239
recommended measures, 239
subglottic suctioning, 238
ventilator bundle, 236
SAPS II score, 230
surveillance definitions, 229
treatment, 234–235
Ventricular fibrillation, 486
Ventricular premature complexes, 487
Ventricular tachycardia
nonsustained, 488
PVT (*see* Polymorphic ventricular tachycardia (PVT))
sustained, 488–489
Villa, E., 537
Villanueva, C., 554, 597

Vital signs
acute reperfusion therapy, 187
blood pressure
aging, 171
autoregulation, 174
brain-heart distance, 170–171
central *vs.* peripheral measurement, 173–174
CVP, 169
Giraffe theory, 170–171
IDACO study, 172
intensivist/anesthesiologist, 172
JNC 8 treatment, 172
MAP, 169, 175–176
measurement, 171
NIBP *vs.* IAP, 172–173
organ failure and death, 175–176
PAMELA study, 172
SBP *vs.* MAP, 172–173
sex difference, 172
TPR, 169
circulatory shock, 176–177
EWS, 191
hypercapnia, 184–185
hyperoxemia, 186
hyperoxia, 184, 186, 187
hypoxemia, 179–180, 186, 187
hypoxia, 184, 186
ischemia, 186
oxidative killing, 187
oximetric waveform analysis, 188–189
oxygen tension, 186
pulse oximetry
alveolar hypoventilation, 184
arterial blood gas analysis, 183–184
conscious sedation, 179
Fallot's tetralogy, 182
fifth vital sign, 179
FiO_2, 179, 185
oxygen–hemoglobin dissociation curve, 180, 181
PaO_2, 180–182, 185, 186, 188
plethysmograph, 180, 181
SaO_2, 180–182
SUPPORT study, 183
pulse rate, 177–178
respiratory rate, 178–179
ROS, 185, 186
RRT, 191–192
Shock Index (SI), 191
SSI, 187–188
stroke volume, 189–190
supplemental oxygen therapy, 187
supplemental postoperative oxygen, 188
TBI, 186
temperature, 179
threshold values, 190, 191
Vocal cord dysfunction, 388
Volume controlled intermittent mandatory ventilation (VC-IMV), 295, 299–300
von Willebrand factor (VWF), 613

W
Wacker, C., 114
Waddell, D.S., 502
Walsh, M., 175
Walsh, T.S., 597
Wanahita, A., 803
Wang, F., 238
Waterer, G.W., 266
Watkins, P.B., 736
Weekers, F., 15
Weigner, M.J., 484
Weil, M.H., 7
Wells, G., 14
Wetterslev, J., 17
White cell scans, 803
Whiteley, W.N., 676
Wolff-Parkinson-White (WPW) syndrome
atrial fibrillation, 481–482
orthodromic atrioventricular reentrant tachycardia, 486
Wollersheim, T., 500
Words of wisdom, 811–812
Working Party for Hepatic Encephalopathy, 527
Wouters, P., 15
Wright, M.O., 226
Wunsch, H., 805

Z
Zaloga, G.P., 647
Zandstra, D.F., 514
Zaten, 246
Zaza, T., 798
Zhang, Z., 121