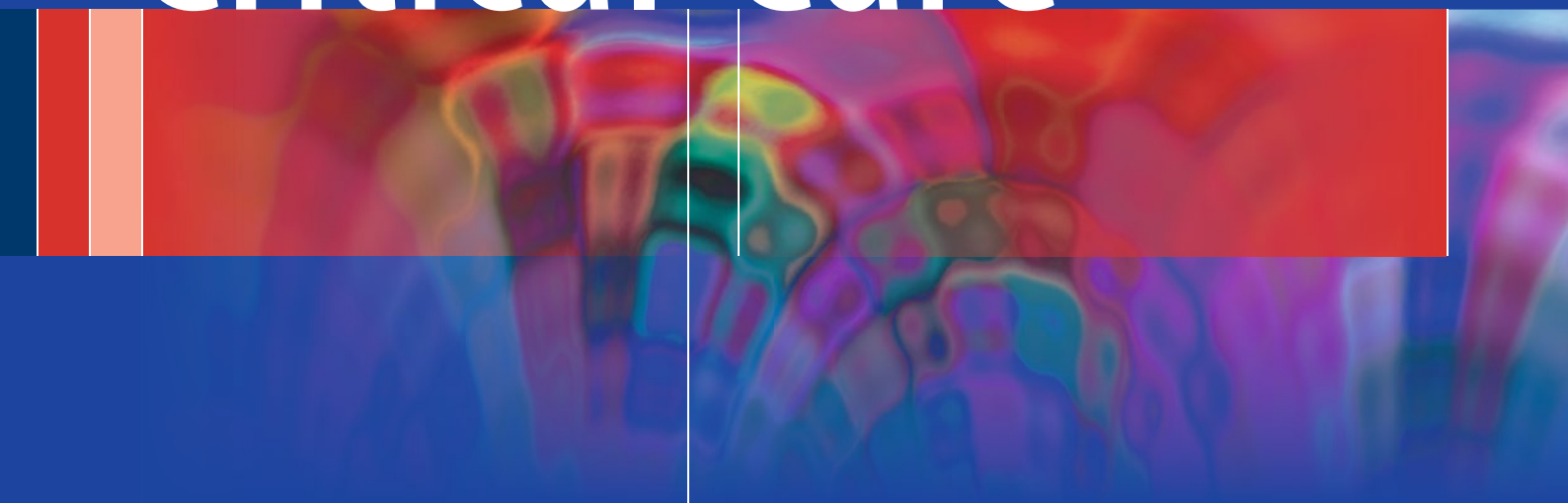
Principles of Adult Surgical Critical Care



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Foreword

Critically ill surgical patients are a diverse lot. So too are the maladies that befall them, or may if not prevented. Such patients may have widely divergent patterns of injury, or immunosuppression from injury, transfusion, neoplastic disease, or therapy (e.g., glucocorticoids, solid organ transplantation). Critically ill surgical patients have diverse (abnormal) physiology and responsiveness to stress, especially at the extremes of age. Elderly patients, in particular, have senescent immunity and impaired wound healing, and may have cardiovascular disease or diabetes mellitus that may impair responsiveness to injury-related stress, or disorders of mobility that may impede recovery.

Despite this diversity, there are crucial commonalities among the disease states of critically ill surgical patients and the care provided to them. Acute care surgery (trauma, emergency general surgery, surgical critical care) is inherently invasive. Incisions, percutaneous interventions, and physiologic monitoring catheters all breach epithelial barriers that protect the host against invasion by pathogens, posing incremental risk to a vulnerable population. Many patients require several such interventions, often in short order. Nosocomial infection is an ever-present risk, which in turn has been associated with increased risk of morbidity and mortality related to multiple organ dysfunction syndrome. The human and financial burdens are enormous, and survivors of complicated ICU courses may need months or years to achieve full functional recovery and return to productive society, if ever.

That the most unstable, at-risk patients often need the most aggressive, invasive care to achieve favorable outcomes is the great paradox of critical surgical illness. Great expertise is needed to restore homeostasis while also preventing the next potential complication. The experienced acute care surgeon must be facile and adroit with normal and pathologic anatomy, physiology, biochemistry, pharmacology, and immunology, and must possess the requisite technical skill to intervene effectively while not placing the patient at further risk. Knowledge of monitors, devices, medical imaging, and biomaterials requires familiarity with biomedical engineering. Proficiency with rehabilitation medicine, medical ethics, communication skills, and team building serves to keep information flowing to facilitate effective functioning of the team of physicians, nurses, therapists, nutritionists, dieticians, and family members that is integral to the decision making necessary for the successful outcome of every single patient. Some patients may be unable to recover; they too must be treated with skill and compassion in their time remaining.

Across the intensive care unit, complex integration of pathophysiology and therapy to balance risk and benefit must occur continuously and in parallel for multiple issues in several patients, and must often be accompanied or followed by decisive interventions. There is no substitute for experience, especially in that computerized decision support systems and artificial intelligence engines remain in their infancy.

This volume is directed appropriately and suited especially to medical students, surgery residents, and fellows in acute care surgery or surgical critical care. Described herein are all of the common maladies that may require surgical critical care, and the complications that may develop. Described are procedures that may be indicated in daily practice in the surgical intensive care unit or the trauma bay. It is hoped that the readership will be guided and inspired to master these “pearls of wisdom” and techniques, and to incorporate them into their own practices.

Much more than just a “how-to” manual, disease-state information is provided herein to orient the reader to the appropriate use of interventions. Mastery of these techniques combined with command of a vast body of knowledge is needed to practice acute care surgery effectively and safely.

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Foreword

As the volume and complexity of available information appropriate for intensivists explode, the bedside clinician would benefit from a structure from which to evaluate that information. Accordingly, this work is designed to provide the underpinnings upon which we all rely while providing bedside care, didactic education, or family counseling. Trainees, fellows, and attending staff alike will find an easily digestible exploration of relevant topics spanning from nutrition support to advanced ventilation: from antimicrobial stewardship to palliative care. This textbook is timely and incorporates current information to provide clinicians, regardless of parent training discipline, the key data needed to provide high value and high quality bedside care. The authorship reflects a multi-professional approach to education in deliberate parallel to the multi-professional fashion in which we help patients, families and each other navigate the complexity of critical illness. In this fashion, Drs. Martin and Kaplan have infused their text with the dedication, passion, and sensitivity that drew them and each of us to the ICU to serve the critically ill and injured to the very best of our abilities.

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Preface

This 1st edition textbook *Principles of Adult Surgical Critical Care* is intended to fill the literature gap that exists between standard medical critical care and the surgical complexities that coincide with critical illness. In the past decade, the value of surgical critical care has been realized in practices throughout the world, resulting in an influx of practitioners and trainees, all with a need for an advanced yet concise source of current information.

This textbook is focused on practitioners embarking on the final stages of training as well as those maintaining or expanding their existing clinical skillset. It therefore is not a basic text, but instead assumes a working knowledge of the underpinnings of critical care. Our format embraces evidence-based topic reviews focused on the care of the critically ill or injured surgical patient.

Reflecting the multi-professional nature of our bedside teams for optimal care, the contents target multiple practitioner domains across the critical care continuum. As a result, the chapter authors have included subject matter designed to comprehensively expand the reader's knowledge base for immediate bedside use, as well as objective test preparation.

For ease of use, this textbook is organized by organ systems, special populations, and pertinent topic sections. Each section contains several chapters addressing relevant disorders and monitoring and treatment modalities, as well as outcomes. Chapter authors have been personally selected based on national or international acclaim within their respective areas of expertise. As editors, we humbly offer thanks for the innumerable hours our authors have spent in preparation and refinement of their work. Without their efforts, this comprehensive volume would only be a dream instead of the learning tool we envision.

Finally, we would like to dedicate this textbook to all those in the final stages of training who are preparing to embark on a rewarding career caring for critically ill and injured patients. On a personal note, we are deeply indebted to our families for supporting us through the countless hours we devoted to this book on top of the hours we spent at the bedside – just like each of you do on a daily basis.

Philadelphia, PA, USA — Niels D. Martin, MD, FACS, FCCM
Philadelphia, PA, USA — Lewis J. Kaplan, MD, FACS, FCCM, FCCP

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Pain, Agitation, Delirium, and Immobility in the ICU

1

Juliane Jablonski

Introduction

Historically in critical care practice, patients were deeply sedated while receiving mechanical ventilation. This practice developed as a necessary need for patients to maintain synchrony with older versions of mechanical ventilators [1]. Along with significant technological advancements in respiratory therapy, a discriminatory approach is prudent in determining when critically ill patients have a clinical indication for continuous, deep sedation, such as refractory intracranial hypertension or certain types of severe acute respiratory failure. Sedation requirements can vary between patients depending on clinical circumstances; however, targeting lighter levels of sedation has been shown to lead to better patient outcomes [2–7].

Current pain, agitation, and delirium (PAD) evidence-based guidelines from the Society of Critical Care Medicine (SCCM) direct the practice of targeted "light" sedation, incorporating an analgesia-first approach, spontaneous awakening trials, the judicious use of non-benzodiazepine sedatives for symptoms refractory to analgesia, and non-pharmacologic means to alleviate discomfort and minimize delirium [7]. Translating evidence into daily practice can be challenging. Using patient-centered approaches that aim to empower patients and their surrogates to express their symptoms more precisely, the potential exists to simultaneously relieve unintentional suffering and improve ICU outcomes. The Institute for Healthcare (IHI) developed the concept of practice bundles to help providers deliver the best care for patients. Bundles are small, straightforward sets of evidence-based practices, when performed collectively and reliably have been shown to improve patient outcomes. Past examples include central line insertion and ventilator bundles [8].

The "ABCDEF bundle" is a mnemonic for a structure that can be used to operationalize the SCCM PAD guidelines into clinical practice (see Table 1.1). The ABCDEF bundle is evidence based and aimed to promote the best patient outcomes [9, 10]. The "A" is to assess, prevent, and manage pain first. The "B" represents coordination of spontaneous awakening trials and spontaneous breathing trials. The "C" is for appropriate choice and titration of sedation and analgesia. The "D" is for the assessment, prevention, and management of delirium. The "E" is for early mobility and exercise. The "F" is for family engagement and empowerment. Each concept has a scientific background that will be discussed in detail throughout this chapter.

Research Background

Thomas Petty, a research pioneer in pulmonary medicine, and past president of the American College of Physicians, wrote in a 1998 article entitled *Suspended life or extending death*, "what I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead except for monitors that tell me otherwise" [11]. This quote represents Dr. Petty's recognition and intellectual inquiry of critical care practice that enhances deep sedation and prolonged bed rest. At the same time, research by Kollef et al. [12] showed an association of continuous sedative infusions with prolongation of mechanical ventilation [12]. This study set the foundation for a multitude of high-quality randomized controlled trials that continue to lead current practice changes in the management of pain, agitation, and delirium in critically ill patients.

Kress et al. [2] conducted the landmark randomized controlled trial that investigated the effects of decreased sedative use in 128 medical ICU patients and the first experimental research design to study an intervention called a "spontaneous awakening trial" [2]. The intervention required the spontaneous stopping of all continuous sedative infusions autonomously by the clinical nurse, once a day, to evaluate

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Table 1.1 Society of Critical Care Medicine: ABCDEF bundle

A	Assess prevent and manage pain
B	Both spontaneous awakening trials and spontaneous breathing trials to achieve light sedation levels and weaning from mechanical ventilation
C	Choice of analgesia and sedation
D	Delirium assessment, prevention, and management
E	Early mobility and exercise
F	Family engagement and empowerment

the patient's need for continued infusion of sedatives. If the patient did not tolerate the removal of sedation as evident by hemodynamic instability, or extreme agitation with risk to safety, then the medication was restarted at half the previous dose. In this trial the use of spontaneous awakening trials was shown to decrease cumulative doses of sedative medications, which resulted in 2.4 days less of mechanical ventilation and 3.5 days less in ICU length of stay. Unplanned extubations (i.e., premature removal of device) were the same in each study group.

In follow-up to the Kress et al. [2] study, Girard et al. [3] conducted a randomized controlled trial that combined the coordinated interventions of "spontaneous awakening trials" and "spontaneous breathing trials". All continuous sedatives were stopped once a day, and the patients were trialed on minimal ventilator support using "pressure support" to assess for breathing effort and efficiency [3]. This study is well known as the ABC wake-up and breathe trial because the "A" represents spontaneous awakening trials, the "B" represents spontaneous breathing trials, and the "C" represents the coordination of the interventions. Similar to results shown by Kress et al. [2], this study showed less cumulative use of benzodiazepines, 3.1 higher ventilator-free days, and a 4-day decrease in ICU length of stay in patients who received the intervention. There were more patients in the intervention group with unplanned extubations. The number of patients who required re-intubation, however, was similar between groups suggesting that the patients with unplanned extubations may have had a delay in assessment for earlier removal of the endotracheal tube.

In 2009, Schweickert et al. studied the connection between sedation, delirium, and immobility in ICU mechanically ventilated patients [4]. This was a multicenter, randomized controlled study that evaluated the use of spontaneous awakening trials, spontaneous breathing trials, and the outcomes of aggressive early physical activity of mechanically ventilated ICU patients. Patients with aggressive therapy received physical and occupational therapy 1.5 days after starting mechanical ventilation treatment. The control group received the standard physical and occupational therapy that started 7.4 days after starting mechanical ventilation treatment. Patients in the intervention group had 2 days less of delirium and 2.7 days less of mechanical ventilation. No unplanned extubations were encountered in this study. Fifty-nine percent of patients in the intervention group compared with 35 % in the control group returned to their baseline functional status at hospital discharge. The authors concluded that sedative-induced immobility is a preventable contributor to ICU-acquired weaknesses.

Analgo-sedation is a strategy of using only pain medication for sedation, without benzodiazepines, to provide comfort for mechanically ventilated patients. In 2010, Strom et al. conducted a randomized controlled trial evaluating the effect of a "no-sedation" ICU protocol [5]. This was the first trial to compare the use of intermittent opioid and short-acting hypnotic agents in a benzodiazepine-free sedation protocol. The control group received continuous short-acting hypnotic agents followed by continuous infusions of benzodiazepines and intermittent morphine. The no-benzodiazepine group had 4.2 more ventilator-free days, 9.7 fewer ICU days, and 24 fewer total hospital days. There was no difference in unplanned extubations between groups. In this study, additional resource persons acted as patient sitters and were used throughout the study for providing comfort to the patients and may have served as medical monitors to trigger nursing intervention.

In 2012, a randomized controlled trial compared the use of a sedation protocol with spontaneous awakening trials to a control group without the use of spontaneous awakening trials [6]. The intervention group received less benzodiazepines and opioids, but the overall results show no difference in days of mechanical ventilation, rates of delirium, or length of ICU stay. There was no significant difference in unplanned extubation rates between groups. A subgroup analysis of the trauma and surgical population resulted in an average of 7 days less on mechanical ventilation. A significant weakness in the study is that the stated adherence to the sedation protocol with spontaneous awakening trials was only 72 %. An important clinical finding from the study was that although spontaneous awakening trials were not strictly adhered to, a focus on a structured process for sedation choice in the ICU resulted in lower cumulative amounts of sedative in both patient groups.

Augustus and Ho [13] published a review of randomized controlled trials comparing a practice that uses continuous sedative infusions combined with daily spontaneous awakening trials to a practice that uses continuous sedative infusions and a physician-driven daily decreases in the sedative infu-

sions as desired. The review includes five studies and a total of 699 patients in the meta-analysis [13]. The summary of the meta-analysis concludes there are similar reductions in cumulative sedative exposure, and no significant difference in the ventilator days, or ICU length of stay between the groups. In conclusion, either interventions of using spontaneous awakening trials or targeted light sedation strategies are shown to reduce sedative exposure and therefore may reduce the complications of the cumulative effects of oversedation.

The challenge of any practice protocol is translation within the clinical setting. National survey data have demonstrated that many providers identify the availability of practice guidelines and sedation protocols within their institutions but self-report challenges of low adherence, inconsistent use of ICU assessment tools, and gaps in communication between caregivers [1, 14]. Only 60 % of critical care units in the USA report instituting a protocol for sedation and analgesia, and those with protocols self-report variable compliance [15, 16].

One example of a descriptive study includes the distribution of surveys to 41 North American hospitals and the American Thoracic Society e-mail database [17]. Eighty-eight percent of hospitals report using validated sedation assessment tools, and only 50 % use validated delirium screening tools. Research shows that despite the reported use of validated sedation tools, clinicians typically prescribe target sedation levels only 24.9 % of the time, and only 34.7 % of the patients actually met the prescribed target [17, 18]. Physician and nursing assessment behaviors interestingly show that even when patients are minimally arousable, these patients are being judged as oversedated only 2.6 % of the time [18]. Personal beliefs about adequate sedation have been described to effect actual provider choices in medication and the desired level of sedation of the mechanically ventilated patients [14, 19–21].

Pain, Agitation, and Delirium Assessment Scales

Valid and reliable tools are recommended for the evaluation of pain, agitation, and delirium [7]. Multiple research protocols using validated pain and sedation scales with targeted "light levels" of sedation have been shown to maintain patient comfort while decreasing practice variation and cumulative sedative exposure [22–24]. Using assessment tools decreases subjective evaluation and allows for an objective framework when assessing pain, agitation, and delirium. The use of a common language allows for providers to promote goal-directed therapy. Similar to titrating medications for blood pressure and mean arterial blood pressure (MAP) goals, valid and reliable tools for pain, agitation, and delirium should guide pharmacologic treatment parameters.

Pain

Adult ICU patients routinely experience pain not only related to surgical procedures but during routine nursing care and at rest [25–27]. All healthcare professionals should be patient advocates for effective pain control. The "A" in the ABCDEF bundle exemplifies the importance of prioritizing pain management for all critically ill patients. For patients with a deep level of sedation, assessment for pain and delirium is limited, leading to a potential delay in recognition and treatment [1, 28, 29]. This is important because unrecognized, uncontrolled pain has been shown to be a risk factor for the development of delirium, and both early ICU deep sedation levels and delirium have been shown to be predictors of mortality [29–31].

Vital signs should not be used alone as an indicator of pain but are a cue to continue with an in-depth evaluation [27, 32]. Because pain is subjective by nature, patient self-report of pain level using a numeric pain score (NPS) is considered the gold standard of practice. When patients are unable to self-report pain, the most valid and reliable behavioral scales for monitoring of pain are the Critical Care Pain Observation Tool (CPOT) and the Behavioral Pain Score (BPS) (see Tables 1.2 and 1.3). According to the SCCM PAD guidelines, the CPOT and the BPS have good inter-rater reliability, discriminant validity, and criterion validity when evaluated against four other pain scales. A CPOT score of greater than two has a sensitivity of 86 % and specificity of 78 % for predicting the presence of pain [32]. A BPS of greater than 5 is the score indicative of the presence of pain [33].

Opioids are a mainstay of treatment for pain in critical care [17]. A variety of medications may be used as alternatives or adjuncts to opioid administration. Some examples include nonsteroidal anti-inflammatory drugs, acetaminophen, or anticonvulsants [25]. Non-pharmacological complimentary

Table 1.2 Behavioral Pain Scale (BPS); range 0–12, goal ≤5

Items	Description	Score
Facial expression	Relaxed	1
	Partially tightened (eyelids lowered)	2
	Fully tightened (eyelid closing)	3
	Grimace	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but mostly tolerating ventilation	2
	Fighting ventilator	3
	Unable to control ventilation	4

Reproduced with permission from Payen et al. [33]

interventions may include music or relaxation therapies; pet therapy, massage, acupressure, acupuncture, and aromatherapy are underexplored in the ICU by comparison.

Agitation-Sedation

Providers commonly use the word "agitation" to describe hyperactive patient behaviors [34]. Synonyms include disquiet and unrest. In the ICU, "agitation" covers a broad range of patient signs and symptoms from mildly restless behavior to dangerously thrashing about in the bed. It is important to adopt a standard validated tool for assessing a patient's level of agitation and sedation. This will allow for a common taxonomy when describing patient behavior and assist in developing an appropriate treatment plan.

The Richmond Agitation-Sedation Scale (RASS) [35] and the Riker Sedation-Agitation Scale (SAS) [36–38] are considered the most valid and reliable scales for assessing quality and depth of sedation in ICU patients (Table 1.4). According to the SCCM PAD guidelines, the RASS and the SAS yield the highest psychometric scores when reviewed against eight other subjective sedation scales reported in the literature [7]. Psychometric scores are based upon content validation, inter-rater reliability, discriminant validation, feasibility and directive of use, and relevance in clinical practice for goal-directed therapy. The goal of an agitation-sedation scale is to evaluate level of consciousness, but there is a limitation in determining the presence of acute delirium.

Table 1.3 Components of the Critical Care Pain Observation Tool (CPOT); range 0–8, goal ≤3

Indicator	Score
Facial expression	Relaxed, neutral = 0
	Tense = 1
	Grimacing = 2
Body movements	Absence of movements = 0
	Protection = 1
	Restlessness = 2
Muscle tension Evaluated by passive flexion and extension of upper extremities	Relaxed = 0
	Tense, rigid = 1
	Very tense or rigid = 2
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement = 0
	Coughing but tolerating = 1
	Fighting ventilator = 2
Vocalization (extubated patients)	Talking in normal tone or no sound = 0
	Sighing, moaning = 1
	Crying out, sobbing = 2

Modified from Gelinas and Johnston [27]

Delirium

In 2001, two ICU delirium assessment tools called the Confusion Assessment Method for the ICU (CAM-ICU) [39] and the Intensive Care Delirium Screening Checklist (ICDSC) [40] gained recognition. Ely et al. from Vanderbilt University conducted the original validation study for the CAM-ICU [39] (see Fig. 1.1). Bergeron et al. from the University of Montreal conducted the original validation study for the ICDSC tool [40] (see Fig. 1.2). Currently there are a total of nine validation studies for the CAM-ICU with

Table 1.4 Comparison of the RASS and the SAS

	Richmond Agitation-Sedation Scale (RASS) [35]	Riker Sedation-Agitation Scale (SAS) [36]
Agitation	(4) Combative, violent, immediate danger to self	(7) Dangerous, pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
	(3) Very agitated pulls to remove tubes or catheters; aggressive	(6) Very agitated requiring restraint and frequent reminding of limits, biting ETT
	(2) Agitated frequent non-purposeful movement, fights ventilator	(5) Agitated anxious or physically agitated, calms to verbal instructions
	(1) Restless anxious, apprehensive, movements not aggressive	
Awake and calm	(0) Spontaneously pays attention to caregiver	(4) Calm and cooperative easily arousable, follows commands
	(−1) Drowsy but sustained eye contact ≥10 s	
Sedation	(−2) Light sedation briefly awakens to voice (eyes open and contact <10 s	(3) Sedated difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
	(−3) Moderate sedation movement or eye opening to voice (no eye contact)	(2) Very sedated arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
	(−4) Deep sedation no response to voice but movement or eye opening to physical stimulus	
	(−5) Unarousable	(1) Unarousable
	No response to voice or physical stimulus	Minimal or no response to noxious stimuli, does not communicate or follow commands

Medscape

Confusion assessment method for the ICU (CAM-ICU) flowsheet

Delirium can only be assessed in patients more alert than RASS –3 or SAS 3

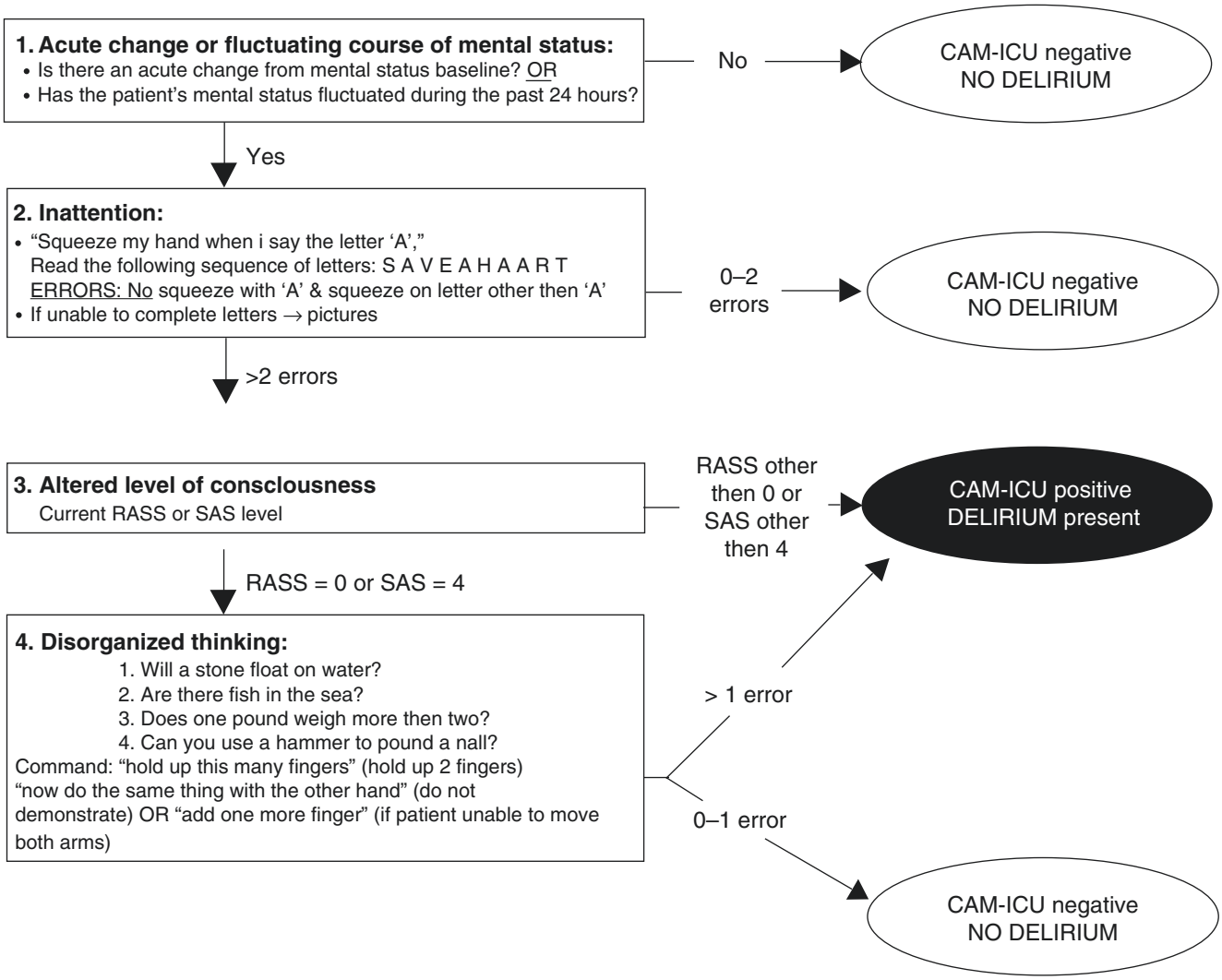

Fig. 1.1 Delirium screening: Confusion Assessment Method for the ICU (Brummel et al. [41])

a combined sample size of 969 to show the CAM-ICU having a pooled sensitivity of 80% and a specificity of 95.5% [42]. There are a total of four validation studies and a combined sample size of 391 to show the ICDSC with a sensitivity of 74% and a specificity of 81.9% [42]. The CAM-ICU is the most frequently used assessment tool for institutions that perform routine delirium monitoring [17].

The following four features are characteristic of delirium: acute onset or fluctuating course, inattention, disorganized thinking, and altered level of consciousness. According to the American Psychiatric Association [43], delirium is defined as a fluctuating disturbance of consciousness, with inattention, accompanied by a perceptual disturbance that develops over a short period (hours to days) [43]. Delirium is transient and usually reversible [44]. There are three types of delirium: hyperactive, hypoactive, and mixed. Hyperactive delirium is more easily recognizable as the symptoms include moderate to severe agitation and confusion. Hypoactive delirium is more discreet as the person appears calm and quiet and is only evident with focused interaction.

Delirium occurs in up to 50–70% of critically ill patients [30, 45]. ICU delirium, previously termed ICU psychosis, was once thought to be an inconsequential and uncontrollable

Intensive Care Delirium Screening Checklist (ICDSC)

1. Altered level of consciousness Deep sedation/coma over entire shift [SAS = 1,2; RASS = –4,–5] = Not assessable Agitation [SAS = 5,6 or 7; RASS = 1–4] at any point = 1point Normal wakefulness [SAS = 4;RASS = 0] over the entire shift = 0 point Light sedation [SAS = 3; RASS = –1,–2,–3] = 1 point (if no recent sedatives) = 0 points (if recent sedatives)	No	0	1	Yes
2. Inattention Difficulty following instructions or conversation; esily distracted by external stimuli Will not reliably squeeze hands to spoken letter "A":S A V E A H A A R T	No	0	1	Yes
3. Disorientation In addition to name, place, and date, dose the patient recognize ICU caregivers? Does patient know what kind of place they are in? (list examples such as dentist's office, home,work,hospital.)	No	0	1	Yes
4. Hallucination, delusion,or psychosis Ask the patient if they are having hallucinations or delusions (e.g., trying to catch an object that isn't there). Are they afraid of the people or things around them?	No	0	1	Yes
5. Psychomotor agitation or retardation EITHER: Hyperactivity requiring the use of sedative drugs or restraints to control potentially dangerous behavior (e.g., pulling IV lines out or hitting staff). OR: Hypoactive or clinically noticeable psychomotor slowing or retardation.	No	0	1	Yes
6. Inappropriate speech or mood Patient displays inappropriate emotion, disorganized or incoherent speech, sexual or inappropriate interactions, or is apathetic or overly demanding.	No	0	1	Yes
7. Sleep-wake cycle disturbance EITHER: frequent awakening /<4 hours sleep at night. OR: Sleeping during much of the day	No	0	1	Yes
8. Symptom fluctuation Fluctuation of any of the above symptoms over a 24-hours period.	No	0	1	Yes
Total shift score (Min 0 - Max 8)				

Fig. 1.2 Delirium screening: Intensive Care Delirium Screening Checklist (ICDSC) (Adapted from Bergeron et al. [40])

complication of critical illness. Now both modifiable and non-modifiable risk factors are being reported in the literature. The first step is to recognize the presence of delirium though daily consistent monitoring with valid and reliable scales as described earlier. Expounding the exact etiology of delirium is a challenging component in determining appropriate management. Delirium may be disease induced such as organ dysfunction in severe sepsis; iatrogenic such as with exposure to sedatives and opioids; or environmental, related to noise, poor sleep hygiene, immobilization, and the use of physical restraints.

Predisposing risk factors for the development of delirium include but are not limited to age >65 years and the presence of a baseline cognitive disorder. Precipitating factors are multiple and include fluid and electrolyte disturbances, hypoxemia, drug withdrawal syndromes, uncontrolled pain, and polypharmacy. Figure 1.3 presents one delirium assessment algorithm for critically ill patients. Medications with a high psychoactive activity or anticholinergic potential have been associated with an increased risk of delirium [46].

Scientific research into the biological changes that underlie delirium is underway as there is poor understanding of the complex interactions between and within organ systems during delirium [44]. The following neurotransmitters that modulate the control of cognitive function, behavior, and mood may have

a role in the pathogenesis of delirium: acetylcholine, serotonin, dopamine, and gamma-aminobutyric acid [47]. Other potential causes may be related to inflammatory processes involving C-reactive protein, pro-inflammatory cytokines, or fluctuations in cortisol levels [44] or an oxidative impairment that leads to cerebral dysoxia and dysfunction [46].

Patient descriptions of ICU delirium experiences included frightening hallucinations with feelings of fear and panic. The overall themes of ICU delirium include fear, panic, fluctuations between reality and unreality, discomfort, and remorse [48]. Perhaps most importantly, these memories may persist after the delirium has cleared and impacts the incidence of the post-intensive care syndrome.

Benzodiazepines are the most frequently used sedatives to treat agitation in the ICU [17]. Lorazepam (Ativan) is a benzodiazepine that has an odds ratio of 1.2 as an independent risk factor for ICU delirium [49]. Every 1 mg dose of lorazepam in the previous 24-h period is significantly associated with a 20 % increase in the daily transition to delirium. When 20 mg or more is given in a 24-h period, there is a 100 % probability of transitioning to a delirious state. A systematic review that included 38 level III studies without a meta-analysis showed that benzodiazepines are consistently associated with an increased risk for developing delirium [50]. Other risk factors for delirium included depression, anticholinergic drugs, and age.

Delirium is associated with the non-beneficial outcomes of increased mortality and institutionalization. While there is limited randomized controlled data showing that benzodiazepines may increase ICU LOS or mortality, their use has been significantly correlated with increased rates of delirium in all adult ICU populations, regardless of predisposing risk factors [51–53]. These potentially conflicting viewpoints have been well addressed in current guidelines and recognize benzodiazepines as second-line medication for agitation-sedation [7].

Atypical antipsychotics, most notably haloperidol and quetiapine, are weakly recommended in the current SCCM guidelines as therapy for delirious patients as a means of reducing total delirium days. Only a limited number of studies have explored their use to reduce days of delirium in the ICU. Prophylactic use of atypical antipsychotics has not been shown to reduce rates of delirium in the ICU [54]. This practice is not recommended in current guidelines [7].

Non-pharmacological Approaches

Intubated patients are often frustrated by not being able to talk and communicate their thoughts and needs [14, 19]. Qualitative research with ICU survivors shows that patients become anxious when there is uncertainty regarding daily plans and moment-to-moment changes in care. Restraints and awakening to unanticipated, painful care appear to exacerbate anxiety and may precondition such a response to all care. The critical care team should develop communication skills and techniques to keep patients informed. Traditionally, patients use picture boards and write questions and comments on paper. More innovative approaches include using communication applications that are available on I-pads. Enhanced communication is enabled by reduced sedative use and the more recent emphasis on noninvasive ventilation as opposed to endotracheal intubation and mechanical ventilation.

Multicomponent non-pharmacological approaches are effective in reducing the incidence of delirium as well as falls in older non-ICU hospitalized patients [55, 56] (Fig. 1.1). Examples of non-pharmacological approaches include but are not limited to music therapy, noise reduction, exposure to natural light, and educational programs for staff. Inconclusive evidence exists for the role of non-pharmacological interventions in the treatment of ICU delirium with only limited studies that have been conducted in the ICU. Two available ICU studies conclude that treatments such as music therapy [57] and the use of earplugs [58] may be beneficial in reducing the need for sedatives. Early mobility for critically ill patients may reduce the total days of delirium in mechanically ventilated ICU patients [4].

Early Mobility

It is common for critically ill adults to have limited mobility due to deep sedation, hemodynamic instability, invasive procedures, and treatment with sophisticated lifesaving but bed tethering machines such as ECMO. One should note that such notions have been challenged and there are multiple reports of ambulating patients on mechanical ventilation coupled with ventricular assist devices. Prolonged bed rest has deleterious effects on multiple body systems [59–61]. Severe neuromotor weakness, deficits in self-care, and poor quality of life are being reported in patients for up to 5 years after discharge from the ICU [62].

Early mobilization of critically ill adults has been a focus of research over the past 10–15 years [63]. Early mobilization is not standard or clearly defined in the literature but generally refers to a process of sedation minimization along with supporting patients to first sit on the edge of the bed to sitting out of bed in chairs, standing, marching in place, and eventually ambulating [64]. Benefits of early mobilization are a reduction in hospital costs by decreasing the days of mechanical ventilation, duration of delirium, ICU length of stay, and overall hospital length of stay [4, 63, 65, 66]. Equipment to support and facilitate patient exercise in the ICU is essential to such programs.

Barriers to wide dissemination and implementation of early mobility programs include gaps in knowledge and concerns for patient safety. Providers may fear removal of invasive lines and tubes, cardiac complications, and patient falls. Multiple studies show that early mobility is both safe and

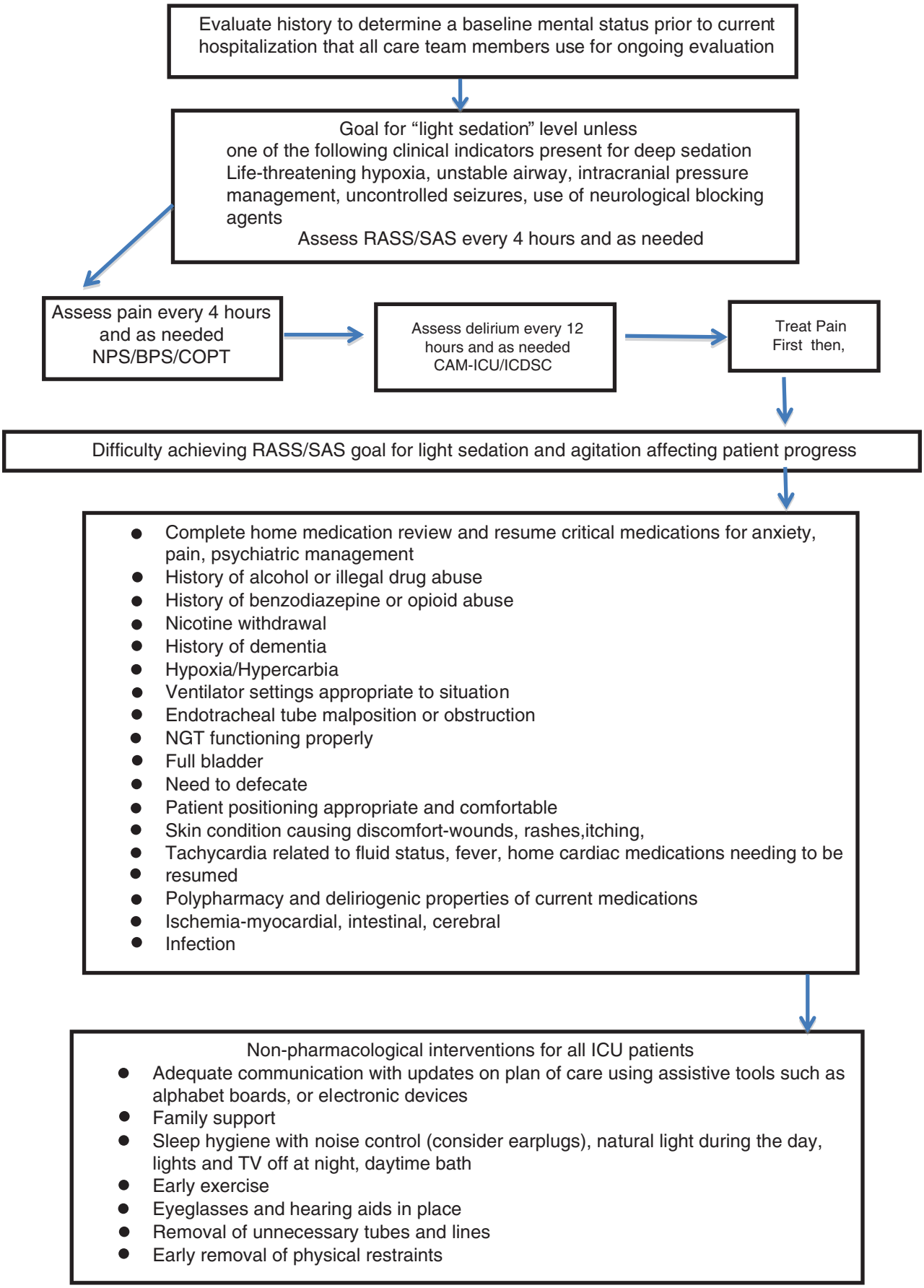

Fig. 1.3 Pain, agitation, and delirium assessment algorithm for critically ill patients

feasible [4, 67–69]. Early mobility requires a team approach with physicians, nurses, respiratory therapists, and physical and occupational therapists; family members are increasingly engaged in the process as well. Time constraints and staff resources are challenges, and therefore institutional commitment to this evidence-based therapy is necessary for programs to flourish. Table 1.5 provides evidence-based criteria for determining when to safely mobilize critically ill patients and when to consider termination of a mobility session.

Post-intensive Care Syndrome

Advanced treatments in critical care medicine are resulting in reduced mortality rates and an increasing number of survivors of critical illness [70]. ICU survivors may suffer from both physical and cognitive impairment after being discharged from acute care. About 15–35 % of patients may experience post-traumatic stress disorder (PTSD) symptoms [71, 72]. Symptoms of PTSD involve flashbacks or nightmares, avoidance behavior, or hyperarousal with irritability and difficulty sleeping. ICU survivors can experience flashbacks related to delirium causing frightening delusions or hallucinations experienced in the ICU. It is not thought to be the duration of delirium but the quality of a patient's delirious experience that is associated with later post-ICU PTSD [71]. Patients experiencing PTSD score lower on health-related quality of life scores (HRQOL) [73]. Preliminary research shows that patients who suffer from PTSD are at an increased risk of rehospitalization over the follow-up first year [72].

Post-intensive care syndrome (PICS) is a newer term used to define the compilation of new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization [74]. This term applies not only to the burden of critical illness for individual patients but to their families (PICS-F). Increased emphasis is being directed toward improving resources and opportunities of post-hospital care for both patients and families. More collaboration is developing between critical care and community specialists in primary care, physical, and mental health. Some institutions have created post-ICU clinics to support the special needs of this population.

Symptoms of PTSD are not related to events that actually occurred and were accurately processed by the ICU patients [71]. Research findings support the use of diaries and pictures compiled throughout an ICU stay by patients and families to use during post-ICU care. This process may help to demystify delusional memories and gaps in time that appear to be lost with delusional frightening memories. This is also reinforcement of the need for critical care providers to adopt evidence-based PAD guidelines and to rethink practice where heavy sedation and ICU psychosis were previously considered the norm.

Table 1.5 Criteria for holding or terminating a physical or occupational therapy session in critically ill patients in the intensive care unit

Heart rate	>70 % age predicted maximum heart rate
	>20 % decrease in resting heart rate
	<40 beats/min, >130 beats/min
	New onset dysrhythmia
	New antiarrhythmic medication
	New MI by ECG or cardiac enzyme
Blood pressure	Systolic blood pressure >180 mmHg
	>20 % decrease in systolic/diastolic pressures
	MAP <65 mmHg, >110 mmHg
	Presence of vasopressor medications with new vasopressor need or escalating dose of vasopressor medications
Respiratory rate	<5 breaths/min or >40 breaths/min
Pulse oximetry	>4 % decrease in oxygen saturation during activity
	<88–90 % oxygen saturation
Mechanical ventilation	Fio2 requirement ≥0.60
	PEEP requirement ≥10
	Unresolved patient-ventilator asynchrony
	Mechanical mode change to assist control
	Tenuous, unstable airway
Alertness/agitation and patient symptoms	Patient deeply sedated or coma
	Patient agitation requiring addition or escalation of sedatives
	Patient complains of dyspnea on exertion
	Patient refusal

Reproduced with permission from Adler and Malone [63]

Conclusion

Practice guidelines from the Society of Critical Care Medicine (SCCM) recommend institutions implement an evidence-based ICU pain, agitation, and delirium (PAD) bundle. The evidence-based goal is to focus on systematically identifying and managing pain, agitation, and delirium in an integrated fashion. Clinicians will optimally use validated assessment tools to achieve "lighter sedation" levels and target specific, individualized treatment for pain, agitation, and delirium mitigation. Strategies for management incorporate an analgesia-first approach, the judicious use of benzodiazepine sedatives, reduction of continuous infusions, and the promotion of early mobilization. Regular development and deployment of communication techniques that facilitate recognizing and responding to patient and family needs both during the ICU stay and through convalescence may reduce the occurrence of agitation, sedation, delirium, and the post-intensive care syndrome.

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Bedside Neurologic Monitoring

2

Bryan J. Moore and Jose L. Pascual

Introduction

While in some centers, patients with neurologic emergencies may be admitted to a neurointensive care unit and cared for by neurointensivists, across most centers in the United States and Western Europe, such patients are admitted to general surgical or medical intensive care units. It is thus essential that all intensivists be familiar with the basic diagnostic tools and treatment pathways related to neurologic monitoring. This chapter will focus on the methods that providers can use to monitor neurological status in the intensive care setting.

Cerebral Physiology Overview

The Monro-Kellie doctrine is a fundamental principle of cerebral physiology which states that the total cranial volume is fixed by the rigid nature of the skull. Under normal physiologic conditions, the intracranial contents are brain tissue, the blood, and cerebrospinal fluid (CSF). In pathologic states, a mass lesion may compete for the same cranial volume. This may be a tumor, extravascular blood in the form of an intraparenchymal hemorrhage, or another process. Any increase in volume within the skull must coincide with a compensatory decrease in brain tissue, the blood, or CSF. Unless this occurs, intracranial pressure will increase. The first mechanisms of compensation for increasing intracranial volume are displacement of CSF into the spinal subarachnoid space and displacement of intracranial venous blood into the extracranial venous system [1]. Brain tissue has an extremely limited ability to buffer against increases in volume, and this minimal buffering occurs over a long period of time through changes in brain tissue compliance [2].

Cerebral blood flow (CBF) may become compromised in conditions of rising intracranial pressure and is most commonly monitored by a close surrogate, cerebral perfusion pressure (CPP). Cerebral perfusion pressure is determined by the pressure gradient between the extracranial blood pressure entering the cranial cavity, the mean systemic arterial pressure (MAP), and the intracranial pressure (ICP) [3] whereby:

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP}$$

Cerebral blood flow can be modeled with Poiseuille's law which describes the flow (Q) of a fluid as determined by vessel radius (r), fluid viscosity (η), vessel length (L), and the pressure gradient between inflow and outflow within the vessel:

$$Q = \left(\Pi r^4 \Delta P\right) / \left(8 h L\right)$$

In Poiseuille's equation, increasing the radius of the vessel will cause the largest increase in coincident flow, as the vessel radius is the only contributor with an exponential factor. Consequently, cerebrovascular autoregulation is most powerfully and acutely determined by changes in intracerebral vessel radius. With intact cerebrovascular autoregulation, cerebral blood flow can increase or decrease via changes in cerebral arterial radius in order to maintain a constant blood flow over a relatively wide range of cerebral perfusion pressures [4]. Under normal conditions, CBF can be kept constant within a CPP range of approximately 60–160 mmHg [5]. Outside this range the boundaries of cerebrovascular autoregulation are exhausted, and CBF will change passively with increases or decreases in CPP.

The cerebrovascular system is exquisitely sensitive to changes in circulating carbon dioxide as driven by the arterial carbon dioxide tension ($PaCO_2$) [6]. An increase in a patient's $PaCO_2$ will cause cerebral vasodilation, and conversely, a decrease will cause vasoconstriction. Cerebral

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blood flow is also regionally governed by cerebral metabolism, with increased local metabolism resulting in increased regional cerebral blood flow. There are numerous metabolites involved in this regional circulation shift, and their interactions will be discussed in further detail in the relevant subsections below.

The Neurologic Exam

Entire textbooks have been dedicated to the neurologic physical exam in the critical care setting. The most important tenet to understand and embrace is that the neurologic exam is the gold standard in bedside neurologic monitoring. In the critical care setting, this should include documentation of mental status and level of consciousness, preferably quantified with a scale to reduce inter- and intra-observer variation. The Glasgow Coma Scale and the Full Outline of UnResponsiveness (FOUR) score are commonly used for this purpose. Characterization of the mental status exam should also include brief testing of the six neurocognitive domains: attention, executive function, perceptual-motor function, language, memory, and social cognition. Patient sedation can be quantified by the Richmond Agitation-Sedation Scale (RASS) [7]. Cranial nerve examination should also be documented, with attention to pupil size and reactivity, extraocular movements, and brainstem reflexes. Sensory and motor exams should be performed with special attention to asymmetries concerning for pathologic processes. Cerebellar testing and specific testing of reflexes are also useful. Special scales should be used as appropriate, such as the American Spinal Injury Association (ASIA) grading scale for spinal cord injury [8].

Systemic Hemodynamic and Metabolic Monitoring

In the United States and Western Europe, invasive ICP monitoring is the standard of care in the management of traumatic brain injury (TBI). Chesnut et al. conducted a multicenter, parallel-group trial where patients with TBI were randomly assigned to care guided by ICP monitoring or care guided by imaging and clinical examination. The study showed that management of TBI guided by ICP monitoring was not superior to management based on imaging and clinical examination [9].

It is imperative that patients with brain injury be closely monitored for metabolic and hemodynamic derangements. Systemic hypotension, hyperglycemia, hypoglycemia, and hypoxia have all been associated with worse outcomes after brain injury. In TBI, hyperglycemia is associated with increased mortality and prolonged hospital length of stay [10]. Both systemic hypoxia (P_aO_2 <60 mmHg) and hypotension (systolic blood pressure <90 mmHg) can result in secondary brain injury after TBI [11]. Pre- and in-hospital hypotension can worsen outcomes in the setting of severe TBI [12]. Brain Trauma Foundation (BTF) guidelines recommend that blood pressure and systemic oxygenation should be monitored and that hypotension and hypoxia should be avoided [13].

Continuous Electroencephalography and Electrocorticography

Continuous electroencephalography (cEEG) and intracortical electrocorticography (ECoG) are becoming more prevalent in the critical care setting. Guidelines on the use and indications of EEG in the ICU were lacking until recently when Claassen et al. conducted a systematic review on 42 studies to establish consensus recommendations [14]. Urgent EEG is recommended in all critically ill patients with convulsive seizure activity that do not return to their functional baseline within 60 min of receiving antiseizure medication. This enables providers to rule out continued nonconvulsive, subclinical seizure activity as the etiology of the patient's inability to return to baseline.

Patients that are admitted for treatment of TBI are at increased risk for nonconvulsive seizures [14]. Nonconvulsive seizures that evolve to nonconvulsive status epilepticus have been associated with elevations in ICP [15] and worse outcomes. To date no study has been able to demonstrate a cEEG role in detecting ischemia after TBI. Urgent EEG is recommended for all TBI patients with unexplained encephalopathy.

Seizures occur in up to 30 % of patients that remain comatose after a cardiac arrest [14]. Continuous EEG can diagnose nonconvulsive seizures after cardiac arrest and can also differentiate subcortical myoclonus from myoclonic status epilepticus, with the latter being associated with a poor outcome [16]. Continuous EEG is commonly used during the therapeutic hypothermia period and through 24 h after rewarming [17].

As scalp EEG has poor spatial resolution, ECoG is now being used for research into clinical applications. A depth electrode may be placed through a port in an intraparenchymal monitor, or strips and grids of electrodes may be placed after a craniotomy in patients with epilepsy. At present, ECoG is being used to monitor for cortical spreading depression and to study the clinical relevance of mini-seizures that can only be recorded via depth electrodes. More research is needed to determine whether or not quantitative ECoG can lead to earlier detection of cerebral ischemia.

Transcranial Doppler

Transcranial Doppler ultrasonography (TCD) can be used to determine the velocity and the pulsatility of blood flow within cerebral vessels. It is frequently used in the critical care setting to monitor patients for cerebral vasospasm after aneurysmal and traumatic subarachnoid hemorrhage, to evaluate cerebrovascular autoregulation (CA), and to screen for risk of hyperperfusion injury after carotid revascularization procedures. Cerebrovascular autoregulation is often impaired after TBI, with the level of impairment being highly variable among patients with similar conditions [18]. Static CA assessment provides an initial cerebral blood flow velocity (CBFV) that is measured at a constant baseline mean arterial pressure (MAP). This is followed by another measurement of the CBFV at both the lower and upper limits of the MAP in which CA is intact in normal healthy humans (usually between 60 and 160 mmHg) [19]. Cerebrovascular autoregulation is considered intact if MAP changes do not significantly impact CBFV, where the correlation coefficient (r) between CBFV and MAP ranges between zero and 0.5 [20]. Even mild cerebral injury may result in impaired CA [21].

Transcranial Doppler is also useful in patients after carotid revascularization procedures including carotid endarterectomy (CEA) and carotid stenting (CAS). It may also be useful to detect hyperperfusion syndrome, a serious complication after CEA or CAS. Baseline mean flow velocities are recorded prior and several hours after an intervention, with doubling of middle cerebral artery blood flow velocity indicative of hyperperfusion. Treatment must be initiated immediately to reduce MAP goals [22]. Transcranial Doppler examination requires an appropriate insonation window through which to render measurements. When no acceptable insonation window is available, and there is no fidelity in the neurologic examination, invasive pressure monitoring is reasonable.

Intracranial Pressure Monitoring

2007 guidelines published by the Brain Trauma Foundation (BTF) for the management of severe traumatic brain injury include a level two recommendation for placement of an intracranial pressure (ICP) monitor in patients with TBI, an abnormal computed tomography (CT) scan, and a GCS score of three to eight [23]. Despite this recommendation there is controversy about the clinical utility of ICP monitoring compared to care based on neuroimaging and the neurologic exam alone [9].

The external ventricular catheter (EVD) is widely considered to be the gold standard in ICP monitors because of its diagnostic utility and its ability to drain CSF as needed to reduce elevated ICP. Well-established complications of EVDs include ventriculitis, catheter tract hemorrhage, overdrainage of CSF, and occlusion of the catheter by intraventricular blood products requiring flushing with sterile saline.

Intraparenchymal ICP monitors are inserted through a small burr hole in the cranium and provide a local pressure measurement (Fig. 2.1). They may miss a compartmental elevation in ICP within the intracranial space if the monitor is not directly in contact with a pressurized cranial compartment. Other disadvantages of intraparenchymal monitors are the potential for "drift" whereby beyond 1 week of use, ICP measurements tend to become increasingly inaccurate [24].

Monitors placed in the subarachnoid space through a cranial bolt are not currently recommended for ICP monitoring in TBI [21]. Epidural, subdural, and subarachnoid bolts are occasionally used in clinical practice for other non-TBI conditions. Various noninvasive methods for ICP monitoring are still undergoing research to determine their clinical applicability, including measurement of optic nerve diameter, transcranial Doppler, tympanic membrane displacement, and ophthalmodynamometry [2].

Cerebral Oxygenation

Cerebral tissue oxygen ($P_{bt}O_2$) is measured by the partial pressure of oxygen in the interstitial space and indicates the availability of oxygen for aerobic metabolism [25]. $P_{bt}O_2$ is defined as the product of the CBF and arteriovenous oxygen difference (AVO_2) whereby:

$$P_{bt}O_2 = CBF \times AVO_2$$

Hypoxia within brain tissue can cause both primary and secondary brain injuries. Primary hypoxic injury is seen due to global cerebral anoxia after cardiac arrest. In TBI brain hypoxia may also lead to secondary injury with frequent hypoxic episodes associated with poor functional outcome [26]. Prolonged episodes of partial brain tissue oxygenation less than 10 mmHg are an independent risk factor for poor outcome after TBI [27].

Intracranial pressure and CPP should not be used as surrogates for $P_{bt}O_2$ as cerebral oxygenation varies independently from intracerebral pressure [28]. Both CPP and ICP may be normal during discrete episodes of cerebral hypoxia. Indeed, many clinicians support independent monitoring of $P_{bt}O_2$ in TBI using a brain tissue oxygen monitor. There are numerous technologies to monitor brain oxygen, including near-infrared spectroscopy and oxygen-15 positron emission tomography (PET). Of these, direct brain tissue oxygen tension monitoring is most commonly used in North American neurointensive care units. A small catheter is placed through a skull bolt into the cerebral white matter which yields a continuous measurement of $P_{bt}O_2$. Many of these devices use

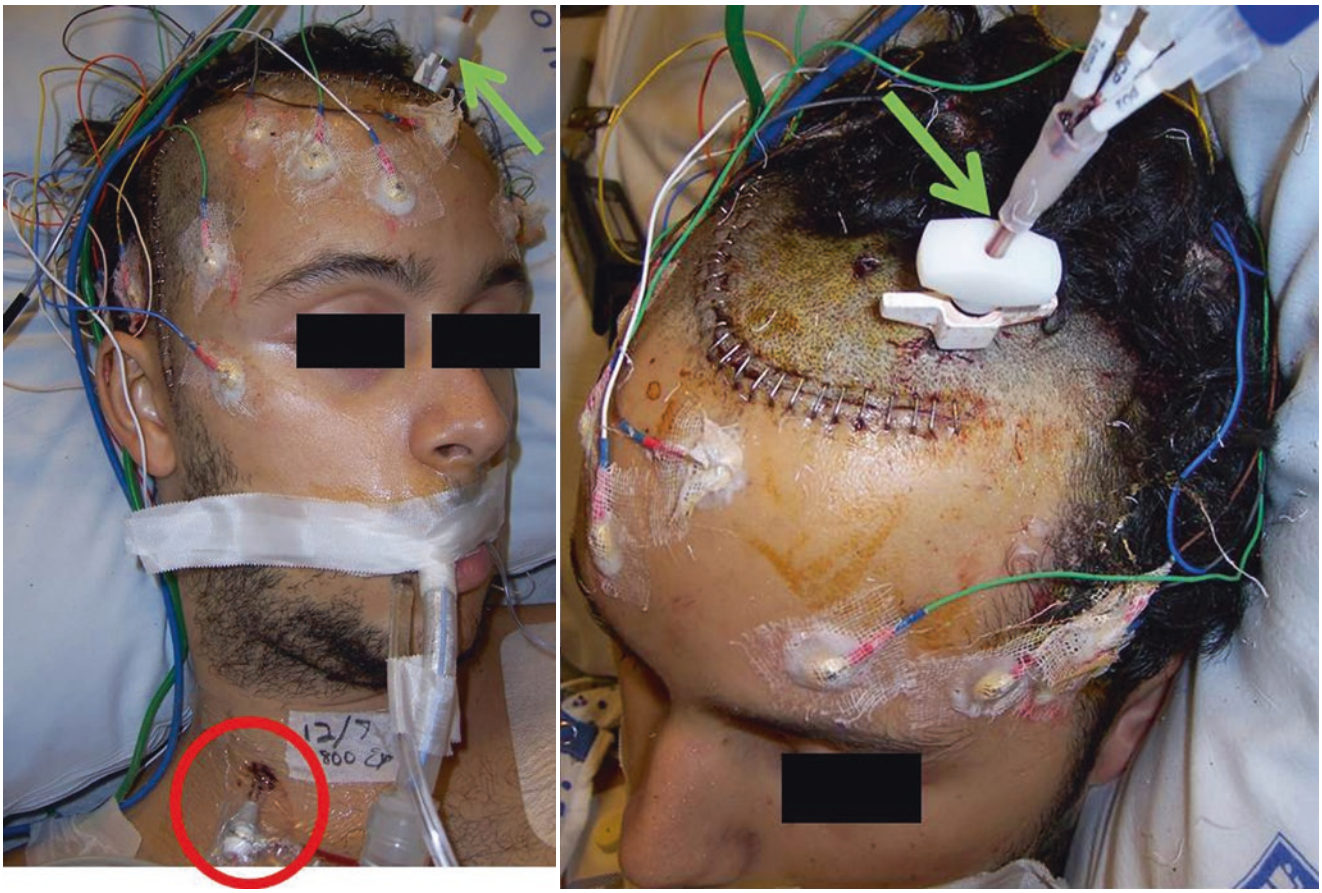

Fig. 2.1 A patient with EEG in place as well as an intraparenchymal monitor measuring brain temperature, ICP, and $P_{bt}O_2$

a Clark electrode with two metallic components contained within an electrolyte and an outer oxygen-permeable membrane. Oxygen diffuses through the membrane and becomes reduced, causing a change in voltage between the two metallic electrodes [29]. There is controversy as to whether measured $P_{bt}O_2$ values are reflective of global brain oxygenation. If the $P_{bt}O_2$ probe is placed in an area remote from the pathologic process, then it may correlate well with global brain oxygenation. However, if the probe is placed in close proximity to the area of pathology, then the measurement will reflect regional oxygenation and will correlate poorly with global brain oxygenation [30]. Brain Trauma Foundation guidelines recommend correcting brain oxygenation when the $P_{bt}O_2$ is less than 15 mmHg [31].

Cerebral Blood Flow

Under normal physiologic conditions, the human brain is able to match oxygen delivery and consumption through variations in cerebral blood flow (CBF) dictated by the cerebral metabolic rate of oxygen consumption ($CMRO_2$). Only 45 % of comatose TBI patients exhibit physiological coupling of CBF and $CMRO_2$, with the majority demonstrating CBF variation independent of $CMRO_2$ [32]. Monitoring CBF may allow ICU providers to correct insufficient CBF before brain ischemia and metabolic derangements are manifest. Two technologies that have been developed to provide continuous CBF monitoring are laser Doppler flowmetry (LDF) and thermal diffusion flowmetry (TDF).

TDF technology is commercially available as an intraparenchymal microprobe. The regional CBF (rCBF) microprobe contains a thermistor and a temperature sensor that can generate continuous rCBF values with high sensitivity [33]. The probe is inserted via a burr hole in the skull with the tip in the subcortical white matter approximately 25 mm below the dura [34]. The associated monitor displays rCBF continuously in real time. Real-time monitoring of rCBF has applications in ischemic stroke, in TBI, and in syndromes of hyperemia seen after carotid revascularization procedures. In an observational study of severely head-injured patients, Sioutos et al. showed that in patients with poor outcomes, CBF changed little over the course of their illness, whereas in those with good outcomes, final CBF measurements were greatly increased from levels obtained upon admission [35]. Additionally, CBF only normalized in patients with good

outcomes, whereas patients with poor outcomes had markedly reduced final CBF. The authors also found that management driven only by ICP derangements ultimately resulted in interventions that could be detrimental. For example, treatment of elevated ICP with hyperventilation in the setting of preexisting reduced CBF can cause reductions in CBF and greater cerebral ischemia.

An rCBF probe can also be used to gauge cerebrovascular autoregulation (CA), calculate carbon dioxide vasoreactivity, and detect vasospasm as a risk factor for delayed cerebral ischemia after subarachnoid hemorrhage. Regional CBF monitors have also been used to monitor hemodynamic changes during bypass surgery, cerebral aneurysm clipping and coiling, and tumor and arteriovenous malformation resections [36].

A technical limitation to rCBF monitoring with a TDF device is that commercially available devices have a shutdown feature in the setting of increased brain temperature, most frequently encountered during fever. Similar to brain parenchymal oxygen monitors, rCBF monitors only yield information about a small, local area of brain tissue at the tip of the probe and thus may not be reflective of global cerebral blood flow.

Cerebral Microdialysis

Cerebral microdialysis (MD) is used to measure extracellular levels of cerebral chemicals and to detect early alterations that may be indicative of metabolic derangement within the brain tissue. Early recognition of these changes may lead to interventions that can salvage brain tissue at risk and improve patient outcome. MD catheters consist of a thin tube lined with a semipermeable dialysis membrane that is perfused with a physiologic solution (the perfusate) at ultra-low flow rates [37]. Molecules smaller than the membrane's pores diffuse from the extracellular fluid into the perfusion fluid. Highly concentrated analytes in the extracellular fluid will readily pass through the membrane into the perfusate. As the perfusate flows along the length of the membrane and is removed at a constant rate, the concentration gradient across the membrane is maintained along its length. The perfusate flows along the membrane, eventually exiting through outflow tubing into a microvial [38]. These microvolume samples can then be analyzed at bedside or can be sent to the lab where enzyme spectrophotometry or liquid chromatography can be performed [39]. The ratio between the actual extracellular concentration of an analyte and its dialysate concentration is termed the *relative recovery* [40]. Flow rate is inversely related to the relative recovery, so by using lower perfusate flow rates, the relative recovery can approach 100 % yielding the true measurement of analyte concentrations in the brain extracellular fluid [41].

Numerous analytes can be measured using MD, including energy-related metabolites (adenosine, glucose, lactate, pyruvate), neurotransmitters (GABA, aspartate, glutamate), inflammatory markers (cytokines, potassium), and administered therapeutic agents. Commercially available MD measures glucose, lactate, pyruvate, glutamate, and glycerol. Brain cells metabolize glucose to pyruvate to produce ATP in a reaction that requires NAD^+. During periods of ischemia, pyruvate cannot be aerobically metabolized in the citric acid cycle, and to regenerate NAD^+, pyruvate is anaerobically metabolized to lactate [42]. As both pyruvate and lactate are able to diffuse through cellular membranes, an increasing extracellular lactate/pyruvate ratio (LPR) reflects increasing ischemia. Increased lactate may also result from excessive levels of glutamate and potassium (also associated with brain tissue ischemia) as these drive astrocyte lactate production [43]. An LPR increase above the established upper threshold of 25 is associated with poor outcome after TBI and subarachnoid hemorrhage [44, 45].

Cerebral ischemia can lead to increased release of the excitatory amino acids glutamate and aspartate. Some studies point to an association between increased glutamate concentration and poor outcome after TBI and subarachnoid hemorrhage [41].

Any process that leads to brain tissue energy failure can result in an intracellular calcium influx and induction of phospholipase, which leads to neuronal cell membrane disintegration and the release of glycerol and free fatty acids into the extracellular fluid [46]. Extracellular glycerol levels correlate with severity of parenchymal damage after TBI and are associated with a poor outcome [47]. Levels of glycerol in the cerebral extracellular fluid must be interpreted in the context of concurrent serum levels as glycerol leaks through a damaged blood brain barrier and causes spuriously high cerebral microdialysis values [46].

As changes in cerebral MD measurements may occur before alterations in ICP, altered MD values may identify either patients suffering ongoing secondary brain injury or those at risk for impending brain injury. These MD values may manifest well before changes in the patient's neurologic exam, ICP, or imaging, making MD a technology that warrants further study as a clinical tool for the intensivist.

Jugular Bulb Oximetry

The "jugular bulb" is a dilation of the internal jugular vein located at the jugular foramen that serves as the final common pathway for venous drainage from the ipsilateral cerebral hemisphere, cerebellum, and brainstem [48]. Jugular bulb oxygen saturation (SjO_2) or the arterio-jugular oxygen content difference ($AJDO_2$) can be used as a marker of global CBF in relation to the $CMRO_2$. Placement of a catheter in the

jugular bulb allows sampling of the blood originating almost exclusively from the intracranial circulation. Although some interindividual variability exists in cerebral venous drainage anatomy, the right internal jugular vein is the preferred insertion site as it is most frequently the dominant vessel [49]. The catheter is advanced under ultrasound guidance in a rostral direction from the standard internal jugular insertion site, placing the catheter tip at the level of the first or second cervical vertebral body, just above the point at which the jugular venous system receives contributions from extracranial venules. Catheter position is confirmed with a lateral cervical spine X-ray [50]. SjO_2 can be measured either continuously via a fiber-optic catheter or intermittently by blood sampling and lab analysis. Known internal jugular vein thrombosis is a contraindication to jugular bulb catheter insertion. Caution must also be used in patients with a coagulopathy or neck trauma.

Normal SjO_2 values range between 50 and 75 % [51]. In the absence of cerebral infarction, the $AJDO_2$ and CBF are inversely related [32]. Low cerebral blood flow will raise tissue oxygen extraction and increase the $AJDO_2$. Jugular bulb oximetry acts as a global monitor, and, as such, it is not useful in detecting regional changes in arteriovenous oxygen content. Coles et al. demonstrated that, on average, 170 mL of brain parenchyma needs to be ischemic before SjO_2 levels dropped below normal [52]. SjO_2 correlates poorly with $P_{bt}O_2$ in patients with focal cerebral ischemia and in patients progressing toward brain death due to shunting [53]. There may also be significant differences in SjO_2 measurements between left and right cerebral hemispheres.

Increased SjO_2 may be a consequence of decreased cerebral metabolism, limited oxygen diffusion or extraction due to infarction or inflammation, hyperemia, polycythemia, or increased systemic oxygenation leading to cerebral hyperoxia [54]. Decreased SjO_2 may be a consequence of increased cerebral oxygen consumption from hyperthermia, seizures, or sepsis. Alternatively, decreased SjO_2 may also be a consequence of decreased oxygen delivery to the brain due to anemia, impaired cardiac output, intracranial hypertension, systemic hypotension, systemic hypoxia, or hyperventilation.

Cerebrovascular Pressure Reactivity Index (PRx)

Numerous post-injury mechanisms can lead to impaired CA: cerebral ischemia, vasospasm, compression of cerebral blood vessels by astrocytic edema, ion channel dysfunction, and free radical damage [55]. Given the diversity of clinical situations where CA is impaired, a physiologic context must be established to guide interventions aimed at restoring normal cerebrovascular physiology. Impaired CA has been associated with poor outcomes after TBI [56].

Fluctuations in mean arterial blood pressure (MAP) produce changes in ICP [57]. Quantification of spontaneous MAP and ICP slow waves can determine a pressure reactivity index (PRx) that acts as a gauge of cerebrovascular autoregulatory efficiency. The PRx is obtained by collecting time-averaged values of ICP, MAP, and CPP via arterial catheter waveform analysis and an ICP monitor. In a study by Czosnyka et al., the above parameters were used to calculate waveform time integrations sampled at 50 Hz and averaged over 5-s intervals [56]. If cerebrovascular reactivity is intact, then an increase in MAP will result in vasoconstriction, a reduction in cerebral blood volume, and a decrease in ICP [57]. On the other hand, with impaired CA an elevation in MAP will lead to increased cerebral blood volume and consequently raised ICP. Linear moving correlation coefficients between 40 past consecutive 5-s averages of ICP and MAP are computed to produce the PRx. Commercially available software can be used to compute the PRx at bedside.

A positive PRx indicates a positive association between the slow components of MAP and ICP, indicating passive, nonreactive cerebral vessels. A negative PRx indicates normal cerebrovascular reactivity, with MAP increases causing inversely correlated reductions in ICP [56]. The PRx is reported as a correlation coefficient with a standardized range from −1 to +1, allowing for easy interpretation over time in a given patient or between different patients. In theory the PRx can be used to guide individualized cerebral resuscitation interventions.

Brain Temperature

Cerebral hyperthermia has been associated with worse outcomes after brain injury [58]. Though baseline metabolic activity in brain tissue is higher than in other organs, the injured, hyperthermic brain may harbor even higher metabolic rates due to ongoing inflammation [59]. The difference between brain temperature (BT) and core body temperature ranges from 0.3 to 1.1 °C, with brain temperature exceeding systemic temperature particularly after TBI [60]. Heat is transferred from the brain parenchyma to entering arterial blood such that venous blood exiting the cranium has a significantly higher temperature than the systemic circulation. This makes cerebral heat dissipation dependent on both the rate of cerebral blood flow and the systemic arterial temperature. In cases of reduced cerebral blood flow or systemic hyperthermia, heat transfer from the brain to the intracranial blood may be impaired due to a reduced gradient between the brain and systemic temperatures.

As brain temperature rises, cerebral metabolic rate also increases, which leads to an increase in CBF and in some cases results in ICP elevation. Although a causal relationship has not been established, elevated brain temperature may

increase inflammation, increase neuronal excitotoxicity, and increase free radical production, all of which may lead to secondary brain injury [61]. Most importantly for the clinician, hyperthermia is associated with worse outcomes after TBI and stroke [62, 63].

As brain temperature is not accurately determined by systemic monitors, intracranial temperature probes have been developed to trend brain temperature. Specifically, the Hemedex CBF monitor (Hemedex Inc., Cambridge, MA) uses temperature to monitor local cerebral blood flow based on the principle that cerebral thermal conductivity varies proportionally with CBF [64].

At present, there is insufficient data to recommend whether or not interventions aimed specifically at a targeted brain temperature range will improve patient outcomes or reduce mortality.

Near-Infrared Spectroscopy

Infrared electromagnetic radiation uses wavelengths slightly longer than the visible light spectrum, ranging from 1,000 to 700 nm. Changes in recorded infrared light levels can result from variations in circulating chromophore concentrations such as oxyhemoglobin, deoxyhemoglobin, and cytochrome oxidase [65]. The noninvasive near-infrared spectroscopy (NIRS) monitoring technique utilizes these optical relationships. NIRS detects changes in serum chromophores to compute changes in cerebral blood volume, brain tissue oxygenation, and cerebral blood flow [24].

In TBI patients, changes in oxyhemoglobin registered by NIRS closely correlate with changes in SjO_2, TCD, and laser Doppler flowmetry [66]. Unfortunately, NIRS is significantly limited in its clinical application by extracranial structures such as the skull and overlaying skin that limit the transmission of near-infrared light. Additionally, NIRS monitors global variations in chromophores in arteries, capillaries, and veins and can thus only yield a "mixed cerebral blood" measurement.

Evoked Potentials

Evoked potentials are used in several monitoring techniques that have been used by physicians and scientists for decades: somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), motor evoked potentials, and visual evoked potentials. SSEPs and BAEPs are of particular importance as they are most commonly used in the intensive care setting.

Testing SSEPs involves stimulating either the median or tibial nerve with an electrical pulse via two electrodes on the skin surface. This stimulation determines the integrity of the neural pathway connectivity from peripheral nerves to cortical projections [67]. Thus, SSEPs rely on intact communication through the peripheral nerve receptor, the dorsal root ganglion, the dorsal column of the spinal cord, the medial lemniscus, the thalamus, and the cortical projections. Increased latency, reduced amplitude, and the absence of an SSEP indicate abnormality in nerve conduction. Bilateral absence of SSEPs after TBI is associated with a poor prognosis [68], and temporal changes in median nerve SSEPs have been shown to precede a rise in ICP in patients with severe TBI [69]. SSEPs may also be useful in patients with spinal cord injury and in patients with hypoxic ischemic encephalopathy.

BAEPs can be used for the diagnosis of demyelinating brainstem diseases and to differentiate brainstem dysfunction from metabolic disorders. They are also used for intraoperative monitoring during cerebellopontine angle surgery and to supplement EEG in the evaluation of brain death [67]. BAEPs reflect the integrity of the neural pathway connecting the auditory nerve, the olivary complex, the brainstem, the lateral lemniscus, the medial geniculate body, and the auditory radiations.

The benefits of EPs are numerous. They are noninvasive, provide objective values that can be trended, demonstrate stability in patients under sedation or with metabolic derangements, and can be obtained at relatively low cost. Evoked potentials are not useful for characterizing the type of pathology causing an abnormal peripheral nerve response [70].

Conclusion

There are numerous bedside neurologic monitoring modalities available to the intensivist. Each technique has advantages and disadvantages, and, in isolation, none can replace the bedside neurologic exam as the gold standard for patient monitoring. As clinicians become familiar with these different monitoring devices, they will realize the benefits of integrating results from different modalities to ultimately alter management interventions. Such integration of the immense quantity of available bedside monitoring data is the focus of intense research. Critical care providers will need this familiarity with different neuromonitoring techniques to deliver cost-effective care and ultimately improve patient outcomes and reduce ICU mortality.

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Status Epilepticus

3

Emily J. Gilmore and Emad Nourollahzadeh

Case Example

A 75-year-old male with history of hypertension, atrial fibrillation on warfarin, and diabetes mellitus type II and distant history of ischemic stroke, who recently underwent a renal transplant, was admitted to the SICU for management of high blood pressure, confusion, and multiple falls. On hospital day 1, the nurse pages you to bedside for an acute change in the patient's mental status; he is now "unresponsive." What are the first steps in the diagnostic workup and management of this patient's neurological deterioration? We will review this particular case at the end of this chapter.

Introduction

Patients that are critically ill such as those in the surgical ICU are at a high risk for seizures [1, 2]. Moreover, seizures in critically ill patients are mainly nonconvulsive, and, thus, status epilepticus is readily underdiagnosed [1–12]. It is essential for an intensivist to be familiar with the seizure evaluation paradigm in patients with fluctuating neurological symptoms or in those with an unexplained impairment of level of consciousness. Prompt recognition and early treatment of seizures and status epilepticus are critical as prolonged seizures lead to increased morbidity and mortality [13]. Extensive work has shown that seizures – including nonconvulsive seizures – in the acutely injured brain can initiate a variety of adverse physiological effects, such as increases in cerebral blood flow, intracranial pressure, metabolic demand, and mass effect. Additional deleterious effects include acute elevations in lactate, glutamate, and neuron-specific enolase levels as well as delayed hippocampal atrophy and chronic epilepsy [14, 15].

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Classifications and Definitions

Seizure is the occurrence of abnormal and synchronous neuronal activity that can lead to various clinical manifestations [16]. It is useful to recognize and classify specific seizure types, as it can help guide both the diagnostic workup and treatment. The latest classification by the International League Against Epilepsy (ILAE) divides seizures into three broad categories of generalized, focal, or unknown according to clinical and EEG manifestations. Generalized seizures involve bilateral networks within the cortical or subcortical areas of the brain, while focal seizures originate from networks limited to one hemisphere [17]. An electrographic seizure is defined by [18]:

1. A paroxysmal pattern that evolves in morphology, frequency, and/or spatial distribution OR
2. Generalized spike-wave discharges ≥3/s
3. Clearly evolving discharges of any type that reach a frequency >4/s (can be focal or generalized)
4. A paroxysmal electrographic pattern (which does not meet the above criteria) that is different from the background EEG pattern and is associated with a clinical correlate

Convulsive status epilepticus (SE) is operationally defined as ongoing seizure activity for more than 5 min or two or more seizures between which the patient does not return to baseline [19]. Where convulsive SE has clinical motor manifestations (tonic or rhythmic jerking of the extremities), nonconvulsive SE often manifests as decreased level of arousal without overt signs of ongoing ictal activity [20]. Though the definition of nonconvulsive status epilepticus can be rather nebulous, attempts at standardization exist [21]. A commonly used definition of nonconvulsive status epilepticus in critically ill patients is >30 min of ictal EEG activity within a single hour of recording.

When SE fails to cease after the administration of two intravenous antiepileptic drugs (AEDs), it is denoted as

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refractory SE, which occurs in 43 % of patients with SE and is associated with increased length of hospital stay, morbidity, and mortality [8, 22, 23].

Epidemiology

In the United States, the annual incidence of SE has increased from 3.5 to 12.5 per 100,000 between 1979 and 2010 [24], while the mortality rate has remained stable around 20 %. Moreover, 31–43 % of patients with SE ultimately progress to refractory SE, which is further associated with a worse prognosis [23, 25]. The data on seizure prevalence strictly among surgical ICU patients is limited and likely underestimated as the majority of seizures in the critically ill are nonconvulsive and would be undiagnosed without cEEG monitoring. In the few studies that include SICU patients, between 5 and 11 % of patients with encephalopathy can be in nonconvulsive SE when screened by cEEG [2, 3]. This rate is expectedly higher (~19 %) among encephalopathic neurological ICU patients with acute brain injury screened with cEEG [5, 9, 13, 26, 27].

Etiology

The causes of seizure and more specifically status epilepticus can be broad in the critically ill patient and include those with prior history of epilepsy (22–34 %), remote history of a structural brain lesion (24 %, i.e., ischemic or hemorrhagic stroke, tumor, etc.), acute stroke (22 %), hypoxic/ischemic encephalopathy (10 %), metabolic derangements (10 %), and alcohol withdrawal (10 %) along with other causes as shown in Table 3.1 [28].

It is important to remember that there are a host of clinical scenarios in the ICU that may mimic seizures, be associated with seizures, or lower the threshold for developing seizures. There are a handful of life-threatening diagnoses that can mimic nonconvulsive SE and should be considered in the setting of acute neurological deterioration.

Table 3.1 Causes of status epilepticus in adults [24, 28]

Etiology	Frequency
Epilepsy history	22–34 %
Medication noncompliance	
Refractory epilepsy	
Remote structural lesion	24 %
Tumor	
Traumatic brain injury	
Stroke	
Intracerebral hemorrhage	
Vascular malformations, etc.	
Ischemic stroke	22 %
Hypoxic/anoxic encephalopathy	10 %
Metabolic abnormalities	10 %
Hyponatremia (usually <120 meq/L)	
Hypoglycemia or hyperglycemia	
Liver or renal-related failure	
Hypothyroidism	
Alcohol withdrawal	10 %
Other	
PRES (posterior reversible encephalopathy syndrome)	
Infection (sepsis or CNS infection)	
Toxins	
Medications/illicit drugs	

Pathophysiology

In general terms, seizures occur due to instability of neuronal membranes and the inability to inhibit rapid synchronous discharges. Seizures are sustained due to an imbalance between increased excitation and decreased inhibition. The most common excitatory neurotransmitter is glutamate, which acts on the N-methyl-D-aspartate (NMDA) receptor. On the other hand, the most common inhibitory neurotransmitter is gamma-aminobutyric acid (GABA), which can bind to GABA-A receptors to inhibit excitation; this is the site of action for many antiepileptic drugs (AEDs) such as benzodiazepines, barbiturates, and propofol [29]. In addition, voltage-gated sodium channels, which are blocked by various AEDs (e.g., phenytoin, carbamazepine, and topiramate) to selectively inhibit rapidly firing neurons [30], and subtypes of calcium channels, which are targeted by zonisamide, valproate sodium, and lamotrigine, are also involved in seizure propagation [31].

Neurochemical Changes

The first few minutes of seizure onset are characterized by modulation of ionic channels, neurotransmitter release, and rearrangement of receptors on neuronal synapses via endocytosis or exocytosis, which leads to an increased number of excitatory NMDA receptors and a decreased number of inhibitory GABA-A receptors. As status epilepticus continues, the number and/or sensitivity of GABA-A receptors is thought to decrease; in fact, potency of benzodiazepines decreases by 20-fold within just 30 min of chemically induced status epilepticus animal models [32]. This highlights the importance of recognizing seizures as a neurological emergency in which early diagnosis and treatment initiation can improve clinical outcomes. Subsequently within hours to days, there will be seizure-induced neuronal damage and ultimately neuronal death (apoptosis and/or

necrosis) secondary to excitotoxicity [33–35]. The neuronal injury can be shown by nonspecific markers such as elevation of neuron-specific enolase or imaging findings of cerebral edema (vasogenic or cytotoxic) on FLAIR or diffusion-weighted imaging sequences or chronic atrophy especially in the hippocampus [36–38].

Physiological Changes

Within 30 min of convulsive status epilepticus, robust catecholamine release occurs leading to various systemic changes including increased blood pressure, fever, tachycardia, arrhythmias, leukocytosis, lactic acidosis, hyperglycemia, increased pulmonary vascular resistance, and pulmonary edema [29, 39–41]. Early in status epilepticus, cerebral physiology remains relatively stable through a host of intrinsic autoregulatory mechanisms that result in increased cerebral blood flow (CBF) as well as increased oxygen and glucose uptake [29]. However, after 30–60 min, SE typically becomes nonconvulsive and the early compensatory mechanisms fail, leading to excitotoxic damage and compounded neurological injury.

Diagnosis

Diagnosing seizures and status epilepticus can be challenging due to varied clinical manifestations that can represent both positive and negative phenomena (Table 3.2) [42]. Seizure onset is typically abrupt; however, there are several entities that may mimic seizures and status epilepticus, particularly when they are nonconvulsive (Table 3.3) [43]. After early management (see Fig. 3.1), the diagnosis of seizures must be further investigated with a scalp electroencephalogram (EEG). The underlying etiology should be worked up by checking rapidly reversible causes such as hypoglycemia, electrolyte imbalances, as well as renal and hepatic dysfunction. Other laboratory data such as toxicology and CSF analysis or advanced neuroimaging (CT or MR angiography/venography or MRI) may be required depending on the patient's specific history and neurological examination.

Table 3.2 Clinical manifestations of seizure [42]

Cognitive/language/behavioral
Memory loss
Decreased level of consciousness
(Fluctuating or persistent; with severity ranging from confusion to coma)
Echolalia, aphasia, mutism, and perseveration
Psychosis, hallucinations, catatonia, and delusions
Cry and laughter
Motor
Tonic and/or clonic activity and posturing
Eye deviation, blinking, facial twitching, and nystagmus
Autonomic
Tachycardia or bradycardia
Skin flushing, nausea, vomiting, miosis, mydriasis, and hippus

Table 3.3 Seizure mimics [43]

Movement disorders
Chorea, dystonia, tics, myoclonus, and asterixis
Psychogenic non-epileptic seizures
Syncope
Cardiogenic
Cataplexy (narcolepsy related)
Herniation syndromes (posturing)
Delirium
Ischemic events
"Limb shaking" TIA due to severe carotid stenosis
Posterior circulation strokes

Neurological and Physical Examination and History

When evaluating any patient with neurological dysfunction, a full neurological examination is helpful; however, in emergency situations one can do a focused neurological exam to guide subsequent management. At the minimum, in the noncomatose patient, this includes an assessment of mental status (orientation, attention, and concentration), language, memory, and lateralizing motor signs. In a comatose patient, an assessment of level of consciousness with verbal or noxious stimuli (alert, lethargic, stuporous, or comatose) and a cranial nerve examination are paramount. During inspection look for subtle oral, facial, or limb twitching, pupillary changes, and the presence of gaze deviation. Patients in nonconvulsive SE can have pupillary abnormalities, including asymmetry and hippus; however, if their pupils are dilated, pinpoint, or unreactive, other life-threatening neurological emergencies should be entertained, prompting an emergent neurology or neurosurgical consultation. Additionally, in nonconvulsive SE the eyes may be open, but the patient is mute (e.g., eye open mutism), and the eyes may be deviated with or without head version. Not all eye deviation is secondary to seizure and can be seen in cortical, thalamic, and brain stem lesions. In general, with ongoing seizures the eyes will deviate away from the brain lesion (especially if frontal), but with stroke or other lesions, they will deviate toward the side of the lesion. The exception to this rule involves lesions to the paramedian pontine reticular formation, in which lesions in the pons may cause contralateral eye deviation. Facial, eye, or limb twitches may be observed and may be induced with stimulation (SIRPIDs – stimulus-induced rhythmic, periodic, or ictal discharges – only occasionally with clinical correlate). Tone may be symmetrically or asymmetrically

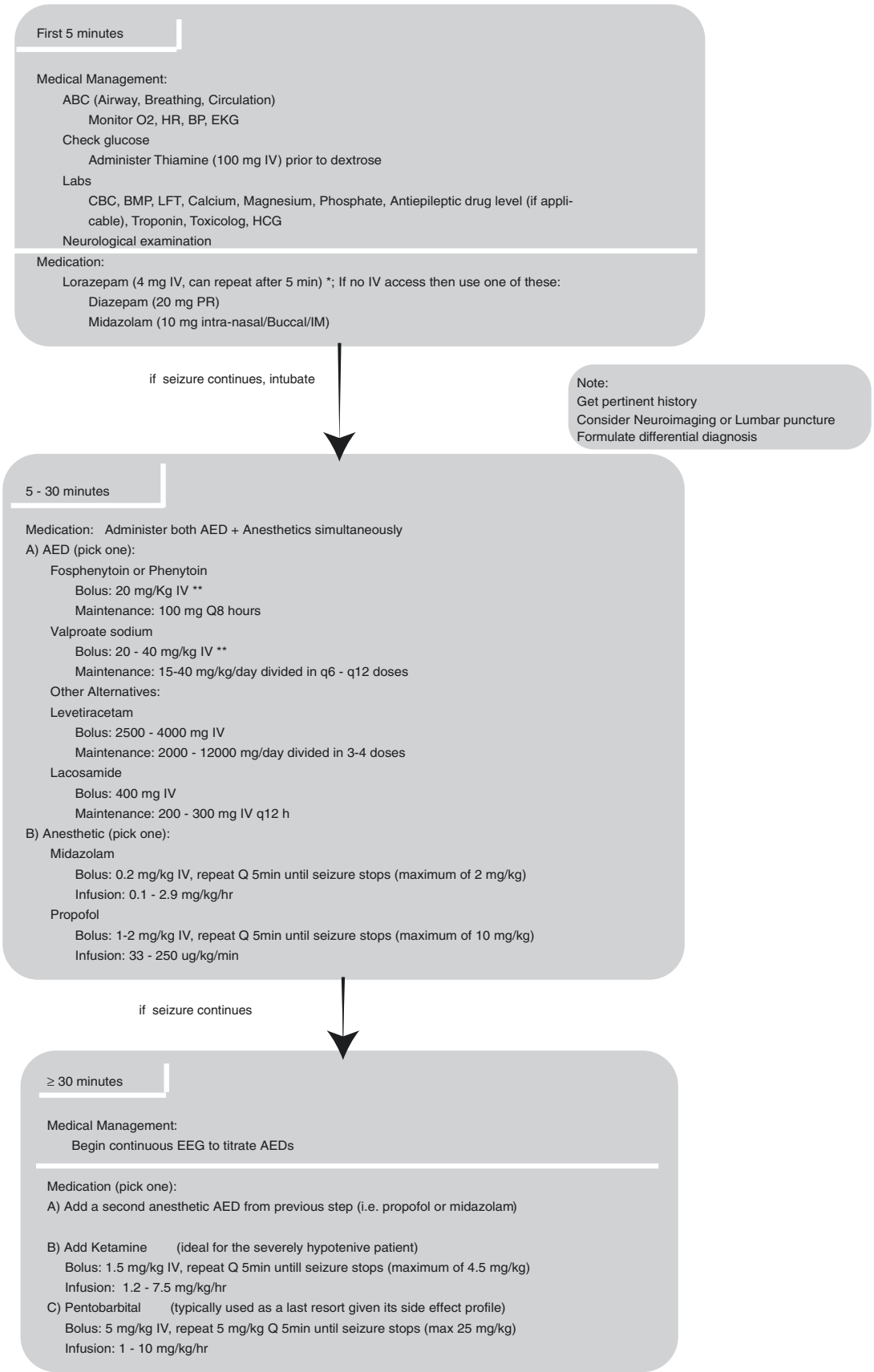

Fig. 3.1 Convulsive status epilepticus treatment algorithm for adults adopted at Yale-New Haven Hospital. *AED* antiepileptic drug, *BMP* basic metabolic profile, *BP* blood pressure, *Ca* calcium, *CBC* complete blood count, *EKG* electrocardiogram, *HCG* human chorionic gonadotropin, *HR* heart rate, *IM* intramuscular, *IV* intravenous, *LFT* liver function test, *O2* oxygen, and *Mg* magnesium. * This is based on 0.1 mg/kg dosing of lorazepam (divided into two doses) for an average adult (about 70 kg). ** Loading dose does not require adjustment for hepatic/renal insufficiency. Post-load serum drug level should be drawn 2 h post-phenytoin/fosphenytoin/valproate sodium

increased with hyperreflexia and clonus. "Awake" patients are more likely to exhibit automatisms (e.g., picking, lip smacking) and behavioral changes (perseveration, agitation, emotional lability, aggressiveness).

Stupor and coma can result from diseases affecting bilateral cerebral hemispheres, thalami, or the brain stem. As a rule, unilateral hemispheric lesions do not produce stupor or coma unless there is sufficient mass effect to raise the intracranial pressure or compress the contralateral hemisphere or brain stem (i.e., partial or complete herniation syndromes). Brain stem lesions produce coma by affecting the reticular activating system. Metabolic disorders impair consciousness by diffuse effects on both the reticular formation and the cerebral cortex.

Brain Imaging

Brain imaging after urgent treatment of status epilepticus, computed tomography (CT) of the head is indicated in almost all patients. If the etiology remains inconclusive, then magnetic resonance imaging (MRI) of the brain may be indicated to assess for diagnosis such as ischemic stroke, encephalitis (i.e., infectious, autoimmune, or neoplastic), or posterior reversible encephalopathy syndrome (PRES). It should be noted that prolonged status epilepticus could also lead to MRI findings in various anatomical locations (typically in the hippocampus, cortex, corpus callosum, thalamus); importantly, these findings may be reversible with appropriate management.

EEG

Early management of status epilepticus must rely on its clinical diagnosis and should not be delayed to obtain a cEEG. However, cEEG monitoring can both confirm and allow one to tailor therapeutics in critically ill patients. Scalp EEG detects seizures only when it involves a relatively large area of cortex (>10 cm^2) as it measures the summation of excitatory and inhibitory postsynaptic potentials of pyramidal neurons [44, 45]. Thus, scalp EEG may be falsely negative in seizures with small or deep foci. In patients who fail to fully regain consciousness, it is imperative to monitor for nonconvulsive SE and/or seizures due to their high prevalence of 15 % and 48 %, respectively [8]. Another important factor to consider is the duration of cEEG monitoring as routine 1 h EEGs can miss up to 50 % of seizures [7]. In critically ill patients, the recommended monitoring duration is 12–24 h for non-comatose patients and 24–48 h for comatose patient as seizure detection can reach up to 95 % and 87 %, respectively [5, 7]. The cEEG should also be continued until the patient is seizure-free for 24 h or has a reliable neurological exam to follow for clinical seizures. The latest Neurocritical Care Society (NCS) and the European Society of Intensive Care Medicine (ESICM) recommend cEEG in all patients with an unexplained alteration of consciousness either with an acute brain injury or comatose ICU patients without an acute brain injury (especially those with sepsis, renal/hepatic failures), in patients with CSE without return to baseline after 60 min, in patients undergoing hypothermia induction and within 24 h of their rewarming, and lastly in comatose subarachnoid hemorrhage patients in order to detect delayed cerebral ischemia (DCI) [46]. The guidelines set forth by the American Clinical Neurophysiology Society (ACNS) mostly mirror the aforementioned recommendations. Moreover, ACNS also suggests the use of cEEG in other settings such as monitoring of sedation or suppressive therapy (to avoid oversedation and undesirable side effects of anesthetic agents) and lastly the use of cEEG to help with prognostication in various neurological diseases [14].

Management

Upon diagnosis, seizures should be managed as a neurological emergency given the association of prolonged seizures and worse outcome. Management includes patient positioning, airway/breathing/circulation (ABC) management, antiepileptic drug (AED) administration, and diagnostic workup of the underlying etiology to further tailor treatment. As seen in Fig. 3.1, these steps should be prioritized and performed within 5–10 min as per the latest subspecialty guideline recommendations from the NCS [47].

Antiepileptic Drugs in Convulsive SE

Prompt AED administration must be prioritized given its association with improved seizure cessation and outcome [48]. It is essential to note that delayed treatment in convulsive SE is twice more likely to lead to systemic complications (respiratory failure, hypotension, and arrhythmia) than treatment with AEDs such as benzodiazepines (see Table 3.4 for list of AEDs) [15, 49]. Benzodiazepines are generally recognized as the first-line AEDs in the treatment of convulsive SE and are superior to phenytoin and phenobarbital [47, 48]. In patients with intravenous (IV) access, lorazepam is the preferred drug of choice. In those without IV access, intramuscular midazolam can be administered, which has a similar efficacy as lorazepam [50]. Furthermore, rectal diazepam is also an acceptable alternative to above agents.

In the critically ill, almost all patients should receive a second-line AEDs unless there is a reversible etiology and the patient has returned to baseline. Second-line AEDs

should be given intravenously and include fosphenytoin/phenytoin, valproate sodium, levetiracetam, phenobarbital, or midazolam [47]. The selection of a second-like AED depends on institutional accessibility, patient's comorbidities, and the type of epilepsy if known and applicable. Typically, fosphenytoin/phenytoin is a preferred choice due to accessibility; however, it is associated with cardiovascular side effects (e.g., hypotension and arrhythmias) and may exacerbate seizures in those with a history of primary generalized epilepsy (PGE). Valproate sodium has been shown to be at least as effective and perhaps superior to fosphenytoin/phenytoin based on two trials; furthermore, valproate sodium is a good choice for the treatment of PGE and has less cardiovascular side effects [51, 52]. Another commonly used AED is levetiracetam due to its efficacy, benign side effect profile, and minimal interactions with other medications [53, 54]. As discussed earlier, the failure of a second-line AED defines SE as refractory and requires the initiation of a third-line AED, typically as a bolus dose followed by an infusion of anesthetic such as midazolam, propofol, ketamine, or pentobarbital. These agents should be titrated to seizure cessation (and not burst suppression) with the help of cEEG. In one study there was no difference in mortality between refractory SE treated by continuous propofol, midazolam, or pentobarbital [55]. Pentobarbital is generally used as a last resort in cases of superrefractory SE (nonconvulsive SE > 48 h) due to its significant systemic side effects. Once seizure suppression is achieved, anesthetic AEDs should be slowly tapered off after 24–48 h to prevent rebound seizures; the taper is typically performed over 24 h [47]. It should be noted that the treatment of status epilepticus (NCSE or CSE) with anesthetic AEDs to reach therapeutic coma (i.e., either seizure cessation or burst suppression on cEEG) has been shown to be associated with worse outcome [56]. Further prospective, randomized trials are needed to validate these findings.

Finally, in certain clinical situations, immune medicated therapies (e.g., high-dose steroids, IVIg, plasma exchange) as well as hypothermia and electroconvulsive therapy may be instituted to manage super-refractory cases.

Antiepileptic Drugs in Nonconvulsive SE and Ictal-Interictal Patterns

Currently, there are no prospective trials to guide or support an algorithmic treatment of nonconvulsive SE. However, given the association with increased mortality, it is reasonable to treat generalized nonconvulsive SE with the same urgency and aggressiveness as convulsive SE. Lastly, there are certain EEG patterns (e.g., lateralized rhythmic or periodic discharges) that are not clearly seizures but suggest different degree of cortical hyperexcitability based on their prevalence, frequency, morphology, spread, and evolution; these patterns could simply be markers of brain injury or severity of illness; however, they have the potential to progress to frank seizure. Currently, there is no clear consensus on the treatment of

Table 3.4 List of commonly used AEDs in status epilepticus [15, 49]

Medication	Loading dose	Maintenance dose	Clearance	Side effects/comments
Lorazepam	4 mg, repeat after 5 min	N/A	Hepatic	Hypotension
Diazepam	20 mg (PR)	N/A	Hepatic	Prolonged half-life
Phenytoin & fosphenytoin	20 mg/kg*	100 mg Q8 hr	Hepatic	Hypotension, arrhythmias, hepatic dysfunction. Monitor free levels if albumin low, or if patient is on valproate sodium
Valproate sodium	20–40 mg/kg**	15–40 mg/kg/d (divided in q6–12 doses)	Hepatic	Platelet dysfunction, thrombocytopenia, pancreatitis, and tremor
Levetiracetam	2,500–4,000 mg	2,000–12,000 mg/d (divided in q6–12 doses)	Renal	Somnolence, behavioral disturbances, and agitation
Lacosamide	400 mg	200–300 mg q12 hr	Renal/hepatic	Bradycardia, prolonged PR interval
Midazolam	0.2 mg/kg, Q5 min prn (max 2 mg/kg)	0.1–2.9 mg/kg/hr	Hepatic	Hypotension, accumulates in fat
Propofol	1–2 mg/kg, Q5 min prn (max 10 mg/kg)	33–250 μg/kg/min	Hepatic	Hypotension, propofol infusion syndrome
Ketamine	1.5 mg/kg, Q5 min prn (max 4.5 mg/kg)	1.2–7.5 mg/kg/hr	Hepatic	Hypertension, rise in ICP (unlikely)
Pentobarbital	5 mg/kg (at 50 mg/min), repeat 5 mg/kg boluses Q5 min prn (max 25 mg/kg)	1–10 mg/kg/hr	Hepatic	Hypotension, gastroparesis, cardiac suppression, and thrombocytopenia

d day, *hr* hour, *ICP* intracranial pressure, *min* minute, *PR* per rectum, and *prn* pro re nata (as needed)

*Target serum phenytoin level is 20 ug/ml (total level) or 2–3 ug/ml (free level)

**Target serum valproate sodium level is 80–120 ug/ml

these patterns; however, most patients are placed on prophylactic AEDs to prevent the emergence of bona fide seizures.

Seizure Prophylaxis in Intracranial Pathologies

Any intracranial process can potentially be a risk factor for a new-onset seizure; however, different diseases are associated with various rates of seizure occurrence. The use of AEDs in neurocritical care patients is controversial, and in this section we will discuss risks and benefits of seizure prophylaxis for common critically ill neurology patients.

Traumatic Brain Injury (TBI)

Seizures in TBI are classified as early or late depending on whether they occur before or after 7 days, respectively. In patients with severe TBI (i.e., GCS ≤8 and/or with parenchymal/subdural hemorrhage, depressed skull fractures, or brain contusions), the incidence of early seizure ranges between 20 and 25 % [57]. In patients with penetrating TBI, the incidence of early seizure is up to 50 %. In a randomized trial, it was shown that patients with severe TBI had significantly lower incidence of early seizures when treated with phenytoin compared to placebo (3.6 % and 14.2 %, respectively); however, phenytoin was associated with decreased functional performance at 1 month [58, 59]. In another randomized trial, valproate sodium was shown to be as effective as phenytoin in preventing early seizures; however, there was a trend toward higher mortality in patients treated with valproate sodium [60]. For this reason, valproate sodium is not used in seizure prophylaxis of patients with TBI. Lastly, levetiracetam has been investigated in small prospective and randomized trials, which showed to be as effective as phenytoin in early seizure prophylaxis. Furthermore, treatment with levetiracetam was associated with improved disability rating scores and Glasgow Outcome Scale [61, 62]. Currently, the Brain Trauma Foundation (BTF) and American Academy of Neurology (AAN) recommend 7 days of seizure prophylaxis in severe TBI patients to minimize the occurrence of early seizures [63, 64]. In many institutions there is a trend toward using levetiracetam (dose ranging from 500 to 1,500 mg twice daily) due to its bioavailability, side effect profile, and minimal drug interactions. Seizure prophylaxis is not recommended for late-onset seizures (>7 days) in severe TBI patients since the incidence of late-onset seizure has not shown to be reduced by any of the investigated AEDs [65, 66]. Lastly, seizure prophylaxis is not routinely recommended for mild to moderate TBI due to low risk of post-traumatic seizures of 0.7 and 1.2 %s [57].

Brain Tumors

Generally about 25–45 % of patients with brain tumor will develop new-onset seizures, with some of the high-risk features including the tumor type (primary tumor vs. metastasis) and location (temporal lobe) [67, 68]. Given the high seizure incidence, prophylaxis has been extensively investigated in multiple randomized controlled trials and meta-analyses. The latest guideline from AAN in 2000 recommends that patients with newly diagnosed brain tumors should not routinely receive AEDs for seizure prophylaxis. This recommendation was based on multiple studies, including four randomized controlled trials, mainly investigating older AEDs (phenytoin, valproate sodium, and phenobarbital) [67]. Since then, there have been multiple meta-analyses with similar findings of older AEDs being ineffective for seizure prophylaxis in patients with primary or metastatic brain tumors [69, 70]. The use of these AEDs is further complicated by their significant drug interaction with chemotherapeutic agents. Further investigation is required to assess the efficacy of newer AEDs such as levetiracetam. However, in patients undergoing tumor resection, the use of levetiracetam for perioperative seizure prophylaxis is reasonable [71].

Ischemic Stroke

In the patients older than 60 years, the most common cause of a new-onset unprovoked seizure is an ischemic stroke [72]. The incidence of stroke-related seizure varies greatly among studies, but it is typically less than 10 % and similar to TBI in that it can occur early or late after stroke onset [73]. There is no clear correlation between stroke size or subtype and the risk of seizure development [74]. As of the most recent American Heart Association/American Stroke Association (AHA/ASA) guideline, the prophylactic use of AEDs is not recommended due to a paucity of data [73].

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH), especially if cortical, is more epileptogenic than ischemic stroke with the post-ICH incidence of seizure ranging from 2.7 to 17 % with the majority occurring close to ICH onset [75]. The incidence of ICH-related seizure is even higher when cEEG is utilized at 28–31 %, likely representing a reporting bias from the use of a more sensitive diagnostic tool [27, 76]. Seizure

prophylaxis in ICH is controversial, however, as two studies (primarily using phenytoin) showed worsened mortality and functional outcome associated with seizure prophylaxis [77, 78]. The latest AHA/ASA guideline recommends against seizure prophylaxis in patients with ICH [75]. It should be noted that in ICH patients with out of proportion or fluctuating neurological exam, it is imperative to screen for seizures using cEEG. In one study, acute seizure after ICH was an independent predictor of increased midline shift [27].

Aneurysmal Subarachnoid Hemorrhage (aSAH)

Patients with aSAH can present with seizure-like events (e.g., posturing); it is estimated that the incidence of seizures spans from 6 to 18 % and typically occurs early in the course [79, 80]. Some of the risk factors for seizure occurrence are location of aneurysm (middle cerebral artery), thickness of aSAH on imaging, the presence of ICH, ischemic stroke or rebleeding, poor neurological exam, history of hypertension, and mode of aSAH (i.e., treatment with clipping) [81]. In the acute phase of aSAH when the aneurysm is still unsecured, seizures can potentially be catastrophic as it can lead to rebleeding [82, 83]. Unfortunately, there are no randomized trials to assess the utility of seizure prophylaxis in this population, and most of studies have focused on the use of phenytoin, which was again associated with worse neurological outcomes [84, 85]. Thus, seizure prophylaxis is only recommended in the acute setting of aSAH for 3–7 days as per both AHA/ASA and NCS guidelines [81, 86]. The drug of choice in most institution remains to be levetiracetam for the aforementioned reasons.

Case Example Explanation

What would be your initial approach to the management of this patient?

The first step in the management of an "unresponsive" patient includes the assessment of ABCs and appropriate stabilization (see Fig. 3.1). This should be followed by a succinct neurological examination to serve as a guide in diagnosis and management. The differential diagnosis should be formulated based on the patient's clinical presentation, comorbidities, and neurological examination. In this particular case, the patient's sudden onset of "unresponsiveness" points to an etiology such as a vascular event (e.g., ischemic/hemorrhagic stroke) or seizures.

After your initial assessment, the patient is hemodynamically appropriate but on neurological examination does not follow commands with eyes closed despite noxious stimulation. Further examination reveals normal cranial nerves, a symmetric motor exam with localization of all extremities, and normal muscle tone. However, you note a right-sided gaze deviation that lasted for 30 s. What are the next steps?

Etiologies such as posterior circulation strokes (i.e., affecting brain stem or bilateral thalami) or herniation syndromes due to mass effect (e.g., intracerebral hemorrhage) must always be considered given the urgency and narrow window of their treatment. However, in this patient such etiologies are lower on the differential given normal cranial nerves and symmetric motor examination. The right-sided gaze deviation can be a clue that is typically either due to seizure or a structural lesion causing gaze deviation away or toward the lesion, respectively. This is due to hyper-excitation (in seizure) or inhibition (in structural lesion) of the frontal eye field center that plays a role in controlling horizontal eye movements. In this particular case, given the patient's normal motor and cranial nerve exam, the right gaze deviation most likely signifies seizure.

After sending appropriate labs (Fig. 3.1), you decide to administer lorazepam. The patient, however, is now unable to protect his airway and requires intubation. The patient's gaze deviation has now resolved, and a CT of his head shows subtle hypodensities in bilateral occipital lobes, consistent with vasogenic edema. It has now been 20 min since the patient was last noted to be at his neurologic baseline. What are the next steps in management?

In the setting of hypertension, immunosuppressive therapy, and radiographic findings consistent with vasogenic edema, PRES is the most likely etiology of his new-onset seizure (Table 3.1). At this point, the patient should be presumed to be in nonconvulsive status epilepticus and treated with a similar urgency as that for convulsive SE (see Fig. 3.1). The patient should be started on an anesthetic AED (e.g., propofol) as well as the administration of a second-line AED. The choice of AED should be tailored based on the drug's side effect profile and patient's comorbidities as shown in Table 3.4. In this patient, levetiracetam may be an ideal agent since, unlike valproate sodium and phenytoin, it does not interact with warfarin. In tandem, the patient should be monitored with continuous EEG for 24–48 h to confirm and/or to tailor AED treatment. Importantly, the patient's blood pressure should also be controlled given the presumptive diagnosis of PRES.

The labs all return normal and on cEEG patient is noted to be in NCSE. This prompts you to bolus and increase the maintenance dose of propofol, which achieves the desired effect. After 24 h of seizure freedom, propofol may be tapered off leading to liberation from mechanical ventilation after returning the patient to his baseline neurological examination.

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Traumatic Brain Injury

4

Sofya H. Asfaw and Niels Douglas Martin

Epidemiology

Traumatic brain injury (TBI) is a major public health concern and is a leading cause of death from injury. While the exact number of individuals suffering is unknown, some studies estimate an incidence of 91–430 per 100,000 per population year [1]. In the United States (US), there are nearly 1.6 million identified head injuries per year and approximately 16 % of those are admitted to a hospital [2]. The US mortality rate is 50,000–60,000 per year and an estimated 80,000–90,000 people per year have long-term disability as a result [2–4]. The bimodal age of distribution peaks between ages 0–4 and 15–19 [3]. The younger ages of injury may reflect injury from child abuse, and the older a predilection toward increased risky behavior. After peaking in the young adult years, the incidence of TBI declines into mid-adulthood [5]. Common causes of TBI include falls, motor vehicle collisions, pedestrian injuries, and assaults [3]. When considering hospital costs, rehabilitation costs, and loss of productivity, TBI costs the US health-care system approximately $100 billion per year [2, 6].

Classification and Types

Neurologic Severity Score

TBI includes a spectrum of brain injuries that can be classified in two ways: (1) by severity and (2) by anatomical location. Glasgow Coma Scale (GCS) is used to grade severity despite its original intent of classification for nontraumatic injuries (Table 4.1). Minor injury is defined by a GCS score of 13–15. Moderate injury is defined by a score of 9–12 and severe injury by a score of 3–8 (Table 4.2). When using GCS as a classification schema, the motor score most accurately predicts ultimate neurologic outcome [5]. In general, mortality is rare in patients with mild TBI. Moderate TBI portends a slightly worse prognosis but with a mortality rate of still <10 %. In severe TBI; however, mortality rates can approach 40 %, and those that survive commonly have lasting deficits [7, 8].

Table 4.1 The Glasgow Coma Scale (GCS) scoring mechanism

Category	Score
Eye opening	
Spontaneous	4
To voice	3
To pain	2
None	1
Verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Motor response	
Follows commands	6
Localizes to pain	5
Withdraws to pain	4
Decorticate/flexion movement to pain	3
Decerebrate/extension movement to pain	2
None	1

Table 4.2 Severity of traumatic brain injury (TBI) by the Glasgow Coma Scale (GCS)

Glasgow Coma Scale score	Traumatic brain injury severity
13–15	Mild
9–12	Moderate
3–8	Severe

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Anatomic Location

Anatomically, TBIs can be focal or diffuse. Focal injuries are classified by anatomic location of injury.

Skull Fractures

Skull fractures are either basilar or confined in the cranial vault. Basilar skull fractures add additional potential complications by communicating with other structures such as the middle ear, nasopharynx, or sinuses. They are also frequently associated with cranial nerve injuries.

All skull fractures are either open or closed, depending on any overlying penetration of the scalp. They are further categorized as either displaced or non-displaced (which is also referred to as depressed or non-depressed). Specific treatment depends on the anatomic location of the fracture and its characteristics that are beyond the scope of critical care.

Intracranial Lesions

Intracranial lesions are also subdivided into focal or diffuse in nature. They are generally caused by disruption of the vasculature which presents as various types of hematomas or parenchymal hemorrhages depending on location. These are commonly direct injuries to the brain and are thus considered primary injuries.

Focal Intracranial Lesions

Intraparenchymal Hemorrhage

Intraparenchymal hemorrhage (IPH) is seen in 20–35 % of severe TBIs and approximately 8.2 % of all TBIs [3, 4]. Initial identification of IPH is critical to recognize as these lesions frequently evolve with resulting increases in cerebral edema and potential for mass effect. Additionally, delayed IPH can occur in up to 20 % of TBI cases but usually within the first 3 days of initial injury [3]. For these reasons, repeat imaging during the first 24 h post injury is recommended (Fig. 4.1a) [4]. The presentation and patterns of IPH are similar to that of cerebral contusions, which can be considered a less severe type of IPH.

Subdural Hematoma

Subdural hematomas (SDH) occur in approximately 30 % of patients with TBI [4]. Shearing forces in the subdural space cause tearing of bridging veins resulting in accumulation of blood between the dura and arachnoid. Radiographically, they follow the contour of the brain parenchyma (in a classically described concave fashion) and can change in appearance over time (Fig. 4.1b). These are generally high force impact injuries, where direct brain and axonal injury can also occur, which can result in a worse prognosis or greater neurologic injury than in the other focal lesions [2]. They are subdivided into hyperacute (<6 h), acute (6 h to 3 days), subacute (3 days to 3 weeks), and chronic (3 weeks to 3 months) timepoints [3].

Epidural Hematoma

Occurring in approximately 0.5–1 % of all head traumas, epidural hematomas (EDH) have a propensity toward males, young adults, and those at the extremes of age, as the dura and inner table of the skull (where EDHs occur) are more fixed [3, 4]. EDHs are impact injuries commonly associated with lateral (temporal) skull fractures that result in tearing of the middle meningeal artery. Only about 10 % of these injuries are due to a venous injury [3]. The classic presentation includes a brief post injury loss of consciousness followed by a lucid interval before a progressive loss of mental status again. Early diagnosis, evaluation, and intervention are essential due to the potential for rapid deterioration and permanent brain injury. Overall mortality rate lies between 5 and 12 % when unilateral and 15–20 % with bilaterality [3, 9]. Imaging studies of EDHs appear as hyperdense lenticular (convex) lesions adjacent to the area of injury. Up to 10 % can appear in a delayed fashion radiographically (Fig. 4.1c) [3].

Subarachnoid Hemorrhage

Traumatic subarachnoid hemorrhage (SAH) is characterized by bleeding between the arachnoid membrane and pia matter. 33–39 % of patients with a head injury have a traumatic SAH on CT imaging (Fig. 4.1d). They usually occur adjacent to the site of injury or impact. They are generally caused by scraping of a vein against a tentorial edge [10]. SAH portends a significantly worse outcome [11, 12]. A large European study showed these patients to be older (mean 45.7 years) than those without subarachnoid hemorrhage (mean 37.6 years) with a worse GCS on admission [12].

Diffuse Intracranial Lesions

Diffuse Axonal Injury

Diffuse axonal injury (DAI) is generally found on the severe end of the TBI spectrum. DAI typically results from an axonal shearing injury or stretch injury following an acceleration or deceleration event. Direct axonal damage can be mild and reversible but is often more severe and permanent. DAI is often not visible on conventional CT scans, which can appear normal in 50–80 % of cases or just have a parenchymal hyper-density in 20–50 % of injuries. MRI is typically used to reveal the loss of gray/white differentiation predominately in the frontal lobes and corpus callosum [3]. Additionally, small petechial hemorrhages can also present where the gray and white matter differentiates. These hemorrhages and their resultant diffuse edema can create brainstem compression [6, 13]. The prognosis of DAI is very poor, with both a high mortality rate and a high incidence of residual neurologic deficits in survivors [5].

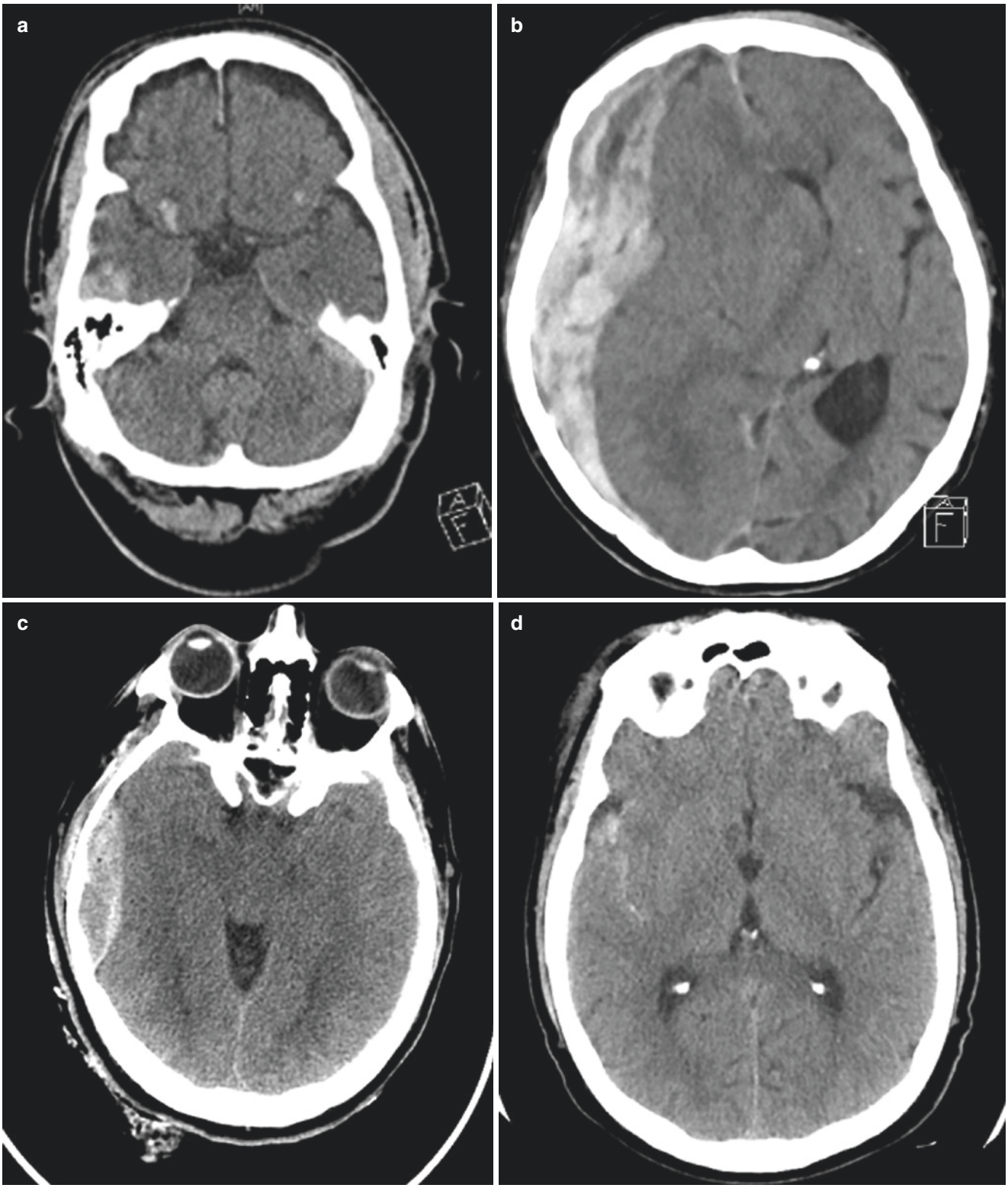

Fig. 4.1 (**a**) Intraparenchymal hemorrhage. (**b**) Subdural hematoma with midline shift. (**c**) Epidural hematoma. (**d**) Traumatic subarachnoid hemorrhage in the right sylvian fissure

Concussion

Concussions are defined as a transient event, often causing a brief loss of consciousness, with non-focal symptoms, and no permanent sequelae after an impact injury to the head. Signs and symptoms can be vague, often going unrecognized, and can include headaches, visual disturbances, dizziness, decreased attention/concentration, and amnesia [3, 14]. These symptoms can last from days to months. CT scans may be unremarkable or reveal mild diffuse swelling secondary to hyperemia. MRIs can show pathology in 25 % of the cases where CT scans show no abnormalities [14]. However, MRI is generally not indicated for diagnosis or treatment. Repetitive concussions are associated with worse long-term functional outcomes.

Primary and Secondary Brain Injury

Aside from treating the primary brain injury, preventing secondary progression is of the utmost importance to the intensivist when managing TBI. Secondary injuries are caused by the failure of cerebral autoregulation of blood flow and oxygen delivery; loss of this equilibrium can result in propagation of the ischemic penumbra [3]. These injuries progress after the initial impact and can be difficult to control [3]. Because of their insidious nature, watchful anticipation is needed on the part of the intensivist. Secondary injuries are also contributed to by edema, swelling, hypoxia, hypotension, electrolyte disturbances, hypoglycemia, infection, seizure, increased intracranial pressures, and hyperthermia [3, 6, 15]. Management is complex and will be discussed in the following sections.

Evaluation

Physical Examination

Although generally not present during the initial examination of a patient, it is important for the intensivist to be familiar with the initial trauma evaluation and its findings. There is a comprehensive physical evaluation, including a focused neurologic exam. If other injuries take initial precedence, it is important for a thorough follow-up neurologic exam on admission to the ICU. If the neurologic injury is the primary driver of the patient's pathologic condition, especially if it requires immediate treatment, the intensivist must triage for secondary and tertiary systemic traumatic injuries when the brain injury is controlled. This often occurs after the patient has been received in the ICU.

Intensivists should also be aware of commonly associated injuries with TBI. This most notably includes cervical spinal cord injuries. TBI patients often arrive in the ICU with a rigid cervical collar in place. Spine precautions should be continued until the cervical spine is cleared by a trauma or neurosurgeon.

Neurologic Examination

GCS is the most commonly used method of both initial and follow-up neurological evaluation. It evaluates cognitive function objectively and can be assessed by all levels of practitioner. Changes in GCS, even if small, can be an early sign of deterioration and warrant additional evaluation. The neurologic physical examination also includes a head to toe assessment of motor and sensory function, brain stem function, cranial nerve examination, reflexes, and pupillary reactivity.

Pupillary reactivity is a vital component of ongoing physical assessment in the ICU. Abnormalities in pupillary reactivity and size can indicate worsening TBI and is associated with poorer neurologic outcomes [16]. The most critical example is acute pupillary dilation, which can be the result of pending herniation. This is caused by direct compression of the third cranial nerve [17].

Pupillary changes also correlate with brainstem oxygenation and cerebral tissue perfusion and ischemia [16, 18]. Acute pupillary changes should be considered a neurologic emergency as timely interventions can improve outcomes [19].

Imaging

CT Scan

CT scan is the current gold standard for assessing TBI initially. It is quick, available in almost all centers, and can be interpreted expeditiously by both radiologists and intensivists [20]. It can also be obtained in serial fashion as prompted by changes in physical exam. CT brain imaging is obtained without contrast in the acute TBI setting so as to accentuate any acute blood products in the cranial vault. Guidelines for initial CT scan imaging for TBI patients include anyone with a GCS of 14 or lower. CT scans can also be obtained in any patient with risk factors for intracranial pathology including nausea, vomiting, severe headache, age <4 years or >65 years, amnesia, mechanism, neurologic deficits, and those on anticoagulation or antiplatelet agents [20]. Follow-up CT imaging is recommended following most lesions seen on initial CT scan and if any clinical change occurs. Progression usually occurs within 6–9 h after an injury and thus this is the typical window for re-imaging [20].

CT Angiography

Blunt cerebrovascular injury (BCVI) occurs in 1/1000 trauma patients in the United States [21]. Most of these injuries are diagnosed after the development of symptoms, at

which point the intervention window may have passed, resulting in significant morbidity (80 %) and mortality (40 %) [21]. Because of this devastating potential, it is important for intensivists to be diligent about screening patients, maintaining a high index of suspicion, and performing imaging studies where appropriate.

Basilar skull and petrous bone fractures are highly associated with BCVI. CT angiogram (CTA) is the most cost-effective means of evaluation, but if symptoms are suspicious despite a negative CTA, an MRI may be indicated to rule out a carotid or vertebral artery injury [20, 21].

Additional recommendations from the Eastern Association for the Surgery of Trauma's BCVI Guidelines include CTA screening in asymptomatic blunt head trauma patients with a GCS ≤ 8, cervical spine fracture (especially C1–C3 or through the transverse foramen, with rotational component or subluxation), and Le Fort II or III facial fractures.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has the highest sensitivity in revealing TBI, but because of the time constraints involved with obtaining an MRI, it is typically not done in the acute setting. MRI is also the most sensitive at detecting DAI and other nonhemorrhagic contusions [20]. Once the acute phase of resuscitation and stabilization is complete, MRI may offer additional information on primary and secondary lesions and may help to better neuro-prognosticate [20].

Monitoring

Appropriate monitoring for progression of TBI is essential in the ICU and is recommended by the Brain Trauma Foundation Guidelines [22]. Monitoring techniques have evolved over time with technological advances. Key monitoring techniques are briefly discussed below as an extensive review has been provided in that respective chapter.

Intracranial Pressure Monitoring

Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) [CPP = MAP − ICP]. CPP estimates the pressure gradient across vascular surfaces and is an important marker of cerebral blood flow [23]. ICP monitoring is recommended in all patients with severe TBI and an abnormal head CT scan. If the CT scan is normal, it is still indicated if two or more of the following is true: the patient age is over 40 years, there is unilateral or bilateral posturing, or the SBP is <90 mmHg [3, 24]. Monitoring can be subdivided into internal versus external.

Internal ICP Monitoring

Internal monitoring devices are designed to be introduced into different anatomical locations within the brain including the intraparenchymal, intraventricular, epidural, subdural, and subarachnoid spaces. The gold standard in invasive monitoring is via an extraventricular device (EVD) where a catheter is placed into the lateral ventricle percutaneously via a burr hole [23]. The advantage of an EVD is that along with ICP monitoring, cerebrospinal fluid (CSF) and hemorrhagic fluid can also be drained [23].

Microtransducers are also invasive monitoring devices with a very low profile. They are just as accurate as EVDs when it comes to measuring ICP, but they cannot drain fluid and cannot be manipulated once placed due to the fact that most models cannot be recalibrated [23].

External ICP Monitoring

External monitoring devices do not pose the bleeding or infectious risks that invasive monitors have; however, they may not be as accurate. Transcranial doppler (TCD) measures blood flow via the middle cerebral artery which is subject to changes in ICP. Its accuracy is limited by operator placement and interpretation and occasionally due to poor penetration through the skull [23]. Tympanic membrane displacement (TMD) utilizes the communication of CSF and perilymph via the perilymphatic duct. The reflex movement of the tympanic membrane correlates with ICP. Optic nerve sheath diameter (ONSD) also correlates with ICP as it expands with increased ICP. Motion-sensitive MRI is also another option [25].

Brain Tissue Oxygen (PbtO2) Monitoring

Several PbtO2 devices are available for neuromonitoring and frequently integrate with other invasive ICP monitoring devices. They add an additional dimension beyond pressure to evaluate cerebral perfusion and guide management.

Management

The management of TBI can be divided into medical versus surgical management. In the acute phase, medical management is instituted first with the rapid ability to deliver surgical therapy if medical management fails.

Medical Management

Pathophysiology of Cerebral Perfusion

CPP is an important factor in the neurophysiology of TBI as it represents cerebral blood flow (CBF) and oxygen delivery. Under normal circumstances, the brain can autoregulate to

maintain CBF when systemic MAPs range from 50 to 150 mmHg [4]. It is important for the intensivist to recognize that autoregulation is abnormal after a TBI and that tighter control of CPP (which the Brain Trauma Foundation recommends at 50–70 mmHg) is warranted. This is to prevent secondary brain injury, promote adequate oxygen delivery, and reduce the morbidity and mortality of TBI. Cerebral blood flow can be diminished for days to weeks after an injury [3, 4]. Physiologically, low cerebral blood flow can fail to meet cerebral metabolic demands and is thus associated with poorer outcomes [4, 24]. Conversely, high CPP (above 70 mmHg) can be associated with cerebral edema and can result in an increased risk of adult respiratory distress syndrome (ARDS) [24].

The space inside the skull is fixed and the volume of the intracranial contents remains generally constant. In severe TBI where a mass lesion like a hematoma can occupy space, venous blood and cerebrospinal fluid (CSF) can be displaced out of the cranium to maintain a normal ICP. This compensatory mechanism is known as the Monro-Kellie doctrine [4]. However, the limits of this displacement can be surpassed and the ICP can rapidly increase causing further injury. When this occurs, the triad of hypertension, bradycardia, and respiratory irregularities occur; this is Cushing's reflex and is often considered a neurological emergency [26]. Rapid measures to control ICP must be undertaken.

Reduction of ICP

Hypertonic Saline

Intravenous hypertonic saline (HTS) lowers ICP through mobilization of water from the brain tissue across an oncotic gradient. Additionally, CBF and oxygen delivery are improved through erythrocyte deformability and dehydration as a result of plasma dilution and volume expansion [3]. The HTS onset of action is within minutes and can last hours and thus is used in the acute and subacute setting. Optimal serum sodium levels are between 145 and 160 mEq/L [2]. Because of the potential for rapid hypernatremia and risk of central pontine myelinolysis, close serum sodium and osmolality monitoring is essential. Frequency of monitoring and dosing are often via institutional protocol.

Mannitol

Mannitol also uses hyperosmolar therapy to reduce ICP. Mannitol creates an osmotic diuresis. This diuresis similarly creates a reduction of cerebral edema, an expansion of plasma volume, reduced blood viscosity, and increased CBF. Mannitol has an immediate onset of action (minutes) and its effects can last up to 6 h [3]. In the acute setting, the usual dose is 0.25–1 g/kg. As it is an osmotic diuretic, it should not be given to hypotensive patients; in this setting, HTS may be more appropriate. Serum osmolarity must be monitored with a target level <320 mOsm [6].

Hyperventilation

Hyperventilation causes cerebral vasoconstriction and temporarily reduces cerebral volume, thus reducing ICP. However, the effect is short lived and prolonged vasoconstriction can lead to impaired cerebral perfusion [3, 4]. (Importantly, the converse is also true, allowing $PaCO_2$ to rise can cause cerebral vasodilation and an increased ICP [4].) Onset of action is rapid, within 30 s, and generally peaks at 8 min [3]. Hyperventilation strategies can be achieved by either bag valve mask ventilation or more precisely through ventilator manipulation.

When using the ventilator, the intensivist must be aware that positive end-expiratory pressure (PEEP) can increase ICP. Increased PEEP causes an increased intrathoracic pressure and cephalad transmission of increased central venous pressure (CVP) to the brain, disturbing CBF. By decreasing venous return and increasing intrathoracic pressure, PEEP may also cause a decrease in cardiac output thereby reducing MAP and subsequently CPP [27].

Elevation of the Head of the Bed

Elevating the head of the bed (HOB) significantly reduces ICP [28, 29]. The mechanism is twofold: (1) the result of displacement of CSF from the cranial cavity to the subarachnoid space and (2) extenuated brain venous outflow is enabled via gravity [29]. All patients with an increased ICP should have the HOB elevated between 30 and 45° [29].

Optimization of Systemic Blood Pressure and Oxygenation

A main goal in management of TBI patients is the prevention of secondary brain injury, which is often the result of systemic hypoxemia or hypotension. Both prehospital and in-hospital hypotension have a negative effect on severe TBI outcomes [30]. In some studies, a single prehospital systolic blood pressure (SBP) <90 mmHg was a factor associated with worse outcomes in TBI [22]. Similarly, in-hospital hypotension has also been found to be a predictor of increased mortality in TBI patients [31, 32]. It is prudent for the intensivist to prevent systemic hypoxemia and hypotension in order to minimize the effects of these secondary insults. Guidelines for numerical targets adapted from the Brain Trauma Foundation are listed in Table 4.3.

Pharmacologic Management of TBI

Increased pain and agitation can lead to increased ICP, so cautious pain control and sedation is an important aspect of the management of these patients. Appropriate sedation can improve hypoxia, hypertension, elevated ICP, and hypercarbia [1]. If sedatives and analgesics are adminis-

Table 4.3 Target values for management of elevated intracranial pressure (ICP)

	Target
ICP	<20 mmHg
Systolic blood pressure	>90 mmHg
Oxygenation	PaO_2 >60 mmHg or O_2 saturation >90 %
CPP	50–70 mmHg
PbtO2	>15 mmHg

tered, the patient should be carefully monitored to avoid the effects of hypotension, alteration of a neurologic exam, or rebound ICP elevation [3]. Short-acting and continuously infused agents are preferred as there is less disruption in the neurologic exam, and short-lived increases in ICP may be prevented [3]. Fentanyl is a preferred short-acting analgesic agent that is easily titratable and reversible. Propofol and midazolam are commonly used sedatives [1]. Propofol is a hypnotic anesthetic that is also easily titratable, is short acting, and has a rapid onset of action. Because it reduces cerebral oxygen consumption, it may have a neuroprotective effect on TBI patients as well [3, 24].

Barbiturates are central nervous system depressants that lower ICP and reduce cerebral oxygen consumption thereby conferring a protective effect. Because of their risks, their use is limited to cases of uncontrolled ICP refractory to initial medical and surgical therapies [24].

Seizure Prophylaxis

There is an upward of 50 % incidence of seizures in the TBI patient, especially those with a penetrating mechanism [24]. Post TBI seizures can be detrimental in that they can increase ICP, cerebral oxygen demand, and neurotransmitter release, all of which facilitate secondary brain injury. Risk factors for developing post-traumatic seizures include GCS <10, cortical contusions, depressed skull fractures, subdural, epidural, and intracerebral hematomas [24]. Seizures typically occur in two phases: immediately (<24 h) or within a week. For these reasons, the use of anticonvulsant agents in the first week following TBI is highly recommended [1, 24]. The most commonly used agents are phenytoin, levetiracetam, sodium valproate, and carbamazepine [1].

Venous Thromboembolism (VTE) Prophylaxis

TBI patients are at high risk for VTE events as they occur in up to 20–30 % of cases. Prophylaxis should be started as soon as possible, typically within 24 h of stable imaging. If there is an increased bleeding risk, an IVC filter should be considered. Institutional guidelines are highly recommended to defer inter-provider variances [33].

Therapeutic Hypothermia

Therapeutic hypothermia for neuroprotection has been shown to improve neurologic outcomes in post-cardiac arrest medical patients [34, 35]. Therapeutic hypothermia works by reducing cerebral metabolism, ICP, inflammation, lipid peroxidation, excitotoxicity, cell death, and seizures [3]. Active strategies to prevent fever in TBI patients are well proven. Further, prophylactic hypothermia has been associated with improved Glasgow Outcome Scale (GOS) scores when comparing to even normothermia controls [24]. Some studies suggest hypothermia to be 32–33 °C, but this must be balanced with the risks of electrolyte abnormalities, bleeding, and cardiac arrhythmias [24].

Nutrition

TBI patients have increased metabolic demands on the order of 120–250 % of basal caloric needs. Much of this increase is related to muscle tone [24]. An adequate and appropriate nutritional regimen in the ICU is paramount to meet these metabolic needs. For mortality reduction, the Brain Trauma Foundation recommends that full caloric replacement should be achieved, at the latest, by 7 days post injury. In order to accomplish this, feedings should be started, at the latest, within 3 days post injury [3, 24]. Enteral feeding is preferred [3, 33]. Regardless of enteral or parenteral delivery, protein supplementation is important [24]. Strict monitoring should occur to avoid derangements in electrolytes and glucose [36].

Surgical Management

Up to one third of TBI patients will become surgical candidates [37]. Because of this potential, and its often rapid decompensatory nature, all TBI patients should have access to neurosurgical care. Surgical evacuation is generally considered for any mass lesion causing a decline in the patient's level of consciousness, focal deficits, severe or worsening headache, nausea, or vomiting [37]. When patients are intubated or otherwise unable to communicate, indications include a decline in neurologic exam, sustained increase in ICP, or a change in the size of the mass lesion on serial imaging [37]. CT evidence of midline shift >5 mm and/or compression of the basal cisterns is an indication for surgical decompression [33]. In addition to mass lesions, TBI can also lead to cerebral edema which similarly encroaches on the limited space in the cranial vault.

Management of Hematomas

Epidural hematomas can rapidly expand placing direct pressure on the adjacent brain. Collections greater than 30 cc should be surgically treated independent of GCS. If they are less than 30 cc in volume, GCS or any midline shift should be taken into account with management decisions [37].

Hematomas in the middle fossa/inferotemporal lobe should have a lower threshold for surgical evacuation [37].

An SDH with a midline shift >5 mm or thickness >10 mm requires surgical treatment. A patient with a GCS <9 with a midline shift <5 mm or thickness <10 mm should be surgically treated if the GCS has decreased by 2 or more from injury to admission, if there are fixed or dilated or asymmetric pupils, or if the ICP is >20 mmHg [37].

Intraparenchymal hemorrhage (IPH) with neurologic deterioration related to the hemorrhage, refractory ICP elevation, or radiographic evidence of mass effect should be treated with surgical evacuation. Further, if the lesions are frontal or temporal, >20 cc in volume with a shift of >5 mm, or compression of the basal cisterns exists, surgical evacuation should also be considered [37]. If drainage of the lesion is not feasible based on location and/or depth, a decompressive craniectomy can be considered to relieve the elevated ICP.

Decompressive Craniotomy/Craniectomy

Decompressive craniotomy and opening of the dura allows areas of devitalized and injured brain to be removed as needed. In a decompressive craniectomy, the skull flap is not replaced, leaving only the dura and overlying scalp [3]. This allows for maximal pressure release from the cranial vault. When appropriate, this can be performed bilaterally and with substantially large bone flaps.

Burr Holes/Emergency Craniostomy

Emergency craniostomy, or burr holes, allows for drainage of subdural fluid. Although rarely performed, they can be a lifesaving technique, especially when definitive neurosurgical care is not readily available. These situations are more likely in rural areas or developing countries without access to advanced imaging or equipment [38].

Abdominal Decompression

Intracranial, intrathoracic, and intra-abdominal pressures are closely intertwined. Increases in intra-abdominal pressure (IAP) displace the diaphragm upward, leading to an increased intrathoracic (ITP) pressure, which in turn leads to an increased central venous pressure (CVP) and a decrease in cerebral venous outflow (CVO). Decreased CVO can directly elevate ICP ($\uparrow$IAP $\rightarrow$ $\uparrow$ITP $\rightarrow$ $\uparrow$CVP $\rightarrow$ $\downarrow$CVO $\rightarrow$ $\uparrow$ICP). Because of this relationship, decompressive laparotomy has been used as a means to reduce persistently elevated ICP when other measures have failed [39, 40].

Special Populations

Diffuse Axonal Injury

Diffuse axonal injury (DAI) results from a shearing injury of axons. There are no specific focal lesions apparent on head CT scan so MRI is typically employed as the more sensitive imaging modality. The severity of the injury is gauged more by clinical course than by visible injury. Patients with mild DAI have a 15 % mortality rate, while those with moderate DAI have a 25 % mortality rate [26]. Most patients with severe DAI succumb to the TBI [26]. No specific therapies for DAI exist and the treatment is largely supportive in nature.

Management of Skull Fractures

Depressed skull fractures are elevated surgically if the depression is greater than the opposing inner table. Open skull fractures are often similarly treated surgically to prevent infection. One exception is depressed skull fractures overlying the sagittal sinus. These should not be disturbed for fear of disruption of the sinus and the potential for massive, uncontrollable hemorrhage [37].

Management of Concussion

Concussions are generally managed by support care, recognizing the high incidence of headache, amnesia, confusion, and occasional loss of consciousness. Sports-related concussions are an important variant as a large part of their management strategy is prevention of subsequent injuries [3]. Early education and symptom management are also hallmarks of treatment [41].

Outcomes

Glasgow Outcomes Score (GOS)

Prediction of functional status and outcomes after the acute phase of TBI has widespread implications for cost, rehabilitation, and long-term care planning [42]. The GOS is the most widely used tool for measuring outcomes after TBI (Table 4.4) [43, 44]. Additionally, the GOS-Extended (GOSE) was also created to boost sensitivity to less prominent deficiencies in cognition, mood, and behavior (Table 4.5) [45].

Brain Death Exam/Determination

Brain death is characterized by no observable activity in the brain and cessation of all functions of the entire brain and

Table 4.4 Glasgow Outcome Scale (GOS)

Numerical score	Classification
1	Death
2	Persistent vegetative state
3	Severe disability
4	Moderate disability
5	Good recovery

Table 4.5 Glasgow Outcome Scale-Extended (GOSE)

Numerical score	Classification
1	Death
2	Persistent vegetative state
3	Lower severe disability
4	Upper severe disability
5	Lower moderate disability
6	Upper moderate disability
7	Lower good recovery
8	Upper good recovery

brainstem [3, 46]. When determining brain death, there should be no confounding variables like recent sedative, analgesic, paralytic or psychotropic medication administration, hypotension, encephalopathy, hypothermia, or other conditions that may obscure the neurologic exam [3]. The exact process and criteria for brain death determination is variable by state and institutional policies. An important adjunct of assessing for brain death or when suspecting brain death is to determine eligibility for organ donation. Intensivists are the frontline providers to engage their regional organ procurement organization and provide this opportunity to their patients and families.

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Care of the Spinal Cord-Injured Patient

5

Christine E. Lotto and Michael S. Weinstein

Epidemiology

At present, the majority of literature regarding the epidemiology of spinal injury has focused on injury to the spinal cord, while patients with spinal column injuries without SCI have been less well studied [1]. Demographic and epidemiological data related to traumatic spinal cord injury (TSCI) in the USA have been collected by the Spinal Cord Injury Model System and are published by the National Spinal Cord Injury Statistical Center [2]. Over the past 30 years in North America, the incidence of SCI has remained stable [3] and, excluding those who die at the scene, is estimated to be 40 cases per million population. This translates into approximately 12,800 new cases per year given the current population of the USA of 319 million. Similar figures have been reported in Canada [4], but globally the incident rate in 2007 was estimated to be slightly lower at 23 TSCI cases per million [5]. The number of people in the USA as of 2014 living with SCI has been estimated to be approximately 276,000 [2], which is higher than in most other countries [6]. The cost to society is huge, reaching nearly $10 billion each year in the USA. The average age at injury has increased from 29 in the 1970s to 42 in 2010 [2]. This presumably is a result of the increasing population of elderly individuals affected. However, the mode age has remained relatively constant at 19 years [1]. Approximately 80 % of spinal cord injuries occur in males. The leading cause of TSCI is vehicle crashes (38 %), followed by falls (30 %), violence (14 %), and sports (14 %) [2]. Mortality, disability, and cost are, as one might expect, largely influenced by the level and severity of injury. A person injured at age 20 has a life expectancy of 45 years if paraplegic, 39.9 years if tetraplegic below C4, and 35.6 years if tetraplegic above the C4 level [7]. Data from the National Spinal Cord Injury Statistical Center in the USA estimated that in 2013, lifetime costs for a person injured at age 25 are US$4.6 million for high tetraplegia compared to US$2.3 million for paraplegia [8].

The health-care system and income level of the country further influences mortality. Hospital mortality rates in high resource countries is roughly 10 %, while in low resource countries, the in-hospital mortality rate is roughly 30 % [9].

Clinical Assessment

Physical Exam

Evaluation of all patients with suspected spinal injury follows the ABCDE prioritization: airway, breathing, circulation, disability, and exposure. Extreme care should be undertaken to allow as little movement of the spine as possible to prevent further injury, but life-threatening priorities related to other injuries such as systemic hemorrhage and pneumothorax take precedence over spinal injury. A neurologic exam should be completed as soon as possible to determine the level and severity of the injury. Paraspinal soft tissues should be inspected for evidence of swelling, malalignment, or bruising [1]. Palpation of the spinous processes of the entire spinal column should evaluate for tenderness or gaps between processes. A rectal exam including rectal tone, pinprick sensation, and voluntary contraction should also be performed to evaluate for sacral root function. Physical examination alone, however, is not adequate for determining the need for imaging in patients at risk of spine injury. Age and high-risk mechanisms are better predictors of the need for imaging studies [10].

Classification

The most valid and reliable scale for neurologic assessment in spinal cord injury patients has been the American Spinal Injury Association (ASIA) scale [11, 12]. All spinal cord

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injuries can be classified as neurologically complete or incomplete, where a complete spinal cord injury is one where there is no sensation or motor function caudal to the level of injury [1]. The differentiation is important because incomplete injuries have a greater likelihood of some neurologic recovery. The ASIA classification requires sacral sparing for an injury to be classified as incomplete; however, any sensory or motor function caudal to the level of injury suffices to classify an injury as incomplete, as it signifies at least some continuity along the long white matter tracts of the cord [1]. Spinal shock, a temporary state of spinal cord dysfunction associated with complete areflexia, can complicate this assessment. The completeness of neurologic injury cannot be determined until spinal shock has resolved [1, 13].

A complete injury is graded as an A in the ASIA scale, to designate no preserved sensory or motor function in the S4–S5 nerve roots. Incomplete lesions are further classified as B (sensory incomplete, where sensory but not motor function is preserved below the neurologic level of injury including the sacral segments S4–S5), C (motor incomplete, where motor function is preserved below the level and more than half of key muscle functions below the single neurological level of injury have a muscle grade less than 3), or D (motor incomplete, where motor function is preserved below the level of injury and half or more of key muscle functions below the neurologic level of injury have a muscle grade of greater than or equal to 3). An E grade signals a normal sensory and motor exam in all segments in a patient who had prior deficits [12].

Imaging

Clinicians should have a low threshold to obtain appropriate imaging in patients with possible SCI, as missed injuries may have devastating consequences. Plain X-rays allow for rapid assessment of fractures, alignment, and soft tissue swelling. For a complete cervical spine evaluation, all cervical vertebrae to the top of the C7–T1 junction should be visualized, and anteroposterior, lateral, and open mouth odontoid images should be obtained. It is rare to miss significant injuries with adequately performed and interpreted plain films of the cervical spine [14], but neurologic signs and symptoms of injury with normal plain X-rays require further imaging studies [1].

Plain X-rays in SCI evaluation have largely been replaced by computed tomography (CT). CT in many settings is readily available and can be performed without having to move the patient out of supine position. When a spinal injury is found, CT allows for rapid assessment of other noncontiguous injuries that may be present in up to 15–20 % of patients [15]. CT imaging has been shown to have a higher sensitivity than plain radiographs in bluntly injured patients [16, 17], and some advocate that it should now be the standard of care in evaluating cervical spine injuries [18]. CT provides some assessment of the paravertebral and ligamentous injury but is inferior to magnetic resonance imaging (MRI) in this evaluation.

There are no set indications for using MRI in acute SCI, but it can provide complementary information to CT scans regarding the extent of injury and presence or absence of epidural hematoma and can therefore influence treatment and enhance prognostication. It does yield superior images compared to CT of the spinal cord and ligaments, intervertebral disks, and soft tissues [19]. MRI is also indicated in patients with a negative CT but who are still suspected to have an injury: in a meta-analysis reported case series, 5.8 % of patients who had negative CT scans were found to have a traumatic spine injury on MRI [20]. MRI does have disadvantages. It is inferior to CT in evaluating bone injury and is contraindicated in those with metallic foreign bodies and most pacemakers. It is not usually used in polytrauma or unstable patients due to the time it takes to perform the study, and patients are enclosed during that time, making monitoring difficult or dangerous. Therefore, CT scans and MRI are often complementary imaging modalities in those with suspected axial vertebral column and spinal cord injury.

Clearing the Cervical Spine

When clearing the cervical spine, one must ensure that no injuries are present. Classically, there are two algorithms used for alert patients: the NEXUS low-risk criteria and the Canadian C-spine rules. The Canadian C-spine rules have been found to be more specific and sensitive [21]. Patients who temporarily cannot be assessed (i.e., those with distracting injuries or intoxication) can be reassessed 24–48 h later once normal mentation and concentration return. Controversy still persists regarding cervical spine clearance of the obtunded patient. There are two options, both with support from the literature. The first is to use only a multi-detector CT scan, as despite detecting further abnormalities; most additional abnormalities detected by MRI require no further treatment and many are false positives [22, 23]. The second is to obtain an MRI if the CT is normal, as some point to the high incidence of new abnormalities that are identified with additional imaging as well an occasionally unstable injury [24].

Intensive Care Management

Cardiovascular Complications

Interruption of autonomic pathways in spinal cord injury, especially if the injury occurs above the level of T6, can lead to loss of thoracic sympathetic outflow, vasodilation, and

unopposed cardiac vagal stimulation. This results in hypotension, cardiac arrhythmias, and neurogenic shock [25, 26]. Neurogenic shock refers to the combination of hypotension and bradycardia identified after acute SCI. Maintaining adequate blood pressure in this setting is crucial to ensure sufficient perfusion to end organs and to the injured spinal cord to limit secondary ischemic injury [27, 28]. It must be noted that in the injured patient, hemorrhagic shock evaluation and management takes priority over acute SCI. One must not assume that hypotension stems solely from neurogenic shock. Initial therapy for both is generally plasma volume expansion except in the setting of obvious hemorrhage where judicious mean arterial pressure management may help to limit hemorrhage prior to definitive control. Invasive hemodynamic monitoring may be useful to more precisely guide volume expansion so as to avoid salt and water excess that may lead to further cord swelling causing secondary injury [27].

Persistently low mean arterial pressure despite adequate resuscitation necessitates vasopressor support. Agents with mixed α and β receptor effects are typically used first as concurrent bradycardia is also often seen in SCI [26]. Optimal mean arterial pressure goals have yet to be elucidated, as most data is derived from case series or extrapolating from management of patients with cerebral ischemia. Nonetheless, a MAP goal of 85–90 mmHg is most commonly suggested as a therapeutic goal to support both bulk and microvascular flow and oxygen delivery [26, 28–30]. The author's current practice maintains elevated MAP for a period of 3–7 days post-injury. Hypotension and especially orthostatic hypotension often persist long after the initial injury owing to loss of peripheral sympathetic tone, with a prevalence rate as high as 82 % for tetraplegia [31]. Although not well evaluated, the use of midodrine, a specific α_1-agonist, is commonplace to better allow mobilization and liberation from the ICU.

Severe bradycardia seen with acute SCI can also contribute to hypotension and require intervention, including administration of atropine, as well as on occasion transcutaneous or transvenous pacing. This phenomenon is more often noted in patients with high cervical spinal cord injury (C1–C5) [32] and most commonly occurs within the first 2 weeks following SCI [33]. Bradycardia is frequently triggered by endotracheal suctioning causing increased vagal stimulation. As most symptomatic bradycardia resolves over a matter of weeks, permanent pacemaker placement is rarely required. Theophylline and other methylxanthines have been utilized to reduce the incidence of bradycardia in this population as has nebulized albuterol [34, 35].

Autonomic dysreflexia is a potentially life-threatening complication seen in patients with an injury level above T6 and occurs weeks to years after injury. There are case reports, however, that describe this phenomenon after only 1 week [36]. It occurs as the result of uncontrolled sympathetic discharge in response to stimuli, often urologic (distended bladder) or gastrointestinal (severe constipation). Symptoms include headache, hypertension, and diaphoresis. Treatment consists of removing the trigger for the autonomic dysreflexia and managing symptoms to prevent complications [37]. All tight clothing or devices should be removed and the patient should be positioned upright to take advantage of orthostatics. Blood pressure should be closely monitored, and rapid-onset antihypertensive agents should be used, including nitrates, hydralazine, or intravenous labetalol [38].

Respiratory Complications

Physiologic Respiratory Changes After Spinal Cord Injury

Changes in pulmonary function following SCI frequently result in complications and are directly related to the extent of neurologic injury and level of injury. The higher the level and more complete the injury, the more likely there is to be respiratory dysfunction [39–41]. With the exception of the sternocleidomastoid, cervical nerve roots innervate all the main muscles of inspiration including the diaphragm, scalenes, and intercostals. Complete injury above C3 leads to complete paralysis of respiratory muscles leading to acute respiratory failure. Unless ventilation is initiated at the injury scene, these patients do not survive. Injury at C3–C5 still causes significant impairment to muscles of respiration, and mechanical ventilation is generally necessary early in the post-injury period. In the acute setting, patients with SCI also use pharyngeal and laryngeal muscles to push air past the glottis called glossopharyngeal breathing. These muscle groups are generally only utilized in the acute SCI setting and not typically considered muscles of respiration.

Muscles of expiration, including the rectus abdominis, obliques, and internal intercostals are innervated by thoracic nerve roots. Normal expiration is passive and use of these muscles is not needed for normal exhalation; however, forced exhalation such as required for coughing and expectorating is impaired if injury occurs in or above the thoracic level. Additionally, in cervical or thoracic SCI, paralysis of these muscles cause decreased stability of the rib cage during inspiration. This leads to both decreased volume of air inspired and decreased diaphragm efficiency, as the normal support provided by the thoracic cage musculature for the diaphragm to contract is lost [41–45].

In addition to changes in the muscles of respiration, patients with tetraplegia exhibit abnormalities in the sympathetic and parasympathetic innervation of the pulmonary parenchyma. Administration of ipratropium bromide, an anticholinergic agent, has been shown to cause an increase in expiratory airflow. This is thought to overcome the unopposed vagal parasympathetic (bronchoconstrictor) tone from disruption of sympathetic innervation of the lung from injury

[46, 47]. Abnormalities of nervous system innervation may also be the cause of bronchial hyperresponsiveness seen in quadriplegics after SCI [48]. However, the clinical benefit of routine administration of inhaled anticholinergics and bronchodilator has not been established.

Ventilator Management in Patients with SCI

The need for mechanical ventilation after spinal cord injury is quite common, especially in those with injury above the C6 level. Optimal ventilator management for those with cervical or high thoracic SCI has not been determined. Typically, conventional settings that are adjusted in response to arterial blood gasses and underlying lung disease are used. One area of debate is whether to use high or low tidal volumes. Due to respiratory muscle weakness, recurrent atelectasis may occur, so some centers opt for greater tidal volumes of 10–15 mL/kg ideal body weight [49]. We generally use lung protective strategy in the early phase of injury with tidal volumes of 6–8 mL/kg and progress to higher tidal volumes once lung injury and other factors resolve. Higher PEEP levels and the use of continuous pressure and variable flow modes are alternatives to using higher tidal volumes to maintain alveolar recruitment.

For patients requiring mechanical ventilation as a complication of SCI, gaining ventilator independence can be quite challenging. This group of patients usually has injuries in the cervical region. Patients with injuries at or above C3 are generally not considered for ventilator weaning, though some patients can generate spontaneous tidal volumes with use of the sternocleidomastoid muscle, which is the only muscle of respiration spared in high cervical SCI. Patients with injuries at the C5 level and above commonly require tracheostomy [50, 51]. For patients with cervical spinal cord injury, early tracheostomy (before day 10) is warranted [51].

For liberation from the ventilator and avoidance of pneumonia, a protocolized approach appears beneficial [51]. Most facilities use the IHI ventilator bundle to reduce ventilator-associated infection and some form of progressive weaning that enables respiratory therapy to engage in progression along the pathway. Both of these interventions appear beneficial in terms of ICU and ventilator LOS as well as resource utilization.

For patients who are unable to liberate from the ventilator, consideration of phrenic nerve pacing is appropriate. There are several diaphragm pacing devices that are approved for implantation. Pacing requires a functional phrenic nerve, so the best candidates for pacing are those with injuries above the C3 level, in whom upper motor nerve innervation of the phrenic nerve is the main component [52]. Pacing may be similarly beneficial in other patients for ventilator liberation and as a bridge to independent ventilation [53].

Patients in whom the phrenic nerves do not respond to stimulation are usually considered not able to be weaned from the ventilator [53]. However our group and others have begun to use nerve transfer techniques in combination with pacing to allow ventilator independence in such patients [54, 55]. Such techniques are not widely available at present.

Deep Venous Thrombosis and Venous Thromboembolism (VTE)

Deep venous thrombosis (DVT) is a common complication following acute spinal cord injury due to immobility and altered fibrinolytic activity [26]. DVT and VTE incidence varies with the method of diagnosis, varying from 12 to 64 % when diagnosed clinically [56] and to up to 80 % when diagnosed with venography and impedance plethysmography [57]. Most occur within the first 3 months post-injury [58]. It is imperative therefore that these patients receive prophylactic treatment within 72 h of injury and continue with therapy for 3 months [26] so long as there are no other injuries that would preclude prophylaxis. The use of low molecular weight heparin (LMWH) has been shown to result in fewer thrombotic events than low-dose or adjusted heparin [59] or mechanical prophylaxis [60] and is currently the treatment of choice [61].

Inferior vena cava filters are an option for patients who have contraindications to LMWH. These too have complications such as migration and erosion and may even have higher complication rates in patients with SCI [62] possibly due to loss of abdominal muscle tone and the need for the "quad cough" maneuver [63]. In multitrauma patients, temporary filters placed at the bedside under ultrasound guidance in the ICU may offer some benefit during the acute phase [64]. However, there are warning signs in the literature regarding prophylactic IVC filter placement, as some studies have shown this may increase the risk of DVT, especially in those in who temporary filters are not retrieved within an appropriate time period after implantation [26, 65, 66].

Glucocorticoid Use in Acute SCI

The efficacy of glucocorticoid use after acute spinal cord injury remains controversial, as evidence is limited and debated. Two blinded, randomized controlled trials have studied glucocorticoids in patients with acute SCI. The National Acute Spinal Cord Injury Study (NASCIS) II investigated the effect of 30 mg/kg loading dose of methylprednisolone followed by 5.4 mg/kg/h infusion for 23 h compared to naloxone or placebo. At 6 months there was an improvement found in the motor scores of patients treated with methylprednisolone within 8 h of injury, and these improved motor scores persisted at 1 year. Improvements in sensation remained the same in all groups at 1 year [67]. Complications

were higher in the methylprednisolone group, with 1.5 times higher incidence of gastrointestinal hemorrhage, 2 times higher surgical site infection, and 3 times higher incidence of pulmonary embolism. Data from this study is weakened with the absence of functional outcome measures. Also, a beneficial effect from methylprednisolone was only identified retrospectively when an arbitrary 8 h cutoff was imposed.

The follow-up study, NASCIS III, compared three treatment groups: methylprednisolone administered for 48 h, methylprednisolone administered for 24 h, and the administration of a lipid peroxidation inhibitor, tirilazad mesylate, for 48 h post SCI [68]. In all preplanned comparisons, there were no significant differences in neurologic recovery between groups. Similar to NASCIS II, a higher dose of steroids paralleled complication rate, as the group treated with 48 h of methylprednisolone had more severe pneumonia and severe sepsis compared to the group treated with only 24 h of methylprednisolone [69].

Despite two other blinded randomized controlled trials in addition to the NASCIS trials investigating the effect of methylprednisolone in SCI, there is no class I evidence that supports any benefit [67, 69–71]. There has been some class III evidence published showing a neuroprotective effect [67, 72, 73], but these have been inadequate due to small sample sizes and/or incomplete data reporting where such data likely would have invalidated the beneficial effect. Based on the available evidence, in 2013 the American Association of Neurological Surgeons and Congress of Neurological Surgeons agreed that the use of glucocorticoids in acute SCI is not recommended [74].

Nutrition and Glycemic Control

Spinal cord injured patients suffer an obligatory nitrogen debt due to hypermetabolism despite nutritional support that may last up to 2 months following injury [75]. Appetite is often poor and weight loss is expected in the first month of injury. Due to disruption of parasympathetic innervation, patients with SCI may have feeding complications as reduced gastric motility or paralytic neurogenic ileus can increase aspiration risks [76]. Sphincter dysfunction, constipation, and fecal incontinence are also common complications of SCI [77]. However, the potential benefits of enteral feeding as opposed to parenteral include lower infection risk, maintenance of gut mucosal barrier integrity, and reduced expense [78]. Early enteral feeding in acute SCI appears safe but has not been shown to affect neurologic outcome or complication incidence [76, 79].

Elevated blood glucose is also a concern in acute SCI patients. Impaired glucose tolerance and insulin resistance are more commonly seen in acute SCI [26], and glycemic levels may also be augmented by administration of steroid therapy. A target range is yet to be determined specifically for SCI patients. A meta-analysis of studies including patients with a variety of neurologic insults demonstrated that very loose glycemic control is associated with worse neurologic outcomes [80]. Intensive control is associated with increased hypoglycemia and recommended moderate control consistent with current guidelines [81] for other critically ill patients in general targeting a glucose level <180 mg%.

Ethics/End of Life

The main ethical concern that arises in caring for patients with spinal cord injury surrounds decisions for life-sustaining therapies and requests for withdrawal or withholding such therapies. The main focus seems to revolve around mechanical ventilation. Injury is a sudden life-changing event, and spinal cord injury results in a dramatic alteration in function, which in severe injuries, will be permanent. In our experience, thoughts of not wanting to live with spinal cord injury are common. Yet, the ability of humans to adapt to life with a spinal cord injury is impressive.

Support of the spinal cord injured patient includes slow and methodical disclosure of the nature of injury and prognosis to both patients and families, including a discussion of expected physical abilities and function. Physical medicine and rehabilitation (PM&R) consultants are invaluable for this conversation. At times, especially in the early phase of injury, a delay in full disclosure may be appropriate, but most patients will be aware of their paralysis and will want to know what has and will happen. Denial is common in both patients and families and should be expected. Palliative care medicine consultation is ideal in helping patients and families to cope with a major change in life circumstance and need not be exclusively focused on end-of-life care.

Some patients will request that life-sustaining therapies should be withdrawn. While patients have a right to decline or accept medical therapies, such situations are quite nuanced. The first step is acknowledgement of the patient's concerns and fears and that the health-care team will work with the patient and their family to direct care that meets his or her goals. A capacity assessment is crucial and should involve a mental health specialist, as acute major depression, reactive depression, or grief may be treated or ruled out. In patients who retain capacity for medical decision-making, a thorough exploration of the patient's goals and values as well as an understanding of what life will be like living with SCI is needed to guide further management.

Decisional duration and consistency is a controversial area [82]. Over what minimal period of time and with what degree of consistency would one consider acceptable to act on withdrawal of life-sustaining therapies (LST) is a vexing

question. Too long of a period potentially results in increased suffering, while too short a period may result in the death of someone who may have changed their mind and found enjoyment in a life with SCI. Some authors advocate not withdrawing LST until the patient has gone through at least some rehabilitation and had more experience as a person with SCI [83]. An individualized approach is warranted and ideally action is taken according to consensus of the patient, family, and health-care team. Responses to requests for withdrawal of LST in spinal cord injury are and should be labor intensive and time consuming and often benefit from palliative care medicine consultation.

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Nontraumatic Neurological Conditions

6

Christopher R. Becker and Jose L. Pascual

Various neurological impairments other than traumatic brain injury (TBI) are routinely encountered in critically ill populations. While in some US centers these are managed by neurointensivists, in most cases these patients are cared for by general intensivists in consultation with a neurologist. The following chapter will describe common and important neurological conditions related to the ICU patient that the intensivist must know with familiarity.

Major Ischemic Stroke Syndromes

Ischemic stroke encompasses a wide spectrum of conditions with varying modes of presentation, clinical course, and outcome. The most serious of these involve occlusion of the principal arteries, mainly, the carotid artery, middle cerebral artery (MCA), or basilar artery. While some patients suffering these strokes will have poor functional recovery, aggressive management in selected patients may yield reasonable outcomes. Recognition of the clinical patterns of large artery occlusions is paramount as it allows for rapid stroke severity assessment and possibly helps predict neurological deterioration.

General Management of Ischemic Stroke

Stroke may present with a variety of symptoms, not all of which may be focal. When a stroke is suspected, no matter the severity or anatomical location affected, early interventions are universally recommended. The first priority will always be to manage and stabilize the ABCs. Cardiac monitoring must be initiated while providing supplemental oxygen to maintain O2 saturation >94 % and establishing IV access (preferably 20 gauge to allow for IV contrast administration). Mechanical ventilation is sometimes necessary. In the majority of cases, laboratory tests must be obtained upon symptom recognition including serum electrolytes, renal function tests, complete blood count, markers of cardiac ischemia, coagulation labs, and an EKG to rule out cardiac ischemia [1].

In some patients it may be prudent to check a toxicology screen, alcohol level, electroencephalogram (EEG) if seizures are suspected, and lumbar puncture (if subarachnoid hemorrhage is suspected and head CT is negative for blood). It is paramount to establish the time the patient was last known to be neurologically intact or behaving normally as the knowledge of the time of symptom discovery is not sufficient. A brief but thorough neurological exam must be performed evaluating elements of the National Institutes of Health Stroke Scale (NIHSS). This standardized assessment helps facilitate communication, quantify severity of stroke, and potentially help select patients for intervention. One must remember that the NIHSS does not assess posterior circulation strokes well. A non-contrast head CT is obtained and interpreted expeditiously. If negative for intracerebral hemorrhage and no other contraindications exist (Table 6.1), alteplase is given. Alteplase must be administered within 3 h of symptom onset; however, the window is often extended to 4.5 h if no contraindications are present [1]. An important point to keep in mind is that the benefit of alteplase therapy is time dependent and treatment should be initiated as quickly as possible.

It is strongly recommended to also obtain a noninvasive intracranial vascular study during the initial evaluation of an acute stroke if either intra-arterial fibrinolysis of mechanical thrombectomy is being considered [1]. Under no circumstances, however, should obtaining vascular imaging delay administration of alteplase. Expert consultation by a neurologist should be obtained simultaneously while the initial

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Table 6.1 Contraindications for the use of alteplase in patients with stroke (United States guidelines)

Active internal bleeding
Previous intracranial hemorrhage
History of a stroke within the past 3 months
Onset of symptoms >3 h
Minor deficit or symptoms rapidly improving
Severe stroke seen on brain imaging (>1/3 cerebral hemisphere)
Heparin use within 48 h and elevated aPTT
Platelet count <100,000/mm^3
Patient receiving oral anticoagulant and INR >1.7
Seizure at onset of stroke
Severe or dangerous bleeding within prior 21 days
Suspected subarachnoid hemorrhage
Puncture of a non-compressible blood vessel within prior 7 days
Myocardial infarction in the past 3 months
Major surgery within past 14 days
Significant head trauma in past 3 months
Systolic blood pressure >185 or diastolic >110 mmHg or aggressive management necessary to reduce blood pressure to these parameters
Glucose <48.6 mg/dL
Intracranial neoplasm, arteriovenious malformation, or aneurysm

From De Keyser et al. [30]

steps of stroke management are already occurring. Before alteplase can be administered, blood pressure must be controlled to systolic levels less than 185 mmHg and diastolic levels less than 110 mmHg. Once alteplase is being administered, the blood pressure range must remain less than 180/105 mmHg to reduce to the risk of intracranial hemorrhage (ICH). Ten to 20 mg of IV labetalol may be administered for this purpose but should not be repeated more than once (two total doses) [1]. If unable to control blood pressure with labetalol, nicardipine infusion is the optimal second agent and can be titrated to maximum of 15 mg/h. Other agents may be used as necessary (hydralazine, enalaprilat, etc.) [1].

If fibrinolytic therapy is contraindicated, then permissive hypertension is recommended. In this setting, a blood pressure goal is set at 220 mmHg systolic and 120 mmHg diastolic unless there is evidence of end-organ damage. Certain conditions may coexist with an evolving stroke such as myocardial infarction, aortic dissection, heart failure, or renal failure and may be exacerbated by arterial hypertension. There is no stated blood pressure goal for these specific medical conditions. If they occur concurrently with a stroke, the blood pressure target should be based on best clinical judgment for the specific scenario. A reasonable estimate is to lower the systolic blood pressure by 15 % and monitor for neurological deterioration related to pressure lowering [1].

With few exceptions, intravenous heparin utilization during an acute stroke is almost never indicated. It is, nonetheless, recommended to administer IV heparin to treat an acute stroke secondary to central venous sinus thrombosis [2]. Also, while no randomized studies exist to support its use, IV heparin may be used in cases of extracranial carotid or vertebral artery dissection, stuttering transient ischemic attacks, or basilar artery thrombosis [13]. IV heparin may also be used to treat stump emboli from carotid occlusion (based on the TOAST subgroup analysis) [4].

Malignant Middle Cerebral Artery Stroke

An occlusion of the MCA may lead to extensive and catastrophic brain infarction. The arterial system is comprised of the M1 segment (proximal MCA), proximal to the lenticulostriate arteries, and the M2 segment. The M2 segment is further divided into the inferior and superior trunks supplying portions of the temporal lobe and frontal lobe, respectively. Further down, the M2 segment is divided into the M3 (operculum) and the M4 (cortical) branches. Occlusion of the proximal MCA (or the internal carotid artery leading to the MCA) may manifest as flaccid hemiplegia or hemiparesis of the contralateral arm and milder weakness of the contralateral leg, hemisensory loss of the contralateral arm and leg, hemianopsia, and gaze deviation or preference toward the side of the stroke. If the dominant hemisphere is involved (typically the left hemisphere), an inferior division occlusion will cause a Wernicke's aphasia. A blockage of the superior trunk will cause Broca's aphasia. If the nondominant hemisphere is involved (especially the parietal lobe), neglect will be manifested in lieu of aphasia.

If the stroke involves the lenticulostriate arteries, the basal ganglia will likely suffer infarction as well. In this setting, the greatest concern is that a proximal occlusion may

manifest as a malignant middle cerebral artery infarction (see Fig. 6.1). This may result in ischemic edema and increased intracranial pressure (ICP) resulting in brain herniation and death [5]. This devastating condition occurs in 1–10 % of all supratentorial infarcts [6]. The traditional array of treatments for these strokes has been supportive care and management of increased ICP using sedation, hyperosmolar therapy, hyperventilation, barbiturates, and the strict maintenance of normothermia [15].

As of the publishing of this textbook, no medical therapy or intensive care unit strategies have proven effective in treating brain herniation from stroke syndromes and improving patient outcomes. A review of the numerous prospective studies examining fatality rates demonstrates that mortality in patients admitted with malignant MCA infarctions approaches 80 % with a significant proportion of survivors being left with severe disability [5, 6]. Three large trials (DECIMAL [5], DESTINY [7, 8] and HAMLET [1, 9]) have examined alternative therapies in malignant MCA infarctions and have found that extensive decompressive hemicraniectomy (DHC) with durotomy may be an effective method of treating elevated intracranial pressure and in improving patient functional status (modified Rankin scale (mRS) [10]) at 6 and 12 months and overall survival when compared to medical therapy alone [11, 12]. Current suggested criteria to perform a DHC include age less than 60, stroke territory involving more than half the MCA territory, or DWI infarct volume greater than 145 cm^3 on MRI and ability to proceed to surgery within 48 h. In select patients with late swelling and delayed intracranial hypertension, operative timing may be further delayed. Since the publishing of these three large trials placed decompressive hemicraniectomy in the treatment armamentarium, there has been a smaller trial randomizing patients with malignant MCA strokes to undergo DHC versus medical therapy alone [6].

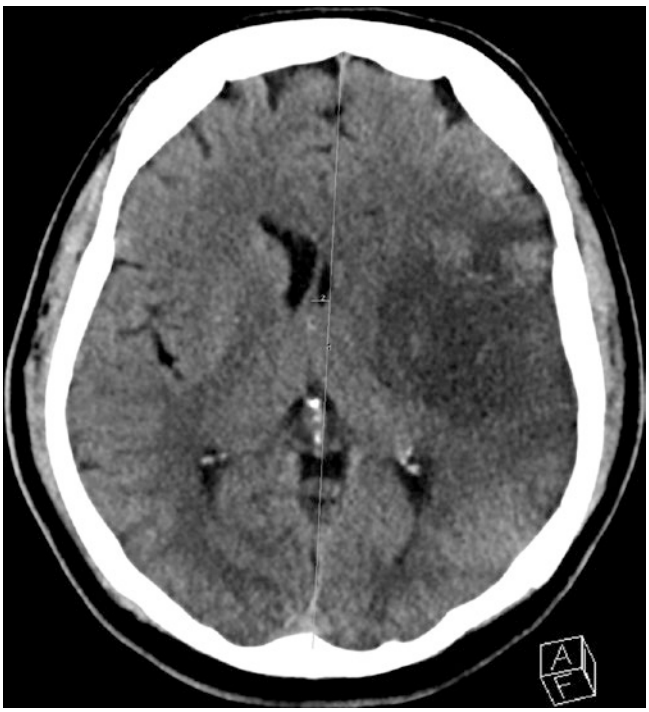

Fig. 6.1 Non-contrast head CT of a malignant left middle cerebral artery (MCA) ischemic infarction. There is a hypodensity in a large portion of the MCA territory with loss of sulci on the left hemisphere, mass effect on the left lateral ventricle, and left to right midline shift

All similar trials found an overall mortality benefit, but some found a greater proportion of survivors with substantial disability (mRS 4 or above) where the patient was unable to walk and was dependent on others for assistance with basic bodily needs [6]. This has led to the ethical controversy of DHC as the only proven lifesaving intervention for this group of devastating strokes but resulting in poor quality of life in survivors. Thus, a discussion with the patient and/or family must be conducted when DHC is considered in these cases and decisions to perform DHC must be made on a case-by-case basis.

Basilar Strokes

Approximately 20 % of ischemic strokes occur in the posterior circulation [3]. Those involving a complete occlusion of the basilar artery bear a considerable potential for a devastating outcomes. The infamous locked-in syndrome that is characterized by quadriplegia, anarthria, and preserved consciousness and perhaps preserved vertical eye movements is the result of pontine pyramidal tract ischemia from a basilar artery occlusion. If the infarct extends to include the medullary centers, respiratory drive and vasomotor control may be compromised. The majority of basilar strokes are caused by local thrombosis or artery to artery thromboembolism with other etiologies such as cardiac emboli or vertebral artery dissections also possible [3]. If left untreated, basilar artery occlusion results in fatality rates up to 90 % [3]. When a basilar artery occlusion is suspected, imaging studies should include vessel imaging in the form of a MRA, CTA, or DSA.

In consultation with a stroke neurologist and interventional neuroradiologist, treatment should be administered immediately with antithrombotic and thrombolytic agents. There is considerable data supporting the use of intra-arterial thrombolysis [13]. Like other strokes, outcomes in patients suffering from a basilar artery occlusion depend on time to treatment (the earlier the better) with other factors such as presenting clinical symptoms and degree of recanalization playing an important role as well [3]. The route of administration of thrombolytics, intravenous versus intra-arterial, does not appear to have significant influence over patient outcome [3]. The chance of recanalization has been shown to be slightly higher after intra-arterial

thrombolysis, and centers that have interventional neuroradiology capabilities should attempt this treatment modality if possible [3]. However, delay in treatment has been clearly shown to result in patient harm and intravenous thrombolysis should be given if intra-arterial intervention is not available [1, 3].

Cerebellar Stroke

Cerebellar strokes can be deceivingly perilous. A small- or moderate-sized stroke in the supratentorium is not usually life threatening, but a similar-sized stroke may be fatal in the cerebellum. The first question to be asked is if there is mass effect or not. If there is no mass effect, the stroke may be observed. If mass effect is suspected, an emergent neurosurgical consultation must be obtained. If there is obstructive hydrocephalus due to compression of the fourth ventricle or neurological deterioration due to brainstem compression, it is recommended to proceed with placement of a ventriculostomy and potentially an urgent suboccipital decompressive craniectomy with durotomy [12]. In the case of a patient without brainstem neurological deficits, hydrocephalus, or radiographic mass effect, close observation may be sufficient. It is reasonable to obtain serial CT scans to monitor for increasing edema, especially in patients with poor baseline mental status. If edema is increasing over a period of 3–5 days, one may consider prophylactic decompressive surgery. One may consider that involvement of the cerebellar vermis is particularly associated with increased risk of neurological deterioration and should lower the threshold for surgical intervention.

Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) fortunately accounts for a small percentage of strokes, between 0.5 and 1 % [2, 13]. Young women are the population most at risk. Multiple other risk factors for CVT have been identified including prior inflammatory diseases (inflammatory bowel disease), pregnancy, dehydration, infection, use of oral contraceptives or substances of abuse, recent surgery, recent trauma, or prothrombotic inherited conditions (e.g., antithrombin III, protein C, and protein S deficiency) [2, 13].

There is no uniform presentation of CVT. Clinical presenting features will vary depending on several factors including thrombosis location, presence of parenchymal involvement, and time elapsed between symptom onset and hospital admission [2, 13]. Headache is the most common symptom, present in up to 89 % of patients [2]. Patients may also suffer focal neurological signs and symptoms depending on CVT location, including but not limited to motor weakness, seizures, papilloedema, and sensory and visual deficits. Other factors that should lead to investigation for a CVT include a stroke without known risk factors, hemorrhagic strokes outside typical vascular distribution, unexplained intracranial hypertension, and ophthalmological symptoms in a patient with recent sinusitis [2].

Once CVT is suspected, a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be obtained. A normal D-dimer level may be helpful to identify patients with a low probability of CVT, but a normal level in the setting of a strong clinical suspicion should not preclude further investigation as up to 10 % of patients with CVT have a normal D-dimer [2, 13]. In the initial evaluation of patients with possible CVT, plain CT or MRI is useful but does not rule out CVT. A venographic study, either CTV or MRV, should be obtained in conjunction with the plain films to ultimately make the diagnosis of CVT [13].

Once the diagnosis is made, anticoagulation with either IV heparin infusion or subcutaneous low-molecular-weight heparin must be initiated if there are no major contraindications; ICH secondary to CVT is not a contraindication [2, 13]. The patient will then proceed with a vitamin K antagonist for 3–12 months with a target INR of 2–3. In patients with persistent or evolving symptoms despite medical treatment or with symptoms suggestive of thrombus propagation, a follow-up CTV or MRV is recommended [13]. If repeat imaging reveals no or mild mass effect, one may consider endovascular therapy, with or without mechanical disruption. If there is severe mass effect or ICH on repeat imaging, one may consider decompressive hemicraniectomy as a lifesaving procedure [13].

The routine use of prophylactic antiepileptic drugs is not recommended; however, even a single seizure with or without parenchymal involvement warrants immediate administration of antiepileptic medications [13]. In patients with evidence of increased intracranial pressure, one may consider treatment with acetazolamide. If there is any concern for visual loss, optic nerve decompression or CSF shunting may be effective and should be considered [13]. Steroid medications have not been found to be beneficial and are not recommended [13].

Primary Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is a devastating injury most commonly related to uncontrolled hypertension. Despite aggressive medical intervention, close to one third of patients with ICH will die and only 20 % will return to functional independence [14]. ICH often occurs in the deep structures of the brain with the basal ganglia (putamen) being the most affected, followed by the thalamus,

brainstem (pons), and cerebellum [14]. The second most common cause in the elderly population is cerebral amyloid angiopathy which causes cerebral bleeds that are mostly superficial and lobar [14]. Other less common but potential causes include systemic anticoagulation, hemorrhagic conversion of an ischemic stroke, vascular malformations, trauma, cerebral venous sinus thrombosis, vasculitis, and intracranial tumors [14].

Like other stroke subtypes, the presentation of ICH will depend on location. Typically there will be a sudden onset of a focal neurologic deficit, often with headache, nausea, vomiting, decreased level of consciousness, and elevated blood pressure [14]. Diagnosis of ICH is relatively straightforward with plain head CT being the preferred diagnostic method for its ease, availability, and accuracy [14]. If a secondary ICH is suspected (young age, no known hypertension or recent trauma, or prominent vascular structures), CT or MR angiography is recommended.

Initial management of ICH should focus on assessing the patient's airway and breathing. Any signs of impending respiratory failure should prompt intubation (aspiration risk, PaO2 <60 mmHg, or pCO2 >50 mmHg) [14]. Any evidence of elevated intracranial pressure should prompt immediate measures to control ICP. ICP management will be discussed in further detail in other sections but include elevating the head of bed to 30° or more, maintaining normocapnia to hypocapnia (pCO2 30–35) and in some cases hyperosmolar therapy (although this may be controversial in setting of acute hemorrhage and should be discussed with expert consultation) [14]. These measures will quickly lower ICP, albeit temporarily. Immediate neurosurgical consultation should be obtained for a definite procedure such as craniotomy, ventriculostomy, or placement of an ICP monitor [14]. Many ICH patients suffer falls prior to presentation, and their cervical spine should be carefully stabilized until any fracture or ligamentous injury is excluded [14].

The optimum blood pressure in this population is still being elucidated. Several studies have shown the safety of acutely lowering blood pressure in ICH in contrast to ischemic strokes where the blood pressure is purposefully allowed to remain elevated [14, 15]. The INTERACT II trial showed the safety of acutely lowering blood pressure to less than 140 mmHg systolic. However, the trial did not show a difference in mortality, major safety events, or hematoma expansion in patients who had aggressive blood pressure control (less than 140 mmHg vs. less than 180 mmHg) [15]. As of the publishing of this textbook, the ATACH II trial is still enrolling patients, attempting to answer the question of optimal blood pressure in the ICH population. For now, it is recommended to maintain systolic blood pressure less than 180 mmHg and, if safe and reasonable, less than 140 mmHg [14–16].

Aneurysmal Subarachnoid Hemorrhage

The most common etiology of subarachnoid hemorrhage (SAH) is traumatic injury. However, nontraumatic SAH contributes a large proportion of the mortality and morbidity from SAH [16]. Of all the nontraumatic causes of SAH, aneurysm rupture is the most common and best studied. There is considerable variation in annual incidence of aneurysmal subarachnoid hemorrhage (aSAH) between different regions of the world and even within the same country. In the United States, aSAH incidence ranges from 6 to 16 cases per 100,000 population, with approximately 30,000 episodes occurring each year [16]. The 2003 Nationwide Inpatient Sample provided an annual estimate of 14.5 patient discharges categorized as aSAH per 100,000 adults [16]. Risk factors for aSAH vary significantly depending on age, gender, and country of origin, with men and the young less likely to be affected. The reported incidence of aSAH is highest in Finland (19.7 per 100,000 person-years) and Japan (22.7 per 100,000 person-years) but lowest in South and Central America (4.2 per 100,000) [17]. Other risk factors include hypertension, history of tobacco use, alcohol abuse, use of sympathomimetic drugs (i.e., cocaine), history of previous aSAH, and family history of familial aneurysms or associated genetic syndromes. Patients suffering from an aSAH may present with diverse clinical manifestations ranging from an isolated simple headache to a comatose state. Other common presenting symptoms include nausea/vomiting, loss of consciousness, and nuchal rigidity. The patient may also demonstrate focal neurologic deficits in the setting of microemboli from the aneurysm itself or in the event of an aneurysm rupture. The initial clinical severity of the aSAH should be determined rapidly by using the Hunt and Hess or World Federation of Neurological Surgeons scales [16]. The risk of vasospasm sequela should also be determined using the Rankin or the modified Rankin scale.

Once an aSAH is suspected, a head CT must be obtained immediately. If the head CT does not demonstrate any hemorrhage, a lumbar puncture is then performed. If both are negative for hemorrhage, the evaluation is complete. If subarachnoid blood is confirmed, then vessel imaging is obtained as next step. Digital subtraction angiography with three-dimensional rotational imaging is most useful; however, a CT angiogram of the head and neck may also be utilized initially in certain cases. MRI may also be used if the head CT scan is nondiagnostic. The fluid-attenuated inversion recovery (FLAIR) sequence is the most sensitive MRI sequence for detection of SAH [17, 19].

After diagnosis of aSAH and identification of the culprit aneurysm, one must expeditiously address the high risk for aneurysmal re-rupture by securing the aneurysm as soon as possible, either via surgical clipping or endovascular coiling. Subsequent re-bleeding is associated with very poor

outcome. There are inherent delays to both surgical (operating room availability) and interventional radiological (summon the radiological team in house) securing of cerebral aneurysms, and during this time, it is essential to narrowly control the patient's blood pressure. While there is no known optimal blood pressure target, it is recommended to aim for a goal systolic pressure less than 160 mmHg although some centers advocate less than 140 mmHg [16]. A titratable continuous infusion agent (i.e., nicardipine) should be used to balance the risk of hypertension related re-bleeding and decreased cerebral perfusion pressure (from excessive blood pressure lowering). In patients with unavoidable extended delays, they may be considered for short-term (less than 72 h) therapy with tranexamic acid or aminocaproic acid to reduce the risk of early aneurysmal re-bleeding [16, 18]. The feared complications of these two therapies are thromboembolic events (i.e., acute myocardial infarction or acute pulmonary embolism). To be considered for this therapy, the patient should be deemed at significant risk of re-bleeding and must not have compelling medical contraindications [16].

Definitive management of aSAH is securing of the aneurysm with minimal delay. When the ruptured aneurysm is technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling is preferred [16]. However, certain aneurysms possess a morphology (neck to dome ratio) and location, whereby they may be better suited for surgical clipping. Further, the choice of available treatment modality may vary between institutions as it also depends on the experience of the staff. In the ISAT [19] randomized controlled trial, both treatment methods were compared in cases suitable for either treatment modality and demonstrated that the endovascular arm fared better overall [16]. Compared to the microsurgery, the endovascular arm resulted in a decreased mortality and disability at 1 year and a lower incidence of epilepsy and cognitive decline. The risk of late re-bleeding, however, was lower in the microsurgery arm with a higher rate of complete aneurysm obliteration [16]. Typically, patients require post-procedural vascular imaging after the aneurysm has been secured by either method. If complete obliteration of the aneurysm is not seen, it is recommended to proceed with repeat coiling or microsurgical clipping [16].

In the post-procedural period, certain basic interventions should be routine in all SAH patients. These measures include maintaining strict normothermia and euvolemia to help prevent delayed cerebral ischemia (DCI) [16]. Careful glucose management with strict avoidance of hypoglycemia should be maintained in all cases and nimodipine should be administered for 21 days (60 mg every 4 h). Nimodipine has been shown to consistently provide a small benefit in morbidity and mortality and is the only class 1 evidence-supported recommendation [16]. If hypotension results, reduced nimodipine administration of 30 mg every 2 h may be considered. Nimodipine has been shown to reduce vasospasm but the exact mechanism of its effect has yet to be elucidated.

Other secondary complications may also occur after aSAH bleeds, both neurological and systemic. Delayed cerebral ischemia, acute symptomatic hydrocephalus, and cerebral vasospasm are most common. Patients should be monitored closely for DCI in an ICU setting by regular hourly neurological exams. Also, transcranial Doppler (TCD) should be performed searching for elevated velocities but more importantly, elevated Lindegaard ratios which are suggestive of vasospasm and risk of subsequent ischemia [16]. Continuous electroencephalography (EEG) should also be used to follow the alpha variability (AV) as poor AV trends may indicate relative ischemia in the affected area. The traditional "triple H" therapy of hypervolemia, hemodilution, and hypertension is no longer recommended [16]. Some evidence suggests that hypervolemia may lead to increased morbidity from fluid overload leading to recommendations of maintaining euvolemia only [16]. Unless baseline hypertension, with evidence of DCI, it is recommended to induce hypertension, ideally to a blood pressure goal resulting in improvement of neurological deficits [16]. In the setting of anemia, packed red blood cell transfusion may be used for this goal though the optimal hemoglobin level has yet to be determined [16]. In patients who fail to respond to hypertensive therapy, it is reasonable to consider intra-arterial vasodilator therapy [16].

Acute hydrocephalus occurs in 15–87 % of patients with aSAH, and chronic shunt-dependent hydrocephalus develops in 8.9–48 % of patients [16]. Both conditions should be treated by CSF diversion, usually via an external ventricular catheter (EVD) or less commonly, via a lumbar drain. Again, neurosurgical consultation is often helpful in this setting to place and manage EVDs. Three retrospective case series have examined aneurysmal re-bleeding with EVD placement, one of which found a greater re-bleeding risk with EVD placement [16, 20, 21]. Daily EVD outputs should be measured and help determine a weaning strategy. Rapid (<24 h) weaning of the EVD does not appear to reduce the incidence of shunt-dependent hydrocephalus [16]. If the patient cannot be weaned from the EVD over 1–2 weeks, a permanent shunt, usually in the form of a ventriculoperitoneal shunt must be placed.

Seizures occurring after aSAH have been discussed at length and remain a topic of controversy. Almost one in four patients experience seizure-like episodes after aSAH but is unclear whether these are actually epileptic in origin [16]. No randomized, controlled trials exist evaluating the existence and management of seizures associated with aSAH and as such, any potential benefit of routine anticonvulsant use in aSAH must be weighed against potential risks. One large,

single-center study found adverse reactions in 23 % of patients taking anticonvulsants [16]. Another single-center retrospective study found prophylactic phenytoin to be independently associated with worsened cognitive outcome at 3 months after aSAH [16]. It is generally accepted to use prophylactic anticonvulsants in the immediate post-bleed period (typically for 7 days) [16], but the routine long-term use of anticonvulsant therapy is not recommended unless the patient is specifically at increased risk due to a history of prior seizure, an intracerebral hematoma, intractable hypertension, cerebral infarction, or middle cerebral artery aneurysm [16].

Aneurysmal SAH may also have non-neurological complications affecting multiple organ systems. Both hyponatremia and hypernatremia occur in 10–30 % of the acute phase after aSAH [16]. Hyponatremia has been associated with development of both sonographic and clinical vasospasm [16], and therefore ICU providers should strive for correction of serum sodium levels in these patients employing agents such as fludrocortisone acetate and hypertonic saline [16]. All patients should have a euvolemic volume status which may be achieved with crystalloid or colloid administration. Using hypotonic fluids is not recommended, particularly in those with signs of intravascular volume contraction [16]. Several animal studies and human case series have shown an association between elevated blood glucose concentration and poor outcome after ischemic brain injury [16]. The mechanism for this effect is unclear but may be associated with promoting brain energy metabolic crisis and lactate-pyruvate ratio elevation. Anemia is common after aSAH and especially those patients at risk for vasospasm may be at risk for compromised brain oxygen delivery.

No optimal hemoglobin goal in aSAH has been established as of the publication of this textbook. While some series have shown worse outcomes with red blood cell transfusions after aSAH [16], other prospective registries and a recent prospective randomized trial have shown the safety and feasibility of maintaining a higher hemoglobin level [16]. Subarachnoid bleeding may also impart a significant risk of developing venous thrombotic events (VTE) such as deep vein thrombosis (DVT) and, also, independently is associated with a high risk (5 %) of heparin-induced thrombocytopenia (HIT) [16]. The risk of developing HIT after aSAH is directly related to the number of angiographic procedures performed but not the use of heparin for DVT prophylaxis [16]. While there is no pragmatic way to prevent either DVT or HIT, it is important to have a raised index of suspicion and make a timely diagnosis when this is suspected. This will allow timely anticoagulation under the guidance of a hematologist.

After hospital discharge, aSAH patients should be referred for comprehensive psychological evaluation including cognitive, behavioral, and psychosocial assessments.

Hypoxic and Anoxic Brain Injury

Anoxic and hypoxic brain injury secondary to cardiac arrest is a devastating condition and outcomes are often poor despite aggressive care. Unlike stroke, cardiac arrest leads to a transient global loss of cerebral perfusion followed by a period of global hypoperfusion during CPR [22]. This period without return of spontaneous circulation (ROSC) causes cessation of cerebral ATP production, which leads to failure of the ATP-dependent sodium-potassium pumps on the neuronal membrane [22]. In turn, this disrupts the blood-brain barrier and leads to intracellular acidosis and neuronal edema [22]. Additionally, other mechanisms have been proposed including glutamate-mediated excitotoxicity, increased intracellular calcium, microthrombi formation in cerebral vasculature from the temporary stasis, and endothelial ischemic injury [22].

After ROSC, cerebral perfusion is restored, but cerebral autoregulation is lost. This results in regional and temporal disparities in cerebral perfusion with some cerebral territories being hypoperfused and others relatively hyperperfused [22]. Both conditions can cause distinct detriments to the patient with hypoperfusion promoting ongoing ischemic neuronal death whereas hyperperfusion causing edema and potentially progression to secondary injury [22].

Cardiac arrest and post-resuscitation care requires a multidisciplinary team. As recommended by the American Heart Association (AHA), early securing of the airway in patients with poor airway protective reflexes should be conducted, and the head of bed should be elevated by 30° to reduce the impact of cerebral edema [22]. Whether on a ventilator or receiving supplemental oxygen, the AHA further recommends titrating oxygen therapy to a goal saturation of greater than or equal to 94 % while maintaining adequate ventilation to a $PaCO_2$ of 40–45 mm [22]. The AHA further recommends a target systolic blood pressure of greater than 90 mmHg and mean arterial pressure greater than or equal to 65 mmHg [22]. Furthermore, they recommend against overly tight glycemic control out of concerns for worsening neuronal metabolism, instead suggesting a goal level between 144 and 180 mg/dL (8–10 mmol/L) [22].

Since the early to mid-1990s, induced hypothermia (IH) has been utilized in the post-arrest setting. While important trials have suggested improvements in cognitive recovery following post-arrest IH, one recent clinical trial failed to show any benefit of hypothermia over maintenance of normothermia [22]. The principle behind hypothermia as a neuroprotective therapy after brain anoxia is to decrease cerebral metabolic rate leading to reduced ATP consumption, improve glucose metabolism, and decrease acidosis [22, 23]. Animal models have shown reduction in glutamate toxicity leading to decreased activity of downstream apoptotic pathways that contribute to neuronal injury. Other proposed effects of

hypothermia include inhibition of reactive oxygen species (ROS) production during reperfusion, associated with inhibited NF-kB expression and reduced inflammatory cell infiltration [22].

Two clinical studies published in 2002 are of prime importance in suggesting a neuroprotective effect in hypothermia in the post-cardiac arrest setting [24, 25]. Specifically, the *Hypothermia After Cardiac Arrest* (HACA) study group randomized cardiac arrest survivors to maintenance of hypothermia (32–34° C) versus standard therapy and utilized cerebral performance categories to define favorable outcomes. Fifty-five percent of patients in the hypothermia group had a favorable outcome versus 39 % in the standard treatment group. Additionally, mortality rate was 25 % lower in the hypothermia group [26]. More than a decade later, after widespread adoption of hypothermia in this patient population, a multinational randomized trial tested the benefit of hypothermia by randomizing patients to hypothermia (33 °C) or euthermia (36 °C) in 36 Australian and European ICUs [25]. The mortality and incidence of poor outcomes were similar in both groups suggesting a benefit of preventing hyperthermia as being, perhaps, more important than inducing hypothermia.

Induction of hypothermia or maintenance of normothermia will require advanced neuromonitoring in the ICU and may be done using different cooling strategies. These include surface blankets and ice; administration of intravenous, intracystic, intrathoracic, or intragastric cold fluids; inhaled ventilator gases; and even venovenous bypass circulation cooling. In all cases this may lead to shivering which may increase cerebral metabolic rate and must be controlled. Several approaches may be used to control shivering including surface counterwarming, sedation (i.e., propofol), neuromuscular blockade, magnesium infusion, buspirone, and use of dexmedetomidine. While sedatives and paralytics work very effectively, they may obscure key physical signs indicative of neurological worsening or progression to brain death.

CNS Infections

Intracranial infections include a vast spectrum of conditions, each with different causative organisms producing unique clinical characteristics. They may progress rapidly and resulting in significant morbidity and mortality if appropriate interventions are not initiated promptly [27]. Patients will commonly present with altered mental status, seizures, focal weakness, or cranial nerve palsies. A head CT scan is frequently the first imaging modality obtained to assess for the presence of hydrocephalus, mass lesions, hemorrhage, or acute brain edema and is often performed prior to lumbar puncture. An MRI may logistically be more challenging to obtain in a critically ill patient but is more sensitive for cerebral spinal fluid infection, leptomeningitis, empyema, ventriculitis, vasculitis, and infarctions [27], particularly when evaluating T1-weighted and diffusion-weighted (DWI) images. MR spectroscopy may also be useful in certain cases. Consultation with a neuroradiologist and neurosurgeon is advised when intracranial infections are suspected.

Acute Bacterial Meningitis

Meningitis, or inflammation of the meninges, is one of the most serious and morbid of all intracranial infections. One must have a high index of suspicion, perform a rapid diagnosis, and initiate treatment expeditiously to prevent severe sequelae and death. Classically, meningitis will be suspected in patient with headache, nuchal rigidity, and subsequent mental status changes. Once suspected, CSF and blood cultures should be obtained and CSF microscopy should reveal elevated white blood cells and hypoglycorrhea. Early empiric intravenous antibiotic initiation is paramount and should be effective against *S. pneumoniae*, *N. meningitidis*, and *S. aureus*.

Early complications of meningitis include hydrocephalus whereby bacterial by-products may obstruct venous sinuses leading to swelling of and hyperemia of the pia and arachnoid matter and interference with CSF drainage. Occasionally an external ventricular drain is necessary to divert CSF and prevent life-threatening herniation from hydrocephalus. Other potential complications of meningitis include brain infarction, ventriculitis, brain empyema, and venous sinus thrombosis; all conditions which may be readily diagnosed with MRI [27].

Acute Encephalitis

Encephalitis is distinguished from meningitis by the presence of abnormal brain function. Though nuchal rigidity is usually absent, patients may present with seizures or focal neurological deficits. One of the most important causative agents of encephalitis is the herpes simplex virus (HSV). As both type 1 and type 2 HSV may produce encephalitis, it is prudent to start antiviral therapy (acyclovir) as soon as viral encephalitis is suspected and to proceed with PCR or viral culture to confirm HSV infection. In these patients, CSF examination will reveal large numbers of red blood cells despite an atraumatic puncture. MRI may also classically demonstrate petechial hemorrhages with a high predilection for the temporal lobes, cingulate gyri, and inferior frontal lobes with a high signal intensity in T2 images [27].

In recent years (after 1999) the West Nile virus (WNV) has become a more common causative infection in acute encephalitis and is most often acquired from mosquitoes.

The incubation period for WNV ranges from 3 to 14 days and approximately 1 in 150 people infected with WNV will develop meningoencephalitis, with the immunocompromised, elderly, and very young at the highest risk [27]. The presenting symptoms are as for other meningitis patients (altered mental status, headache, nuchal rigidity) with the added unique feature of flaccid paralysis (from anterior horn cell disease). The MRI of WNV-infected patients is generally normal, but in some cases, an increased T2 signal has been seen in the lobar area, cerebellum, basal ganglia, and thalamus [27].

While uncommon in the United States, Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi*, may be another causative organism in encephalitis. While the underlying pathophysiology remains poorly understood, neurological complications will occur in 10–15 % of patients including cranial nerve palsies and peripheral neuropathies.

Tuberculosis (TB) remains a common and deadly worldwide infection, and central nervous system involvement is a serious manifestation of chronic infection with manifestations ranging from meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis [27]. CSF acid fast bacillus microbiology is typically the method of choice for diagnosis, and even with effective treatment, the mortality rate for TB with CNS involvement remains high.

Brain Abscesses

Brain abscesses are focal, intracerebral infections that may occur in various anatomical locations. They begin with a localized area of cerebritis that progresses to a discrete collection of purulent fluid that eventually becomes surrounded by a well-vascularized capsule. The etiology of such infections is usually hematogenous seeding from other sources but in some cases may also occur from local spread from infected sinuses, otic or odontogenic sources [27]. Most commonly the culprit organisms are *Staphylococcus* and *Streptococcus* species. In patients with hematogenous dissemination, presenting as a brain abscess, careful evaluation must rule out endocarditis, cardiac shunts, and pulmonary vascular malformations. Cerebral imaging features of an abscess depend on the progression of the infection (pre- or post-capsule formation, etc.). Brain epidural abscesses are usually caused by a contiguous spread of infection from adjacent structures, such as mastoids or paranasal sinuses [27].

Malignant Brain Tumors

Malignant brain tumors will typically present with some type of herniation syndrome (which specific one will depend on location) or present with nonspecific signs and symptoms of globally elevated ICP. If suspected, a head CT is the initial diagnostic test of choice. Immediate medical interventions are directed toward lowering the patient's elevated ICP and in this regard mimic the management of other conditions with elevated ICP (see prior section). Specifically for brain tumors, an immediate bolus of 10–20 mg IV dexamethasone, followed by a maintenance dose of 8–32 mg/day should be administered. Glucocorticoids reduce cerebral swelling by decreasing the permeability of the cerebral capillaries [28]. The routine use of seizure prophylaxis is not recommended [28]. A patient with concern for increased ICP and a GCS of less than 8 should be considered for an ICP monitor as in patients with any other mass lesion [29].

The next and definitive step is resection of the tumor (not every tumor will be amenable to surgical intervention). Neurosurgical consultation should be obtained expeditiously. Typically, once the patient is stabilized, an MRI with and without gadolinium enhancement is obtained for potential surgical planning. Postoperative care should be delivered in conjunction with consultation of intensive care, oncology, and neurosurgical services.

Conclusion

Many of the acute, nontraumatic neurological conditions encountered in critically ill patients ICU can be successfully managed using fundamental critical care techniques in combination with expert neurologist consultation. With an awareness of the basic nuances of specific neurological diseases, proper collaborative care can be delivered to these patients in a timely fashion.

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Hemodynamic Monitoring and Resuscitation

7

Patrick J. Neligan and Jiri Horak

Introduction

Shock is a life-threatening condition that results from inadequate tissue blood flow to maintain homeostasis. Shock results from a reduction in cardiac output (CO) due to loss of circulating volume, a dysfunctional vascular network, or cardiac pump failure. Shock is traditionally classified as hypovolemic (absolute – due to blood or fluid loss, relative due to maldistribution of fluid within the body), cardiogenic (due to a loss of inotropy, atrioventricular synchrony, valvular insufficiency, or ventricular interdependence), vasoplegic (due to sepsis, anaphylaxis, or brain/spinal cord injury (neurogenic)), and obstructive (due to obstruction of the circulation – abdominal compartment syndrome, pericardial tamponade, tension pneumothorax, pulmonary embolism, or valvular stenosis). Critically ill patients frequently present with shock, often from multiple causes, for example, a patient septic shock complicated by abdominal compartment syndrome secondary to fluid overload. Hypotension is not necessary to diagnose shock [1]. This chapter will look at commonly encountered mechanisms of shock and methods employed to diagnose and manage them.

Injury Stress and Fluid Loss

Regardless of the mechanism of injury, patients presenting in shock will manifest clinical signs of the "stress response," a neurohormonal host reaction to injury driven by cortisol and catecholamines and characterized by dramatic changes in fluid and electrolyte distribution in the various spaces within the body. These changes are predictable and follow a characteristic pattern described by Cuthbertson and Tilstone [2] and Moore [3, 4]. An understanding of this process is central to understanding the dynamics of fluid and electrolyte flux in critical illness, and surgical critical care is helpful in guiding therapy.

The stress response has traditionally been described as a biphasic "Ebb and Flow" process. Initially, after an injury or surgical incision, there is a dramatic increase in circulating catecholamine levels. At rest approximately 30% of blood volume is active in the circulation, typically referred to as the "stressed" blood volume. The remainder, pooled in the extremities and splanchnic beds, is referred to as "unstressed" [5]. In situations where blood is lost, there is widespread vasoconstriction of the extremities and the splanchnic bed, and the unstressed volume is mobilized. Blood is principally redistributed into the heart and brain [6]. There is a reduction in blood flow to the intestines, kidney, and liver.

The EBB phase is associated with a reduction in body temperature and an increased peripheral to core temperature gradient. There is a fall in capillary hydrostatic pressure, promoting a rapid shift of protein-free fluid from the interstitium into the capillaries [7]. This is known as "transcapillary refill" [6]. The result is extravascular volume contraction and compensated hypovolemia associated with a dramatic increase in the release of vasopressin (antidiuretic hormone) and activation of the renin-angiotensin-aldosterone system that conserves salt and water. Of note, the mobilization of unstressed blood functions as a form of physiologic reserve, with the result that static measures of circulating volume such as mean arterial pressure, central venous, and pulmonary artery pressure, may fail to identify hypovolemia [5].

The stress response progresses to the hypermetabolic "flow" phase, within hours or following initiation of fluid resuscitation. This is characterized by a dramatic increase in cardiac output, manifest by tachycardia, driven by catecholamines, peripheral vasodilatation, localized or systemic

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capillary leak, and increased core temperature. This is associated elevated circulating cortisol and insulin resistance resulting in hyperglycemia and visceral and systemic protein catabolism. There is increased oxygen extraction in the extremities and elevated serum lactate as a result of increased glycolysis, secondary reduced oxygen delivery and/or increased beta-adrenoceptor activation, and reduced metabolism [8].

The magnitude of the stress response is proportional to the degree of tissue injury or extent of surgery. Significant intracellular fluid deficit may be incurred to maintain circulating volume. Sacral and extremity edema may be present, due to increased capillary permeability. Urinary output falls due to neurohormonal factors and reduced renal perfusion pressure. There is intravascular dehydration secondary to vasodilatation. During this period, patients are typically administered resuscitation fluids to maintain blood pressure, circulating volume, and tissue perfusion. Weight gain ensues and tissue edema worsens. Serum albumin falls in proportion to degree of injury and volume of fluid administered. Depending on the composition of the resuscitation fluids administered, patients typically develop varying levels of hypernatremia and hyperchloremia [9].

Eventually a state of equilibrium arrives, usually day 2 postoperatively or when source control has been achieved, when active extravascular fluid sequestration stops. Subsequently, the patient progresses to a "diuresis" phase, during which the patient mobilizes fluid and recovers. This is known as "deresuscitation." Serum albumin levels recover. Intracellular fluid volume returns to normal, associated with a significant inward shift of ions such as potassium, magnesium, and phosphate. Consequently, hypokalemia, hypomagnesemia, and hypophosphatemia occur at this time, and electrolyte supplementation is usually necessary. Time to recovery and deresuscitation may be influenced by the volume of fluid administered to the patient during critical illness and the quantity of solute (principally sodium and chloride) that must be excreted.

Each stage of the stress response requires a thoughtful approach to the positive and negative impact of fluid resuscitation. Under-resuscitation may result in tissue hypoperfusion and organ injury. Over resuscitation may lead to edema in highly perfused tissues such as the lungs and bowel, resulting in respiratory failure, wound dehiscence, and abdominal compartment syndrome [10, 11]. Failure to mobilize resuscitation fluids and electrolytes may result in prolonged dependence on mechanical ventilation, failure to mobilize, and ileus.

The critical care practitioner may encounter the shocked patient either in the ebb or flow phase, as a result of the patient triggering physiological limits of an early warning system in the hospital. The patient may be symptomatic with hypotension, tachycardia, tachypnea, altered level of consciousness, hypoxemia, or oliguria. In each scenario, the patient requires a full clinical examination, intravenous access, noninvasive blood pressure monitoring, and labs to include complete blood count, serum chemistry, troponin, and a venous lactate level. A patient who has been involved in an assault or motor vehicle collision or whom has undergone surgery within the previous 12 h is likely to be bleeding and in hypovolemic shock.

If there is no obvious injury, the practitioner must distinguish cardiogenic from septic from obstructive shock. Cardiogenic shock is primarily caused by acute myocardial ischemia – there is usually a history of chest pain, dyspnea or cardiac arrest, electrocardiographic changes, and a troponin rise. Following cardiac surgery, bleeding, tamponade, and right ventricular failure should be considered. If the patient has had recent pelvic or major orthopedic surgery, acute cardiogenic shock secondary to pulmonary embolism should be considered.

Septic shock is usually associated with fever, leukocytosis, raised inflammatory markers (such as C-reactive protein or procalcitonin), and a source – that may or may not be obvious. Irrespective of cause, unless the patient is already symptomatic with fluid overload, such as pulmonary edema, rehydration with 30 ml/kg of crystalloid is warranted [12].

If the patient does not respond to fluid and immediate interventions, medical or surgical, to control the source of shock, arterial cannulation and hemodynamic monitoring are indicated. There is a strong argument for using focused cardiac ultrasound at this stage [13]. The goal of echocardiography is to determine whether or not the heart is under- or overfilled, whether it is dilated on either the right or left side, and whether or not there is outflow obstruction. It is important to note that uncontrolled fluid bolus therapy has no role in modern critical care [14], in particular in states where hypotension results from vasoplegia and fluid redistribution [15]. In addition, modern hemodynamic monitors perform poorly in the presence of vasopressors which may camouflage significant volume depletion by mobilizing unstressed blood volume [16]. Importantly, clinicians should also be aware of misdiagnosis or the development of secondary causes of shock, in particular abdominal compartment syndrome [17]. We strongly recommend routine monitoring of intra-abdominal pressure in any patient requiring mechanical ventilation, treated with fluid boluses and vasopressors in ICU [18].

Measuring Hypovolemia

If a patient is bleeding profusely, or is severely hypotensive, then the decision to volume resuscitate is clear. In cases of more subtle volume loss, clinical examination may not uncover hypovolemia, and decision support by way of

Table 7.1 Predictive value of techniques used to predict fluid responsiveness [24]

Most accurate				Least accurate	
Pulse pressure variation (PPV)	Systolic pressure variation (SPV)	Stroke volume variation (SVV)	LV end-diastolic area (LVEDA)	Global end-diastolic volume (LVEDV)	Central venous pressure (CVP)
Derived from:	*Derived from:*	*Derived from:*	*Derived from:*	*Derived from:*	*Derived from:*
Arterial line waveform	Arterial line waveform	Arterial line pulse contour analysis	Echocardiography	Transpulmonary thermodilution (PiCCO)	Central venous pressure
AUC 0.94	AUC 0.86	AUC 0.84	AUC 0.64	AUC 0.56	AUC 0.55

LV left ventricle, *PiCCO* pulse contour continuous cardiac output, *AUC* area under the receiver operating curve

hemodynamic monitors would appear helpful. The simplest monitor is an arterial line, transduced to give invasive arterial pressures and a waveform. Beyond this there are lots of invasive and noninvasive hemodynamic monitoring devices on the market, many offering elaborate and impressive colorful displays and large amounts of information. For the clinician choosing such a device, several questions must be answered: (1) Is my patient hypovolemic? (2) How much fluid should I give initially? (3) When do I know enough is enough? (4) How do I measure ongoing volume loss? (5) Can I monitor fluid removal? Unfortunately no existing monitor provides answers to all of these questions.

Traditional teaching on cardiovascular physiology is based on interpretation of the Frank-Starling curve (FSC). This describes the phenomenon by which increasing diastolic blood volume in the left ventricle (LVEDV), leading in greater stretch on myofibrils, results in increased stroke volume. By increasing preload one may increase cardiac output. This assumes that preload dependence is an indication for fluid resuscitation, and such therapy will benefit the patient. As there is no easy method of measuring preload, surrogate static methods were developed and became popular – the central venous pressure (CVP) to measure right-sided filling pressures and the pulmonary artery occlusion pressure (PAOP) to measure left-sided filling pressures. To accept that these pressures represent "preload," several assumptions must be made: (1) that there is a relationship between CVP/PAOP and right and left ventricular volume, (2) that there is little impact of transmural and transpulmonary pressure on CVP/PAOP, (3) that each patient has an optimal CVP/PAOP that represents a "full" ventricle, and (4) that fluid loading to that CVP/PAOP will optimize cardiac output. In reality, despite decades of belief in CVP/PAOP as "preload," none of these assumptions are true.

Modern approaches to resuscitation require dynamic prediction of "fluid/volume responsiveness." This is an umbrella term that refers to an improvement in cardiac output, stroke volume, and blood pressure following a fluid bolus. Volume responsiveness is considered evidence of efficacy of hemodynamic monitors. These include esophageal Doppler measurement of stroke volume, stroke volume/pulse pressure variability monitors (SVV/PPV), pulse contour analysis, etc. None of these monitors are ideal (Table 7.1). For example, SVV/PPV monitors are accurate only when ideal conditions are present: mechanical ventilation, sinus rhythm, large tidal volumes, and the absence of vasopressors.

In this section we will explore the strengths and weaknesses of the various monitoring devices in current use in the operating room and ICU.

Invasive Blood Pressure Monitoring

Peripheral arterial cannulation is the gold standard for blood pressure monitoring in critically ill patients. The arterial line apparatus generates a characteristic waveform. The mean arterial pressure (MAP) is calculated by integrating the area under the waveform and the systolic and diastolic pressures calculated using an algorithm. This "invasive" blood pressure (IBP) measurement is accurate, continuous, reproducible, and immediate. IBP facilitates early diagnosis and treatment of hypotension. It is considered to be the particularly reliable in hypotensive and vasoconstricted patients [19, 20]. The waveform can also be analyzed by a variety of modern devices to determine stroke volume (SV), cardiac output (CO), and stroke volume variability (SVV).

The major problems associated with invasive blood pressure monitoring are damping and resonance; these can affect the accuracy of the blood pressure waveform and pressure measurement. Damping, caused by kinking or occlusion (e.g., with air bubbles), decreases the rate of signal change, leading to low pulse pressure with low systolic and high diastolic pressure reading. If the waveform is damped, the mean pressure is accurate, but the systolic and diastolic are not. In general, in critical care, MAP is considered the target perfusion pressure of choice, since autoregulated organs such as the bowel, kidney, and brain are MAP dependent (myocardial perfusion is dependent on diastolic blood pressure). The major problem with MAP is that, being a function of cardiac output and peripheral resistance, it is maintained in states of compensated shock and may not fall until up to 40 % of circulating volume is lost. As blood pressure is a function of peripheral resistance, which increases during shock, and stroke volume, which may fall, blood pressure readings may be misleading and falsely reassuring. Also, there is no clear intervention for treating a low MAP – should one give fluid

or should one administer vasopressors, or both? Although textbooks and guidelines suggest a MAP target of 65 mmHg in critical illness [12], there are no clear data to support this contention [21]. Nor is there any clear method of determining the pressure level that the individual patient's organs autoregulate. In practical terms many ICU nurses target at the MAP at which urine flows. Walsh and colleagues have demonstrated that an intraoperative MAP of <55 mmHg is associated with an increased risk of renal and myocardial ischemic insults [22].

In summary, in early critical illness, MAP is a simple metric that can assist in early decision-making for moderate fluid resuscitation and initiation of vasopressor therapy. However, MAP does not distinguish the mechanism of shock nor whether cardiac output or peripheral resistance should primarily be supported.

Central Venous Pressure

Central venous pressure (CVP) has been used for decades to assess volume status and to assess volume responsiveness. Unfortunately, it is useful for neither. The belief that CVP could be used to infer ventricular filling is based on incorrect interpretations of the Starling hypothesis. Although, in some cases, a very low (less than 5 mmHg) or a very high (greater than 20 mmHg) CVP may be helpful in guiding decisions about volume status, in most patients, a single CVP value is rarely helpful [23] nor indeed is the CVP trend. The accuracy of CVP measurement at predicting volume responsiveness is scarcely better than "flipping a coin (area under the curve 0.55 (confidence interval 0.48–0.62))" [24].

The central venous or RA pressure is the pressure within the RA relative to atmospheric pressure. However, right ventricular preload, which is best defined as right ventricular end-diastolic volume (RVEDV), is equally dependent on the intrathoracic pressure and right ventricular compliance, neither of which can be determined reliably at the bedside. A variety of interventions and pathologies may impact the extracardiac pressure – PEEP/auto-PEEP, prone positioning, intra-abdominal hypertension, ARDS, pneumothorax, etc.

Even if CVP correlated with RVEDV, the latter correlates poorly with LVEDV because of discordance in ventricular afterload and contractility. Indeed, lung disease, and the PEEP used to treat it, increases pulmonary vascular resistance and may produce right ventricular failure. Furthermore, since the pericardium limits ventricular dilatation, ventricular interdependence further increases the disparity in LVEDV and RVEDV when differential contractility or loading conditions are present. This occurs because ventricular dilatation displaces the septum laterally and compresses the adjacent ventricle.

CVP has been listed as an endpoint of resuscitation in many international guidelines, such as "Surviving Sepsis [12]." However, there are accruing data that resuscitating patients to high right atrial pressure levels worsens outcomes [25]. It is unclear whether this negative impact occurs due to fluid overload or loss of peripheral to central venous blood flow. Irrespective, we recommend against using a specific CVP level as a resuscitation goal in critically ill patients.

Pulmonary Artery Occlusion Pressure

The pulmonary artery catheter has been in use since 1974, although its use has been declining over the past two decades. Insertion of a PAC involves passing a long balloon-tipped catheter through the right heart into the main pulmonary artery and lodging it in a distal vessel – this process is known as "wedging." A column of blood then exists between the catheter tip and the left atrium that can be transduced as left atrial pressure. The PAC directly measures pulmonary artery pressures, thermodilution cardiac output, core temperature, true mixed venous oxygen saturation, and pulmonary capillary wedge/occlusion pressure (PAOP). Interpretation of these data may be problematic and may lead to poor decision-making [26].

Many clinicians believe that PAOP reliably reflects preload and is useful for the construction of Starling curves. This is unlikely [27]. The pressure-volume relationship of the left ventricle changes dynamically, depending on clinical circumstances, and vascular pressures are altered by changes in ventricular and atrial compliance, ventricular systolic and diastolic function, valvular function, heart rate and rhythm, afterload, intrathoracic pressures, and abdominal pressures. They also change with therapeutic interventions [23, 27, 28].

PAOP pressures should not be used to guide volume resuscitation. The PAC does provide an accurate thermodilution. The so-called "continuous" cardiac output (CCO) monitors use a random sequence of temperature changes generated by a heating coil located in the right ventricle, with a thermistor within the pulmonary artery. The data is averaged over time to produce an accurate series of measurements. Hence there may be a delay of several minutes before the device indicates major hemodynamic changes. Consequently, CCO-PAC are unhelpful for assessing volume responsiveness, as some time may elapse before measured changes in stroke volume may become evident. In addition, significant time may be required to insert a PAC, calibrate it and wait for data, severely limiting its use in acute resuscitation scenarios.

When is the PAC useful? The principal use of PA catheters is currently in states of cardiogenic shock, in particular secondary to right ventricular dysfunction; the majority of utilization follows myocardial infarction or cardiac surgery.

The PAC may also be used to diagnose and treat pulmonary hypertension. This may occur, for example, in patients with severe acute hypoxic respiratory failure, and inhaled nitric oxide or prostacyclin may be administered and titrated using indices derived from the PAC.

Dynamic Measures of Fluid Responsiveness

The ability to predict volume responsiveness will ensure that patients are adequately resuscitated by not volume overloading. Excessive fluid administration has been shown to worsen outcomes in sepsis and ARDS and increase perioperative morbidity [10, 11]. To date, static measures of preload, such as CVP and PCWP, have proven ineffective for plotting FSC in critically ill patients. Dynamic estimates of fluid responsiveness have been developed that look for changes in cardiac output based on heart-lung interactions or following passive leg raising.

Esophageal Doppler

Esophageal Doppler monitoring (EDM) has been widely used in perioperative medicine to titrate fluid therapy, particularly in the United Kingdom. The thoracic aorta is located in close proximity to the esophagus. The device uses Doppler ultrasound to measure aortic blood flow – the flow velocity time – from which stroke volume and cardiac output are derived. The EDM, while small in diameter and pliable, cannot be inserted into nonsedated non-intubated patients or patients with known esophageal disease. The observer needs to be at the bedside, continuously adjusting the probe for optimal signal. Compared with many other noninvasive hemodynamic monitors, there is a substantial body of data to support the use of EDM in the operating room [29]. Insertion is rapid, and data can be derived that are clinically useful within seconds. However, there is a steep learning curve and significant interobserver variability and the need for frequent repositioning that renders the EDM of limited utility in the emergency room and ICU.

Pulse Pressure/Stroke Volume Variability (PPV/SVV)

During inspiration, when the patient is being mechanically ventilated, blood pressure increases. It falls during the subsequent expiration. Positive intrathoracic pressure has multiple effects on both the right and left side of the heart. There is increased right ventricular afterload, due to increased pulmonary arterial resistance, reduced right atrial filling, and impaired venous return, and right ventricular dimensions are reduced. Simultaneously, there is increased pulmonary venous return, resulting in increased left atrial and ventricular filling, with increased LV compliance due to reduced transmural pressure, reduced LV afterload, and reduced ventricular interdependence [30]. Thus LV stroke volume (SV) and associated pulse pressure increases during inspiration, but falls during the subsequent expiration (Fig. 7.1). In the hypovolemic patient, LV is functioning on the steep portion of the FSC. Consequently, small changes in preload, associated with respiration, induce large changes in SV [30]. If the patient is euvolemic, on the flat part of the FSC, the respiratory cycle has minimal impact on SV [31].

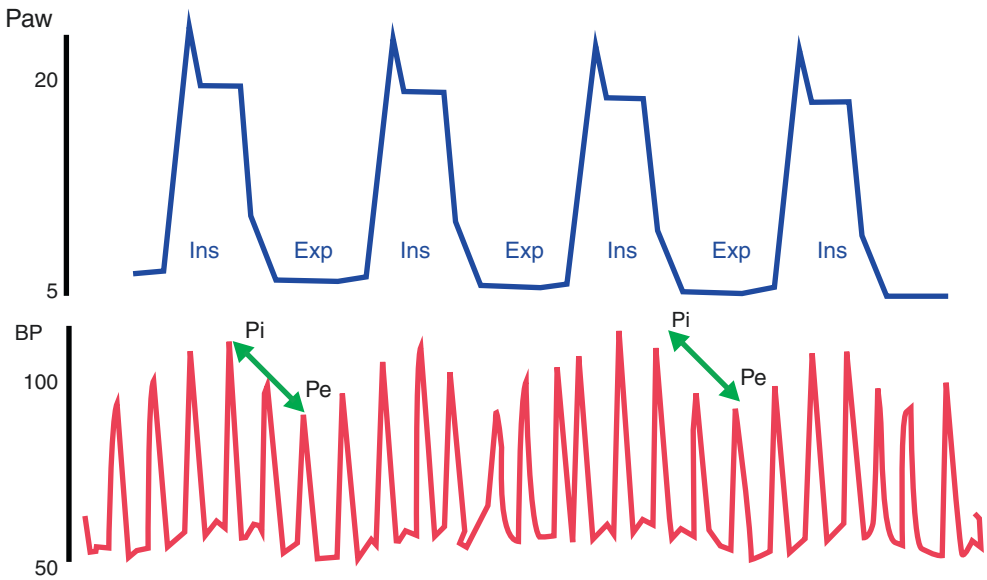

Fig. 7.1 Systolic and pulse pressure variability. *Upper panel*, airway pressure in cmH_2O (*ins* inspiratory phase, *exp* expiratory phase). *Lower panel*, blood pressure in mmHg (*Pi* systolic blood pressure in inspiration, *Pe* systolic blood pressure in expiration). Pulse pressure is systolic-diastolic blood pressure

Early studies of heart-lung interactions during the respiratory cycle used systolic pressure variability (SPV) (Fig. 7.1). However, this was replaced, subsequently, by pulse pressure variability (PPV). PPV predicts fluid responsiveness better than SPV [32] – as pleural pressure has equal effects on systolic and diastolic pressure, and PPV is more reflective of variations in stroke volume. In general, the patient must be mechanically ventilated and have a functioning arterial catheter in situ [33]. The respiratory cycle can be monitored using airway pressure or capnography (Fig. 7.1). A 13 % fall in pulse pressure appears to be a sensitive indicator of fluid responsiveness [32]. The greater the degree of PPV, the more accurate the measurement and the more fluid responsive the patient. PPV can be measured easily using modern ICU monitors (such as the Philips IntelliVue Monitor System), but accuracy depends on several factors: suitable for adults only, respiratory rates of >8 breaths per minute, tidal volumes >8 ml/kg, and no spontaneous ventilation.

The arterial pulse pressure is proportional to the SV (Fig. 7.2). Thus preload responsiveness may also be measured by stroke volume variability during the respiratory cycle. A variety of tools can be used to evaluate stroke volume variability (SVV) (Fig. 7.3).

FloTrac (sensor)-Vigileo (monitor Edwards Lifesciences, Irvine, Ca – F/V) is a hemodynamic monitoring system introduced in 2006 and currently in its fourth generation of software. A single sensor is attached to an arterial line at any site. The F/V device rapidly analyzes the arterial pressure waveform and uses demographic data and an evolving algorithm to calculate cardiac output. Arterial pulsatility is directly proportional to stroke volume. As changes in vascular tone and compliance occur dynamically, the device corrects for this by analyzing skewness and kurtosis of the arterial waveform. These correction variables are updated every 60 s, and the arterial waveform is analyzed and averaged over 20 s, thus eliminating artifacts, jitter, and extrasystoles. F/V does not require external calibration nor the presence of a central line or specialized catheter. Cardiac output is calculated utilizing the arterial waveform and the heart rate. These data may then be used to calculate SVV and hence fluid responsiveness. To date, under ideal conditions these data appear accurate [34].

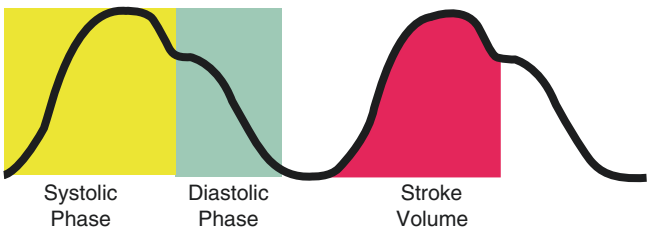

Fig. 7.2 Pulse waveform divided into the systolic and diastolic components. The stroke volume is the area under the curve of the systolic component

Mayer and colleagues meta-analyzed studies on F/V in 2009 [35]. Earlier studies demonstrated poor correlation between F/V and thermodilution methods; with newer software, the correlation has improved [36]. It should be borne in mind, however, that thermodilution methods, although considered the gold standard, are not ideal devices to compare with F/V: measurement intervals and averaging times are substantially longer with all thermodilution methods. Hence it is possible that F/V is more sensitive to dynamic changes in cardiovascular activity. F/V data is likely misleading in patients with aortic valve disease, those with intra-aortic balloon pumps in situ, those rewarming from induced hypothermia, and patients with intracardiac shunts.

Data to date have suggested that F/V is quite accurate at measuring changes in cardiac output associated with volume expansion (preload sensitivity) [37] but not with changes associated the vasopressor use [38–40]. It is unclear whether derived data are of any value in the non-intubated or spontaneously breathing patient [41]. It is likely that the accuracy also depends on the patient having a regular cardiac rhythm and minimal variability in tidal volume [42].

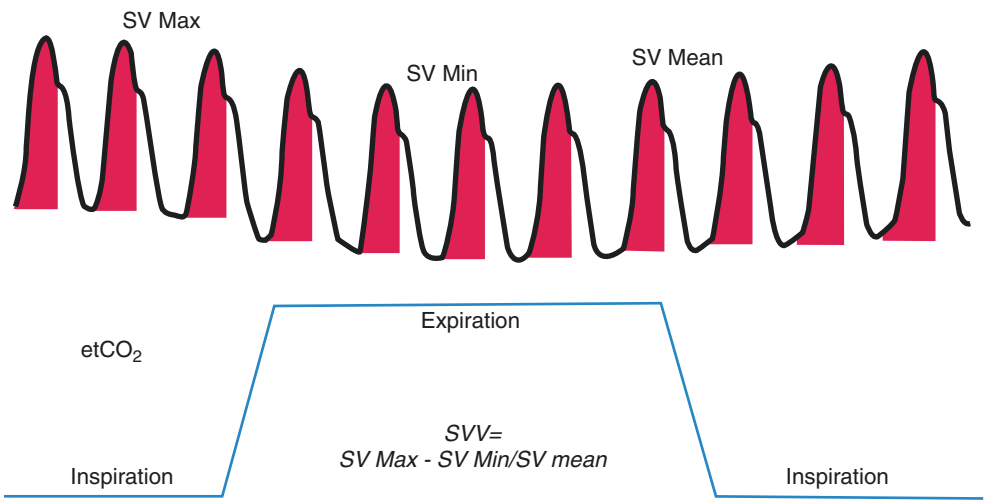

Fig. 7.3 Stroke volume variability (SVV). *SV* stroke volume, *etCO*$_2$ end-tidal carbon dioxide (in mmHg or kPa)

A simplified device that uses the pulse oximeter waveform and the pleth variability index (PVI) has been proposed and promoted. This has the obvious advantage of being truly noninvasive. To date, however, data have failed to demonstrate correlation of PVI with other monitors of fluid responsiveness, although the accuracy of these devices is likely to improve given the obvious commercial potential [43, 44].

Pulse Contour Cardiac Output

Systolic ejection results in the propulsion of a stoke volume into the arterial tree. The aorta and distal arteries distend, and the waveform is characteristic. It reflects the stroke volume and elastic properties of the arterial wall. The shape of the pulse waveform and the area under the curve are proportional to the cardiac output (Fig. 7.2). However, arterial compliance is not constant or consistent – there is tremendous inter- and intrapatient variability. As compliance is the mathematical relationship between pressure and volume, external calibration of the pressure signal with an alternative cardiac output technique is required. Pulse contour devices – Pulse CO LiDCO+ (lithium dilution cardiac output, LiDCO Ltd., Cambridge, UK) and PiCCO (pulse contour continuous cardiac output, PULSION, Germany) – combine pulse contour analysis to calculate stroke volume and indicator dilution or thermodilution cardiac output measurement to calibrate the system.

In addition to calculating cardiac output, devices that analyze pulse waveforms also analyze and display pulse pressure variability that can be used for dynamic preload assessment and fluid responsiveness (in mechanically ventilated patients).

LiDCO

Lithium is (in low doses) a nontoxic substance that is not metabolized. When injected, its concentration is easily measured using an ion-selective electrode. Lithium dilution cardiac output is calculated from the area under the concentration-time curve when injected from a central line and measured peripherally. Injection through the antecubital vein appears to be as accurate as a central line. Pulse CO LiDCO (LiDCOplus) combines pulse contour analysis with lithium dilution calibration.

The major disadvantage of LiDCOplus (LiDCO+) is the injection of lithium and the requirement for calibration of cardiac output at least every 8 h. In addition, in patients that are hyponatremic or have recently received neuromuscular blocking agents, the calibration data may be inaccurate. Data is unreliable with aortic valve disease or with intra-aortic balloon counterpulsation. The major advantage of LiDCO+ is that no specialized central or arterial line is needed, and little specialized training is required. There are few data supporting LiDCO as a decision-making tool [45].

PiCCO

PiCCOplus (PULSION Medical, Munich, Germany) calculates cardiac output continuously from pulse contour analysis of the aortic waveform via an arterial cannula. This must be placed in a large artery – femoral, brachial, or axillary. The system also requires a central venous catheter, usually in the internal jugular or subclavian vein. The central line is required in order to perform transpulmonary thermodilution cardiac output (TTCO) measurement – there is a thermistor in the arterial catheter. TTCO is used to calibrate the system. The principle advantage of PiCCO over a PAC is that there is no requirement to cannulate the right heart. However, two separate lines are required, and in the majority of cases, this involves a second arterial cannulation.

The PiCCO device measures the area under the aortic waveform – the systolic area is identified as that part of the waveform proximal to the dicrotic notch, and this is proportional to the stroke volume (Fig. 7.2). Although beat-to-beat volumes are measured, these are averaged over 30 s, to avoid inaccuracy associated with anomalous waveforms, extrasystoles, and interference. The continued accuracy of PiCCO depends on the frequency of calibration using thermodilution, which should be done at a minimum of eight hourly intervals [46]. By analyzing the changes in stroke volume during the respiratory cycle, stroke volume variability can be estimated (Table 7.1, Fig. 7.3).

In the PiCCO, the temperature differential detected using the arterial thermistor is composed of a series of exponential decay curves as the cold injectate passes through the various compartments of the circulatory system. As the injectate is administered centrally and the temperature difference is measured in a proximal artery, the majority of the temperature change occurs in the intathoracic compartment. Consequently, one can measure intrathoracic blood volume and extravascular lung water, which is helpful in titrating fluid therapy and fluid removal. Finally, in addition to stroke volume variability, the device also purports to measure global end-diastolic volume, hence permitting the construction of Starling curves and volume titration (Table 7.1).

To date, this particular device appears to correlate very well with other thermodilution techniques [47–50] and is widely used in ICU to monitor both resuscitation and "deresuscitation."

End-Expiratory Occlusion (EEO)

During inspiration, the intrathoracic pressure rises, impeding venous return, resulting in reduced end-diastolic volume. Conversely, if the respiratory cycle is halted during

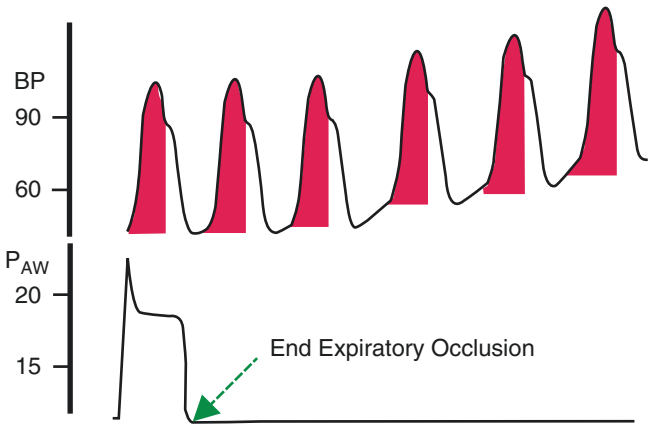

Fig. 7.4 End-expiratory occlusion test: blood pressure rises following a 15 s expiratory occlusion test in fluid responsive patients. *BP* blood pressure in mmHg, *PAW* airway pressure in cmH_2O

expiration, for example, for 15 s or so, then there is an increase in cardiac preload. A 5 % increase in cardiac output or pulse pressure during occlusion predicts fluid responsiveness (Fig. 7.4). A number of investigators have demonstrated the efficacy of this approach as an alternative to a fluid bolus [51–53]. In the majority of studies, transpulmonary thermodilution using PiCCO has been used to measure cardiac output.

The use of EEO appears to be more efficacious than SVV alone in the setting of low lung compliance and ARDS [53]. It also appears to be suitable for patients breathing spontaneously and those with arrhythmias, such as atrial fibrillation as EEO exerts its effects over several cardiac cycles. The magnitude of PEEP does not appear to influence the outcome of the test [53]. EEO has the benefit of simplicity compared with, for example, pulse contour analysis. Although EEO can be performed in patients who are not paralyzed or deeply sedated, recurrent inspiratory efforts may interrupt the occlusion and invalidate the test.

Passive Leg Raising

If a patient is lying supine, raising the legs from horizontal to vertical induces a significant translocation of blood volume from the extremities to the central circulation. Functionally, there is mobilization of unstressed blood volume and an increase in right ventricular preload. This increases cardiac output, which then falls when the legs are returned to the horizontal position. Essentially, the patient receives a fluid bolus without receiving exogenous fluid as a result of relocation of venous blood pooled in capacitance vessels. An increase in cardiac output during this maneuver predicts fluid responsiveness [54]. It does so irrespective of whether the patient is breathing spontaneously or mechanically ventilated or whether the patient is in atrial fibrillation [55], due to the fact that the test exerts its effects over several cardiac and respiratory cycles [56]. Various measures of cardiac output have been used, importantly only those with relatively rapid response are effective: esophageal Doppler, pulse contour analysis, bioimpedence, and end-tidal carbon dioxide ($etCO_2$) [56]. A 5 % increase in $etCO_2$ predicted a 15 % increase in cardiac index in volume responders [57]. Unfortunately, arterial pulse pressure changes in PLR do not predict volume responsiveness [57]. Passive leg raising appears to be more efficacious than SVV alone in the setting of low lung compliance and ARDS [51].

There is a strong argument for performing passive leg raising (PLR) in the semirecumbent rather than the supine position: unstressed blood is mobilized from the legs and the splanchnic circulation, so the volume delivered to the heart is greater and the sensitivity of the test higher [51].

Table 7.2 Targets for FoCUS (cardiac ultrasound) examination

Volume status
LV size and systolic function
Pericardial effusion/tamponade
Gross valvular abnormalities
Gross signs of chronic heart disease
Large intracardiac masses
RV systolic function

Echocardiography

The Current Role of Echocardiography in Critical Care

Echocardiography dramatically increases the intensivist's capability to diagnose a variety of causes of hemodynamic instability. There is a tremendous spectrum of competence in performance and interpretation of echocardiographic images. However, even rudimentary knowledge of bedside echocardiography may provide a life-saving diagnosis in, for example, cardiogenic shock, severe hypovolemia, and massive pericardial effusion/tamponade [58]. This has led to the development of "focused cardiac ultrasound (FoCUS)," a simplified approach that aims to ascertain only the essential information needed in critical scenarios and time-sensitive decision-making (Table 7.2) [59]. A FoCUS examination is brief and addresses a few clinical questions, mainly in a "yes or no" manner: the patient is hypotensive, is this due to hypovolemia – yes or no? Is it due to left ventricular dysfunction – yes or no? Is it due to pericardial effusion – yes or no?

Transthoracic echocardiography (TTE) should be the first modality in most cases of hemodynamic instability, because of its safety, reliability, and rapidity [60]. Image quality can be an issue, due to poor or limited acoustic windows, but new

technology, harmonic imaging and new echo contrast products, have significantly improved TTE signal acquisition [61].

Transesophageal echocardiography (TEE) is indicated, when the TTE study is inadequate, to evaluate of aortic dissection, to diagnose endocarditis of prosthetic valves, or to rule out intracardiac thrombus presence before semi-elective cardioversion. In early shock, TEE is limited by its invasiveness – it is preferable that diagnosis and management of shock precedes intubation, which can often be avoided. However, smaller TEE probes have been developed and in time will be as minimally invasive as a nasogastric tube.

Ventricular Function

Left ventricular (LV) dysfunction in critically ill patients is common and may be caused by ischemia, sepsis, or hyperadrenergic states (such as traumatic brain injury or subarachnoid hemorrhage). When the LV becomes dysfunctional, end-diastolic volume increases to maintain stroke volume, and ejection fraction (EF) falls. In addition echocardiography may also unveil regional wall motion abnormalities, usually associated with myocardial ischemia.

Right ventricle (RV) dysfunction is also very common in critically ill patients. Pulmonary embolism (PE) and acute respiratory distress syndrome (ARDS) are the most frequent causes in medical surgical ICU [62], although RV failure not uncommonly complicates cardiac surgery. Pulmonary hypertension may be uncovered by pulmonary arterial catheterization, but echocardiography is required to diagnose the underlying cause.

The RV is generally small compared with the LV. In the four-chamber view, the ratio between RV and LV end-diastolic area is measured. A diastolic ventricular ratio >0.6 suggests moderate, and ratio >1.0 severe, dilatation [63]. An acute rise in right ventricular (RV) afterload, for example, consequent of profound hypoxic pulmonary vasoconstriction, can cause acute cor pulmonale. The RV dilates, the LV is small and underfilled, and the interventricular septum bows inward into the LV (ventricular interdependence) particularly during diastole [64].

Assessments of Cardiac Output (CO)

Thermodilution of CO measurement is not always accurate in critically ill patients. Very low or very high CO, severe TR, rapid temperature changes, or intracardiac shunt can result in incorrect data. In these conditions, echocardiography can relatively reliably measure SV and thus CO [65]. The most common technique is Doppler-derived instantaneous blood flow measurement through a conduit (LV outflow tract, pulmonic or mitral valve). Stroke volume is equal to product of cross-sectional area (CSA) of the conduit, determined by 2D echo, and integration of instantaneous blood flow, velocity time integral (VTI), through the conduit. CSA = diameter of conduit (D) squared × (pi/4). SV = CSA × VTI. SV multiplied by heart rate (HR) gives CO. CO = CSA × VTI × HR.

Volume Status

Echocardiography is an effective method of estimating volume status and fluid responsiveness. An empty LV, manifest by systolic obliteration, strongly suggests inadequate preload. A dilated LV, defined by an increase in diameter, may reveal a chronically failing heart, which may respond to a volume challenge [66].

In addition to visualizing the heart, significant information can be gleaned from observation of the great vessels. The collapsibility index of the superior vena cava (SVC) and respiratory variation in inferior vena cava diameter (the distensibility index – dIVC) have been validated [67–69]. dIVC is calculated using measurements of maximal IVC diameter during inspiration (Dmax) and minimal diameter during expiration (Dmin) [67].

$$\text{dIVC} = \text{Dmax} - \text{Dmin} / \text{Dmin}.$$

In ICU, this approach is limited due to the high prevalence of IVC dilation in mechanically ventilated patients [70].

Goal-Directed Resuscitation

Shoemaker, in the late 1980s, demonstrated that by driving up cardiac output with fluids and inotropes, perioperative outcomes could be improved [71]. A number of studies in the 1990s and 2000s utilized dynamic flow monitoring devices intraoperatively to hemodynamically optimize the patient. Early studies, using esophageal Doppler, suggested improved outcomes. Later studies were more disappointing [72]. The largest optimization study to date, by Pearse and colleagues, of 734 high-risk patients, undergoing gastrointestinal surgery aged 50 and older, in 17 hospitals in the United Kingdom, failed to demonstrate improved perioperative outcomes [73]. The authors subsequently performed a meta-analysis that included data from previous perioperative GDT trials (38 in total). In this analysis GDT was associated with fewer overall complications (intervention, 488/1,548 [31.5%] vs control, 614/1,476 [41.6%]; RR, 0.77 [95% CI, 0.71–0.83]) [74]. Another meta-analysis of 22 trials that reported cardiovascular outcomes suggested that GDR was associated with reduced total cardiovascular (CVS) complications [OR = 0.54, (0.38–0.76), $P = 0.0005$] and arrhythmias [OR = 0.54, (0.35–0.85), $P = 0.007$] [75]. There was no increase in the risk of pulmonary edema or myocardial ischemia.

In critical care research involving GDT, a surrogate of oxygen consumption, the mixed venous oxygen saturation (SVO_2,) has been used to estimate tissue blood flow by looking at oxygen extraction. Low SVO_2 is indicative of excessive extraction per unit volume, apparently suggestive of hypovolemia.

Critical care studies of GDR in the 1980s that used SvO_2 as the endpoint of fluid and inotrope therapy had disappointing outcomes [76, 77]. These studies were carried out in established rather than impending critical illness. Rivers et al. speculated early GDR may improve outcomes in patients presenting to the emergency room with early signs of sepsis. They randomized 263 patients to "standard" therapy versus aggressive goal-directed therapy that included the use of an oximetric ($ScVO_2$) central venous pressure line [78]. This measured SVO_2 in the superior vena cava distribution. Therapy was directed at CVP (8–12 mmHg), $ScVO_2$ (>70 %), and MAP (>65 mmHg) goals. The patients in the study group received significantly more fluid than the control group in the first 6 h, more red cell transfusions overall and equivalent volume of intravenous fluid over the first 72 h. There was a 16 % decrease in a 28-day mortality (number needed to treat, 6). The implication of this study was that early aggressive volume resuscitation restores tissue blood flow, prevents multiorgan failure, and saves live. Once goals are met, further resuscitation is not helpful and may be harmful.

There were many questions about this trial, not least that it was single operator and single centered. The mortality rate in the control group was apparently high; a number of patients appeared to be missing from analysis, and timing of antibiotics therapy was unclear (all refuted by Dr. Rivers).

Three follow-up studies were performed – ProCESS, ARISE, and ProMISe [79–81]. All three trials looked at volume resuscitation in early sepsis, comparing the Rivers' protocol to "usual care" – which appeared to be aggressive volume resuscitation without the inotropes, central line, and $ScVO_2$ monitor. Obviously, "usual care" had been influenced by a decade of "Surviving Sepsis" – derived mainly from the Rivers' approach. Nonetheless, there was no survival benefit associated with using dobutamine, CVP, and $ScVO_2$ goals. The cost of care was greater in the GDT groups, principally due to increased numbers of central venous cannulations, inotrope use, and ICU admissions [82]. Higher CVP levels have been shown to increase the risk of adverse outcomes [25], and hypervolemia is strongly associated with abdominal compartment syndrome [83].

Taking these data together, it appears that perioperative patients, undergoing major nonvascular surgery, may benefit from IGDVR. Dynamic monitoring of stroke volume is more effective than traditional monitors such as CVP, $ScVO_2$, mean arterial pressure, and urinary output. Patients appear to do better if resuscitated on the day of injury or surgery.

Lactate and Lactate Clearance

Raised serum lactate (lactic acidosis) is the only widely accepted biomarker of shocked states [1]. Lactic acidosis occurs when the production of lactate in the body is greater than the liver's capacity to metabolize it: there is a problem of overproduction or inadequate clearance.

Lactic acid is produced physiologically as a degradation product of glucose metabolism. Its formation from pyruvate is catalyzed by lactate dehydrogenase. Under normal conditions the ratio of lactate to pyruvate ratio is less than 1:20. In anaerobic conditions, for example, following vigorous exercise, lactate levels increase dramatically. In addition, lactate can be produced under aerobic conditions. Activation of beta-adrenergic receptors in skeletal muscle by stress (increased circulating catecholamines) or exogenous infusion (epinephrine/norepinephrine infusions) increases the lactate concentration resulting in aerobic glycolysis. Lactate is converted to glucose in the liver (the Cori cycle) and subsequently to CO_2 and H_2O. Hence the lactate in Ringer's lactate solution is functionally bicarbonate.

Serum lactate and arterial pH should be measured early in any critically ill patient. A lactate concentration >2 mmol/L is clinically significant, and a level of 5 mmol/L in the presence of metabolic acidosis is severe [84]. Isolated hyperlactatemia in the absence of acidosis is of unclear clinical significance [85].

There are two types of lactic acidosis: type A (global inadequate oxygen delivery) is seen in hypovolemic/hemorrhagic shock, while type B occurs despite normal global oxygen delivery and tissue perfusion (usually both coexist in critical illness). Lactic acidosis may also develop in situations where there is significant regional hypoperfusion. Examples include bowel ischemia, where lactate is produced in large quantity due to glycolysis despite global oxygen delivery that is normal. Type B lactic acidosis is associated with hyperadrenergic states where circulating catecholamines (endogenous or exogenous) are in excess. Examples include simple exercise and the hyperinflammatory state of trauma or sepsis. Type B lactic acidosis may also be seen in cyanide poisoning (associated with sodium nitroprusside), with biguanides (metformin), and in hypercatebolic diseases such as lymphoma, leukemia, AIDS, or diabetic ketoacidosis.

Lactic acidosis is a sensitive marker of disease severity [86], and failure to clear the acidosis is a strong predictor of adverse outcomes [87–89]. The presence of a low mixed venous oxygen saturation (SvO_2) with a high lactate is indicative of type A (hypoxia associated) acidosis. Following resuscitation, SvO_2 recovers rapidly and lactate slowly, due to saturated metabolic pathways.

The presence of normal systemic indices of perfusion does not exclude significant regional hypoperfusion or mitochondrial failure [90, 91]. Clinicians frequently misinterpret high serum lactate levels indicative of global tissue hypoperfusion and as a result may continue to administer intravenous fluid [91, 92]. Where possible, following initial resuscitation, fluid responsiveness should be determined by SVV or PPV. Dynamic measurements of lactate over time are better predictors of outcome than static measures [93]. Lactate clearance has been proposed as an endpoint of resuscitation in sepsis [94, 95], as lactate concentration would be expected

to fall with adequate resuscitation [95]. Rapid clearance of lactate has been associated with improved outcomes [96, 97]. A failure of lactate clearance in response resuscitation suggests that global perfusion is not the underlying problem and should prompt a search for a more sinister etiology.

Blood Transfusion

Current Status of Transfusion Therapy

Over the past decade, the approach to resuscitation of patients who are bleeding has changed dramatically. No longer are patients receiving large amount of crystalloid (or colloid) prior to blood transfusion. The emphasis is now placed on damage control surgery with earlier blood component therapy [98]. This approach results from the realization that coagulopathy is the major cause of mortality in the bleeding trauma patient [99], and reversing coagulopathy, in particular with fibrinogen, has resulted in dramatically improved outcomes [100]. Plasma and platelets are administered earlier in increased volume. There has been a corresponding decrease in the use of crystalloids, resulting in less hemodilution, tissue edema, and hypoxemia [101]. The multitrauma-center PROMMTT trial included approximately 1,000 patients involved in major trauma, transfused at least one unit of RCC in the first 6 h [102]. Using a multivariable time-dependent Cox model, it was demonstrated that earlier administration of higher ratios of red cells to plasma to platelets (e.g., 1:1:1) was associated with a significant reduction in mortality [102]. To find the optimal ratio, the PROPPR study was conducted by the same authors – comparing plama/platelets/RCC 1:1:1 (intervention) to 1:1:2 (control) [103]. Six hundred and eighty patients were randomized: 338 to intervention, 342 to control. There was no difference in 30-day mortality, but there were fewer deaths from exsanguination in the intervention group. For bleeding patients, who were not involved in trauma, it is unclear at what ratio blood components should be administered, and accumulated data to date are unhelpful.

It is unclear how these data will translate in the perioperative period, given that in low-risk patients, blood transfusion is associated with a significant increase in perioperative morbidity and mortality [104]. For the majority of patients with moderate blood loss and anemia, transfusion is likely unnecessary and potentially harmful [105].

Key Points

1. Shock is a major indication for referral to critical care services: it may be hypovolemic, cardiogenic, vasoplegic, or obstructive. Hemodynamic monitoring is used to diagnose and treat the cause of shock.
2. Invasive blood pressure monitoring is a standard intervention for monitoring shock. Measured pressures alone are often misleading and unhelpful. The pressure waveform is increasingly been used to titrate fluid therapy.
3. Central venous pressure and pulmonary artery occlusion pressure do not predict fluid responsiveness and therefore should not be used as endpoints of resuscitation.
4. Pulse pressure variability, stroke volume variability, and pulse contour analysis predict fluid responsiveness in a variety of shock settings.
5. Focused cardiac ultrasound is emerging as an essential component in the training of intensive care clinicians and for diagnosing and treating shocked patients.
6. Lactate is the only universally accepted biomarker of sepsis and other shocked states. Elevated lactate reflects increased production and reduced metabolism. A high lactate is an indication for intravenous rehydration, but it is not an "endpoint" of resuscitation.
7. Goal-directed resuscitation is not currently validated in critical care, though it does seem to have a role in the operating room.
8. The bleeding patient should be treated with blood products and minimum crystalloid resuscitation. Blood transfusion has little or no role in the management of the nonhemorrhaging anemia of chronic critical illness.

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Hemodynamic Monitoring in Surgical Critical Care

8

Brett M. Howard and D. Benjamin Christie III

Introduction

Hemodynamic monitoring has been an essential element of medical care and arguably the corner stone of patient care delivery in any acute clinical setting. However, despite medicine's modern evolution and technological advancements, hemodynamic monitoring continues to be a much debated topic with polarized differences of opinion. The debate has existed, and continues to exist, due in part to the historic difficulty that researchers and clinicians have had in identifying a universally acceptable modality to obtain accurate and reproducible data regarding cardiovascular performance, responsiveness to therapeutic interventions, appropriate end points of resuscitation, or therapeutic efforts.

Methods of hemodynamic assessment include indirect and direct perfusion (pressure and flow) measurements and the more recently acknowledged, direct visualization methods. While all modalities have advantages, disadvantages, and some degree of imprecision, no single technique is inadequate or useless nor has any one modality proven to be a stand-alone solution to complex resuscitation scenarios. While research is unceasing in establishing a gold standard for hemodynamic monitoring and an accompanied end point of resuscitation, a thorough understanding of existing and evolving hemodynamic monitoring strategies and concepts is a necessary prerequisite for the practicing intensivist.

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Indirect Perfusion Measurement

The noninvasive manual and automated techniques of blood pressure recording are the most clinically ubiquitous and time-honored hemodynamic monitoring modalities. The most well-known indirect perfusion measurement method is the simple capture of blood pressure values with a sphygmomanometer. First developed in Italy by Riva-Rocci in 1896 and later introduced in the United States by Dr. Harvey Cushing, the method has become the expectation for initial hemodynamic assessments [1]. The technique requires the application of a cuff or sleeve with an inflatable bladder impeded in the cuff fabric which is ultimately fixed to a gauge to measure pressure. The cuff is wrapped around an extremity, preferably an upper extremity, overlying a major arterial structure. The cuff is inflated until the pressure of the cuff overcomes the perfusion pressure of the artery, occluding the structure. The cuff is then slowly deflated allowing the artery to open with the arterial pressure being determined by recording the sound (auscultation or manual method) or the vascular pulsations (oscillometric or automated method) that are created as the artery opens.

Properly sized cuffs are critical to obtaining accurate reliable blood pressure measurements. Cuffs that are too small will record pressures that are falsely elevated. The length of the bladder should be at least 80 % of the circumference of the upper arm, and the width of the bladder should be at least 40 % of the upper arm circumference [2–6].

Considerations: Auscultation/Manual Method

Korotkoff sounds are low-frequency sounds which represent the audible return of blood flow and divided into five phases:

I. First appearance of clear, repetitive, tapping sounds (systolic pressure).
II. Sounds are softer and longer, with the quality of an intermittent murmur.

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III. Sounds again become crisper and louder.
IV. Sounds are muffled, less distinct, and softer.
V. Sounds disappear completely (diastolic pressure).

The systolic blood pressure corresponds to the pressure at which the sounds first appear at phase I. The diastolic blood pressure corresponds to the pressure at which the sounds disappear at phase V [7, 8]. Low-flow states or hypotension can limit the intensity of audible sound and can lead to falsely depressed systolic blood pressure recordings.

Considerations: Oscillometric/Automated Method

Oscillometric measurements have been reported to be consistently inaccurate when compared to invasive or direct blood pressure recording modalities. The disparity may be in part to mal-fitting cuffs or individual manufacturer device variation [9, 10]. Calcific arterial structures also impede the device's capture of arterial oscillation amplitude resulting in falsely depressed blood pressure values. Automated oscillometric devices are quite accurate when capturing blood pressure values in normotensive patients but seem to overestimate values in hypotensive states (i.e., systolic blood pressure less than 80 mmHg) and are consistently lower than direct blood pressure measurements achieved by arterial catheterization [9, 10].

Gastric pH Monitoring

Tonometry is the measurement of the partial pressure of a gas in a fluid or intravascular medium. Gastric tonometry measures luminal CO2 and mucosal CO2 partial pressures (pCO2) as they become equalized across a semipermeable membrane [8]. The general tenet of gastric pH monitoring projects that a decreased mucosal pH implies either an increase in anaerobic metabolic efforts or a low systemic flow state leading to tissue hypoperfusion and, subsequently, an ischemic insult.

Two general methods have been described to perform gastric pH monitoring, conventional gastric tonometry and air-semicontinuous gastric tonometry. Conventional gastric tonometry is the more commonly described technique and involves a transorally inserted catheter or tube with a saline-filled balloon often composed of silicon or latex polymers, as these agents are permeable to CO2. The saline PCO2 and the gastric mucosal PCO2 come to equilibrium. The PCO2 within the saline-filled balloon is now considered physiologically representative of the gastric mucosal CO2 and is measured using a blood gas analyzer. Utilizing the Henderson-Hasselbalch equation, and assuming that the partial pressure of the stomach mucosa and atrial bicarbonate are equal, the intramucosal pH (pHi) can be calculated and perfusion trends established [11].

The air-semicontinuous gastric tonometry uses an air-filled CO2 permeable balloon and rapidly equilibrates with luminal and mucosal PCO2. This is directly measured in a semicontinuous manner, by an infrared sensor.

Considerations

The luminal and mucosal PCO2 generally equilibrate in approximately 30 min, although equilibration times up to 90 min have been reported [12]. A pHi of <7.32 represents mucosal acidosis and can be trended over time. Studies have found that H2 blockers have not been shown to influence luminal PCO2, luminal pH, and pHi in the shock state [13, 14].

Two major assumptions enter into the calculation of pHi [8, 11]. It is assumed that the PCO2 measured through gastric tonometric techniques approximates that of intramucosal PCO2. Secondly, it is assumed that intramucosal and arterial HCO3 measurements are the same. Animal studies exist that support the notion that no differences exist between luminal and mucosal CO2 measurements; however, arterial HCO3 measurements are likely an overestimation of the mucosal HCO3 in the ischemic or shock state [11].

Clinical investigators have shown that guiding resuscitations with gastric tonometry compared to traditional resuscitation techniques do not yield improved outcomes in either overall survival rates or development rates of multi-organ system failure [15, 16]. At one point, gastric tonometry seemed poised to evolve into a monitoring technique for the prevention of mesenteric ischemia insults during prolonged vasopressor use in the setting of refractory shock [8]; however, consistent clinical application of the technique is lacking.

Sublingual Capnography

Similar to gastric PCO2 monitoring, sublingual PCO2 (PslCO2) is measured against the arterial PCO2 in order to define a PslCO2 gap. Interestingly, investigators have demonstrated that the PslCO2 correlates closely with those obtained in the stomach during low-flow states [17–19]. Sublingual capnography does not directly reflect the perfusion quality to the splanchnic vasculature, however; the sublingual mucosal vascular bed shares similar characteristics with the splanchnic circulation, including a rich vascular supply and parasympathetic neural input.

A variety of commercially available devices have been manufactured and proved reliable in clinical application. One of the more widely used devices employs a specific CO2 sensing optode consisting of a CO2-permeable silicone bag with a buffering solution and a fluorescent dye solvent. The

silicone bag is attached to a light source that captures the changes in wavelengths of the fluorescent solvent as it is acted upon by the pH of the buffering solution. This is converted to the measurement of PslCO2. A key to accurate measurement capture is that the patient's mouth must be closed around the monitor [8, 20].

Considerations

Initial research of sublingual capnography was predominately with animal models, but consistent correlations between rising PslCO2 and systemic markers such as arterial lactate were identified [17]. Comparative animal studies where gastric tonometry and sublingual capnography were performed noted parallel increases in both measured gastric PCO2 and PslCO2 gap [18]. Later identified was that PslCO2 values greater than 70 mmHg were predictive of hospital survival and that PslCO2 corrected more rapidly than lactate. A small study found that PslCO2 gap was a better predictor of survival than lactic acid. A recent study has also found correlation between hemorrhage in penetrating trauma and rise in PslCO3, coinciding with increases in pre-resuscitation base deficit and lactate levels [21–23].

Central Venous Pressure Monitoring

Central venous pressure (CVP), as a measure of pressure in the superior vena cava, allows for the extrapolation of right-sided ventricular filling pressure and has been used to estimate intravascular volume and determine fluid requirements in critically ill or injured patients for decades. CVP became rather ubiquitous as a hemodynamic monitoring modality due to its ease of insertion and seemingly straightforward measurement parameters.

While CVP provides the ability to estimate right-sided cardiac filling pressures, it is not a direct assessment of cardiac performance or output, nor a reflection of end-organ perfusion adequacy. CVP can be measured from three sites of central venous access: the internal jugular vein, subclavian vein, and the femoral vein. However, the femoral vein is deemed less optimal as proper catheter positioning calls for the catheter tip to be situated at the atriocaval junction, a position unachievable with most commercially available catheters through femoral vein access. Furthermore, it should be noted that increases in intra-abdominal pressure or pressure of the accessed extremity from injury, edema, or inflammation can erroneously elevate values.

Considerations

Normal CVP in a critical care patient is estimated to range from 0 to 9 mmHg with a standard waveform being composed of three waves (a, c, and v) and two descents (x and y) (Fig. 8.1) [8]. As a measure of intravascular volume, CVP is not only influenced by volume status but by fluctuations of venous tone, presence of tricuspid regurgitation, congestive heart failure, right-sided diastolic dysfunction, pulmonary embolism, pulmonary hypertension, acute respiratory distress syndrome, chronic obstructive pulmonary disease, and mechanical ventilation with positive end-expiratory pressure.

A zero reference point exists for central venous pressures in the thorax located at a point on the external thorax where the fourth intercostal space intersects the midaxillary line, the phlebostatic axis. This anatomical landmark corresponds to the position of the right and left atrium when the patient is in the supine position; therefore, in the lateral position, it is not a valid reference point and will provide an inaccurate CVP reading [1, 24].

More contemporary research has challenged the utility of CVP as reliable hemodynamic monitoring method finding no association between CVP and circulating blood volume and identifying that CVP does not predict fluid responsiveness across a wide spectrum of clinical conditions [25]. Because of these influences, CVP must be interpreted with concern for variations in measurement with general recommendations encouraging the capture of trends in measurement rather than the absolute value.

Pulmonary Catheter Monitoring

Pulmonary artery catheters (PACs) have historically been the definitive clinical tool for assessing hemodynamic performance and responsiveness to therapeutic interventions. PACs were introduced into clinical practice in the 1970s predominately as a monitoring method for patients with acute cardiac insults and transitioned to use as a monitoring instrument for complex resuscitation scenarios, shock states, severe cardiovascular dysfunction, respiratory failure, and intraoperative fluid management.

The PAC allows for the capture of hemodynamic data that assists in defining the cardiovascular status of a systemic insult through the generation of physiologic profile.

The measurement for Q, or cardiac output, and the calculation of systemic vascular resistance (SVR) was touted to enable one to distinguish hypotensive states such hypovolemic shock, cardiogenic shock, or a form of distributive shock (i.e., sepsis). Assessment of pulmonary artery occlusion pressure (PAOP) potentially provides for the differentiation between cardiogenic and noncardiogenic pulmonary edema processes. PAOP may also be used as a guide for fluid resuscitation efforts, estimating left ventricular preload, while trending Q theoretically predicts the need for, or appropriate delivery of, inotropic support. In clinical scenarios of systemic inflammatory response syndrome or sepsis with end-organ dysfunction, calculations of mixed venous oxygen saturation and oxygen delivery variables may assist in

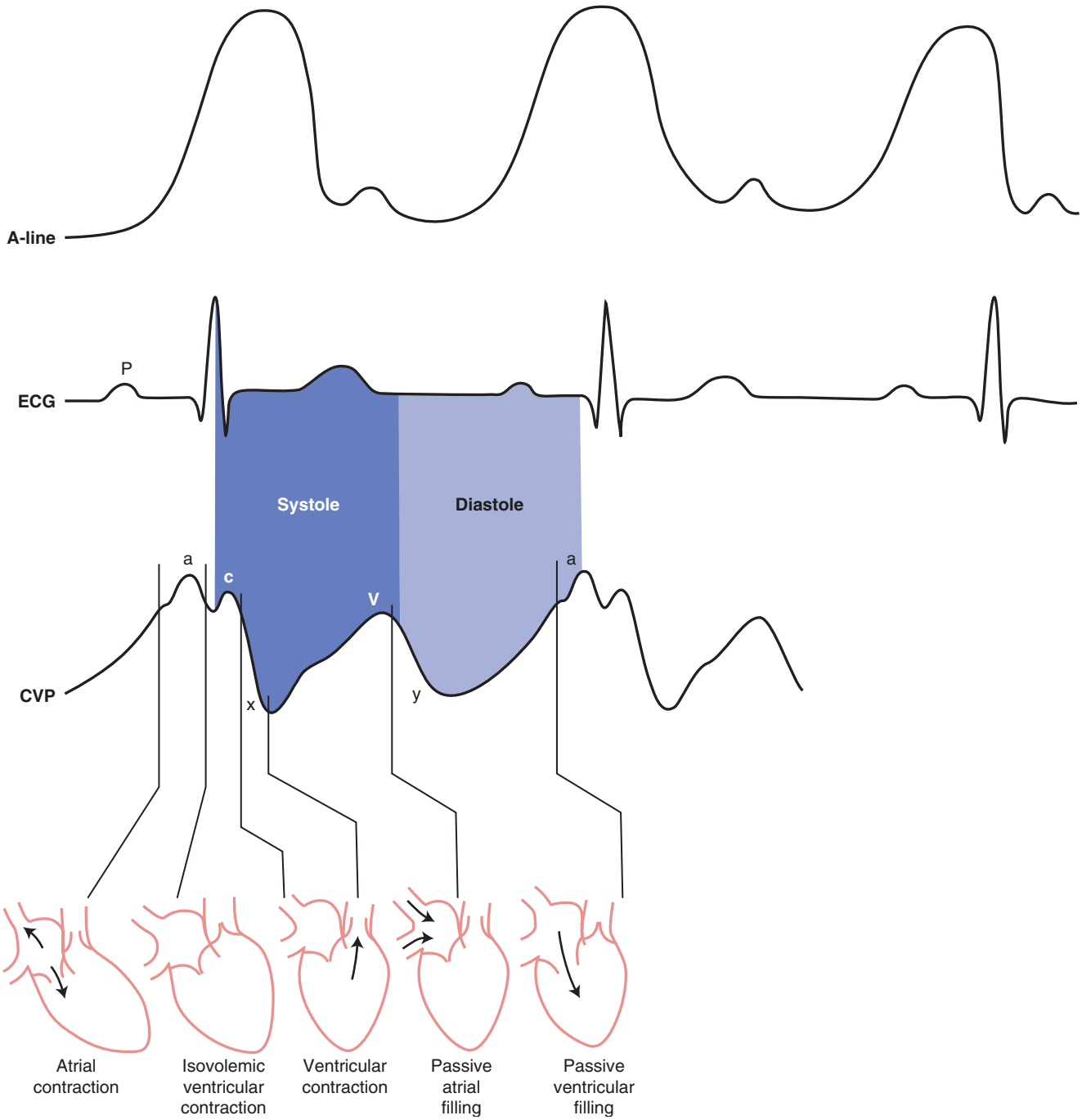

Fig. 8.1 A-line, ECG, and CVP tracings with cardiac function

identifying the presence of tissue ischemia and further direct resuscitation strategies [8].

Access sites for PAC insertion are similar to those of central venous catheters, but proper positioning of the PAC into the pulmonary artery can be challenging and is influenced by many factors. Volume-depleted states, aberrant vascular anatomy, and the difficulties traversing normal vascular and cardiac contours can create difficulty achieving appropriate catheter placement, which is key to obtaining accurate physiologic readings. The most direct access site is the right internal jugular vein, where the PAC only requires one gentle curve through the right ventricle to reach the right pulmonary artery. Left and right subclavian vein access requires the catheter to cross the innominate vein to reach the superior vena cava. Access through the left internal jugular vein also requires the catheter to cross the innominate vein and

demands a greater travel distance. Femoral vein sites are possible alternatives but are often very difficult to pass into the right atrium making this access approach the least desirable and often requiring fluoroscopic control for placement.

After gaining central venous access, a stepwise approach is used to ensure proper catheter positioning. The catheter is flushed, zeroed, and advanced with the balloon deflated to a distance of 12–15 cm. The PAC balloon is inflated, the PAC is advanced, and the pressure waveforms measured at the tip of the PAC are analyzed. The initial waveform is that of a CVP and as the catheter is advanced will convert to a right atrial pressure waveform reading. Within the right ventricle, a high spiking pressure waveform of 20–30 mmHg is encountered, representing the systolic right ventricular pressure. Further advancement of the PAC into the pulmonary artery generates a characteristic step-up in diastolic pressure and a clear dicrotic notch within the waveform. When the inflated balloon reaches a pulmonary arteriolar occlusion position, the waveform flattens. At this point, the balloon should be deflated to confirm the reappearance of the pulmonary artery waveform. With the PAC tip now in an appropriate position, an occlusion waveform will be obtained with balloon inflation of 1.5 mL of air [8].

Considerations

If the occlusion waveform is obtained with less than 1.5 mL, the catheter tip is likely too distal and located in an inappropriate branch. With the balloon deflated to prevent pulmonary artery rupture, the catheter should be withdrawn several centimeters, followed by reinflation of the balloon and re-advancement back to the occlusion position. After registering an occlusion pressure, it is safest to pull the catheter back a few centimeters (with the balloon down), each time between readings to minimize the natural distal migration of the catheter [8]. PAOP is most precisely measured when there is minimal influence from external transmural pressures such as increased intrathoracic pressure. Therefore, accuracy is best achieved when the lungs return to their most relaxed volume state at end-expiration [8].

In review, the lungs are divided into three physiologic zones, based upon the relationship between the pulmonary vasculature and alveolar pressures. In lung zones (i.e., West zones) 1 and 2, the magnitude of alveolar pressure affects the pressure recordings of the PAC. The ideal intravascular pressure always exceeds the alveolar pressure, best achieved in zone 3 of the lung. In non-zone 3 circumstances, alveolar pressures may exceed intravascular pressure; therefore, the degree of alveolar pressure and PEEP may affect the measurement of PAOP [8].

The clinical application of the hemodynamic data generated from the PAC placement requires careful consideration of how the information relates to the given clinical circumstance. PAC hemodynamic profiles have been patterned to suggest several broad clinical scenarios of hemodynamic aberration. However, in current medical practice, controversy surrounds PAC use as the devices' safety and reliability have come into question. The popularity of the PAC has progressively declined over the past decade, as data has accumulated indicating that PAC-directed care does not improve outcome and may in fact worsen them [26, 27]. PAC has also been associated with an increased incidence of pulmonary emboli in randomized controlled trials [26]. The proficient and safe utilization of the PAC is directly dependent on the clinicians' understanding of the measurements provided, the methods through which the data was derived, and how to deliver the proper therapeutic adjustments based on the interpretable data. It is these variables of PAC use that have come under scrutiny [28, 29].

Tissue Oxygenation

The ultimate goal of hemodynamic monitoring is to ensure adequate tissue perfusion and subsequent oxygen delivery to end organs in order to optimize performance in the physiologic stressed state; however, there are no monitoring modalities that can directly measure tissue oxygenation. When cellular metabolic demands for oxygen outpace its supply or delivery, a condition termed dysoxia results with its clinical manifestation being that of systemic shock [30]. Dysoxic states result from cardiogenic and hypovolemic shock states as the oxygen supply is insufficient or in contrast, with septic shock where mitochondrial oxygen utilization appears impaired.

Tissue Oxygenation: VO2

The rate of oxygen uptake from the systemic capillaries (VO2) is an indirect measure of oxygen availability in the tissues [1]. As oxygen is not stored in tissues, the VO2 can also be interpreted as a measure of tissue O2 consumption. Monitoring of VO2 has been suggested as a means to assist in determining the tissue dysoxia that results from hypoperfusion with inadequate oxygen supply to the tissue level. $VO2 = Q \times (CaO2 - CvO2)$.

Considerations

VO2 can be calculated or measured. The calculated VO2 is captured from a physiologic profile from an indwelling pulmonary artery catheter. The directly measured VO2 requires specific equipment and staff trained with the modality use and is not pervasively available in most critical care units, making this method less practical. An abnormally low VO2 (less than 100 ml/min/m^2) can be the result of hypometabolism or tissue dysoxia due to impaired tissue oxygenation [1].

Calculated VO2 cannot be interpreted as a measure of whole-body VO2 as it does not include the VO2 of the

lungs. During pulmonary inflammatory conditions such as acute respiratory distress syndrome or pneumonia, the VO2 of the lungs has been estimated 20 % of the whole-body VO2, allowing for significant underestimation of whole-body VO2 [1, 31].

The derivation of VO2 utilizes four different variables (cardiac output, concentration of hemoglobin in blood, and the percent oxyhemoglobin saturation in arterial and mixed venous blood) and each has its own inherent variability [1]. The variability of the calculated VO2 is 18 % that is equivalent to the summed variability of its components [1, 32–34]. The calculated VO2 must change by at least 18 or 20 % for the change to be considered significant [1]. Correction of VO2 deficits will therefore require discerning clinical data relative to anemic states, inadequate cardiac output, physiologic hypoxemia, and augmenting these components appropriately.

VO2 may not appropriately reflect aerobic metabolism in the septic clinical scenario as tissue oxygenation is not impaired in the septic state [1]. The accelerated activity of neutrophils and macrophages is accompanied by a marked increase in cellular oxygen consumption coined the respiratory burst. The exaggerated oxygen consumption in this process is used to generate toxic oxygen intermediates (superoxide radical and hydrogen peroxide) that are elaborated as part of the inflammatory process contributing to the septic state [35]. Therefore, VO2 will be artificially elevated, through the contribution of the respiratory burst, and inaccurately reflect metabolic VO2 or the rate of aerobic metabolism.

Tissue Oxygenation: Mixed Venous O2 Saturation (SvO2)

Mixed venous oxygen saturation of hemoglobin (SvO2) can be utilized to assess the balance of satisfactory systemic oxygen delivery and effective oxygen uptake. Derived through the established relationship between the rate of tissue oxygen uptake (VO2) and variations in systemic oxygen delivery (DO2), extrapolating SvO2 can imply the efficiency of systemic oxygen delivery [1]. $VO2 = DO2 \times (SaO2 - SvO2)$. The SaO2 and SvO2 are the oxygen saturation of hemoglobin in arterial and mixed venous blood, respectively. The difference in the two variables equates to the degree of oxygen extraction from hemoglobin in capillary blood.

Considerations

Normal values for SaO2 and SvO2 are 95 % and 70 %, respectively, implying a satisfactory O2 extraction of 25 % or, alternatively, that 25 % of the hemoglobin molecules have desaturated as they traverse the capillaries and microvasculature of end-organ targets. A decrease in SvO2 below 70 % indicates that systemic O2 delivery is impaired (or utilization is increased) while a SvO2 below 50 % indicates a global state of tissue hypoperfusion or impending dysoxia. The possible sources of impaired O2 delivery are identified by determinants of DO2 $\left(DO2 = Q \times 13.4 \times Hgb \times SaO2\right)$. A decrease in DO2 can be the result of a low cardiac output (Q), anemia (Hgb), or hypoxemia (SaO2) [1]. Increased O2 utilization is related to hypermetabolism.

The measurement of SvO2 historically required a pulmonary artery catheter as blood from the pulmonary artery is considered to be admixed with venous blood from all tissue beds. A PAC equipped with an infrared sensor at the distal catheter tip was later developed that provided the enhanced feature of performing continuous measurements of the SvO2 in the pulmonary artery blood. Continuous monitoring of SvO2 with this more specialized pulmonary artery catheter has revealed a spontaneous variation that averages 5 % but can be as high as 20 % [1, 36]. In general, a greater than 5 % change in SvO2 that persists longer than 10 min is considered a significant change [1, 37].

Central venous catheters were subsequently developed that allowed for SvO2 for continuous monitoring but have fallen out of favor as the utility of SvO2 as a reliable resuscitation measure has come into question. More recently, transcutaneous devices have been engineered to measure radial artery and ipsilateral digital artery pressures and extrapolate SvO2 through computerized computation methods providing a noninvasive option for capturing this hemodynamic data.

Tissue Oxygenation: Central Venous O2 Saturation (ScvO2)

Central venous O2 saturation (ScvO2) has become an acceptable alternative to SvO2 for monitoring tissue oxygen delivery and utilization as the modality does not require a PAC and can be drawn from central venous catheter. The two methods are reported to correlate well with an estimated variation up to 5 % if multiple measurements are aggregated [38]. However, if comparing single measurements, ScvO2 can differ from SvO2 by as much as 10 % implying that establishing a trend in measurements of ScvO2 is prudent prior to delivery diagnostic and therapeutic decisions [1].

The ScvO2 became an acceptable substitute measure of mixed venous O2 saturation because it precludes the expense and technical challenges associated with the PACs. Previously established guidelines for the management of patients with severe sepsis and septic shock have included achieving an ScvO2 of greater than 70 % as a therapeutic end point [39]. One should note that the foundational basis of this value stemmed from the early goal-directed therapy trial whose conclusions have been directly challenged by three multicenter and randomized trials demonstrating no specific outcome advantage to protocolized as opposed to non-protocolized care for those with severe sepsis or septic shock.

Direct Perfusion Measurement

Invasive monitoring of arterial pressure was first performed in 1733 with the cannulation of a horse's left crural artery by Reverend Stephen Hales [8, 40]. In 1865, the first human invasive blood pressure measurement was taken by Dr. Faivre, a French physician, who cannulated an amputee's superficial femoral artery [8]. The routine application of invasive arterial blood pressure measurement did not become commonplace until the mid-1960s, associated with the expansion of cardiothoracic and vascular surgery as well as the Angiocath cannulation technique, innovated by Barr in 1961 [41].

Intra-arterial cannulation with continuous blood pressure transduction is considered the gold standard for arterial blood pressure monitoring. While there are many indications for invasive arterial monitoring, the most common is the need for continuous blood pressure recordings in a patient at risk for cardiovascular instability [8, 42].

Considerations

Mean arterial pressure is the true driving pressure for peripheral blood flow and does not alter as the pressure waveform migrates distally in a vascular structure, nor is it subject to distortions generated by recording systems, thus making mean arterial pressure superior to systolic pressure for arterial pressure monitoring [1]. In contemporary medical practices, mean arterial pressure is generally measured, although estimated values can be achieved. Modern electronic monitoring devices can measure mean arterial pressure by integrating the area under the pressure waveform and dividing this by the duration of the cardiac cycle (Fig. 8.1) [1]. Intuitively, the electronic measurement is more accurate, reliable, and preferred to the estimated mean pressure. Estimated mean arterial pressure is derived as the diastolic pressure plus one-third of the pulse pressure; a formula is based on the assumption that diastole represents two-thirds of the cardiac cycle, which corresponds to a heart rate of 60 beats/min. Therefore, heart rates faster than 60 beats/min, which are common in critically ill patients, lead to inaccuracies in the estimated mean arterial pressure [1].

Essentially any peripheral artery can be accessed as a cannulation site. Most commonly used sites include the radial, femoral, dorsalis pedis, brachial, and axillary arteries. The appropriate site selection for arterial cannulation is influenced by many factors. Typically the radial artery of the nondominant hand is utilized [8]. When this is unsuitable, alternate sites are chosen based upon the following four criteria: [1] the artery should be large enough to accurately reflect systemic blood pressure [2], the chosen site should be free of cellulitis or nearby infected or devitalized tissue [3], there should be sufficient collateral flow to prevent distal ischemia, and [4] the artery should be proximal to any anatomic aberrations [8].

Invasive arterial blood pressure monitoring carries two categories of complications, infectious or mechanical. The most common mechanical complication is arterial thrombosis, which may be partial or complete, and has been noted to occur in 25 % of patients [43]. However, despite this seemingly high thrombosis risk, investigators identified no significant disability or ischemic damage occurred in most catheter-associated radial artery thrombosis and noted most recanalized within 2–4 weeks after catheter removal [8].

Many clinicians recommend performing a modified Allen's test prior to radial artery catheter site selection in order to assess for adequacy of perfusion and collateral flow to the distal extremity. The modified Allen's test consists of compression of both the radial and ulnar arteries, clinching the patient's fist until it blanches, then relaxing the fist and releasing pressure from the ulnar artery. If the patient's skin becomes hyperemic, the collateral flow is deemed satisfactory for radial artery cannulation [8]. While historically recommended, the Allen's test has not demonstrated a reduction in digit ischemia, nor has an abnormal Allen's test proven to guarantee distal ischemic changes. However, if a grossly abnormal Allen's test is obtained, arterial cannulation should be sought elsewhere [44].

Brachial artery cannulation has conventionally been avoided due to the anatomic consideration of limited collaterals at this level of the upper extremity, theoretically predisposing to increased risks for thrombosis and extremity loss. While an anatomically sensible consideration, research has found no increased Doppler evidence of thrombosis or vascular compromise in a study of brachial artery cannulations, leading clinicians to consider brachial artery cannulations as an acceptable risk in the proper clinical scenario [45]. However, even with this documented support, it is generally recommended to access the axillary artery preferentially to the brachial artery due to its generous collateral circulation.

An additional mechanical complication encountered with arterial cannulation is pseudoaneurysm formation. Improper technique is believed to contribute to pseudoaneurysm development if the posterior wall of the vessel is punctured or when multiple passes at the artery are made, enhancing the risk. Prolong catheter placement and cannulation site infection also predispose to pseudoaneurysm formation [8].

Arterial cannulation infection is the second significant category of complications with the insertion site serving as the most common access for catheter-associated bacteremia. Compared to central venous catheters, research has demonstrated that arterial catheter infections do not increase over time of indwelling, and disciplined aseptic technique on

insertion, access, and dressing care minimizes the infectious risk [46]. One should also be cognizant of impedance mismatch between the patient's artery and the catheter which may lead to over- or underestimation of systolic and diastolic values. Moreover, erroneous placement with partial occlusion may similarly lead to inaccurate pressure measurement. Therefore, one should always assess the waveform quality, to look for whip artifact or a dampened waveform before using the numeric values to trigger intervention.

Direct Visualization Methods

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) has been widely accepted as an excellent, noninvasive, direct visualization modality for the assessment of cardiac anatomy and function. Point of care TTE has been utilized successfully in ICUs for many years, but more recently, intensivists have strongly advocated for its incorporation as a standard of care for hemodynamic monitoring purposes [47]. However, point of care TTE, or intensivist-performed TTE, should be distinguished from a formal, cardiology-driven TTE in several respects. Formal cardiology-driven TTE creates a detailed anatomic report with cardiac functional descriptors relative to the given moment of the exam. Point of care TTE in the ICU is a more limited exam anatomically but allows for the assessment of cardiac filling volumes and chamber performances over a continuum of time [48]. In the critical care setting, TTE can be quickly applied to assess for cardiac filling volumes, chamber functionality, global wall motion abnormalities, and cardiac responsiveness to therapeutic efforts. The exam is quick, noninvasive, and repeatable on demand.

Image Acquisition

Point of care TTE can be performed on any ultrasonographic device with cardiac penetrance. Most modern critical care units have access to advanced ultrasonographic equipment often with exchangeable probes and various examination modes, such as breast, vascular, or cardiac that adjusts penetration needs based on exam site and type.

TTE transducers have a square surface, as opposed to the elongated, rectangular-shaped transducer used for vascular imaging. An inverse relationship exists between sound wave frequency and depth of penetration, with better resolution being achieved with high frequency. Higher-frequency, lower-depth probes are used for vascular imaging with ultrasound. By contrast, an echocardiography transducer emits a variety of frequencies to provide optimal resolution at a range of depths. It also uses a high frame rate to capture cardiac motion and display it smoothly [49].

Examination Views

The views obtainable are essentially those of a standard TTE and include the parasternal long axis (PLA), parasternal short axis (PSA), apical four chamber, and subxiphoid windows (Fig. 8.2):

- Subxiphoid view: The subxiphoid view allows assessment of the IVC, its diameter, and diameter variation with respiration.
- Parasternal long-axis view: The PLA is obtained with prone positioning of the patient between the second and sixth intercostal spaces with the transducer notch oriented toward the right shoulder. Through this view the mitral valve, aortic valve, and left ventricular function can be assessed.
- Parasternal short-axis view: The PSA view is captured with prone positioning of the patient between the second and sixth intercostal spaces with transducer probe now rotated 90°. Through this window the classic donut view of the left ventricle is seen along with the right ventricular chamber. Tilting of the probe allows imaging of the left ventricle from base to apex revealing the papillary musculature, mitral, and aortic valve.
- Apical four-chamber view: The apical four-chamber view is visualized with prone positioning of the patient with the probe placed over the left chest wall at the level of the cardiac apex. The transducer notch is turned to the bed. This view allows for visualization of the left and right ventricular functions.
- Subxiphoid view: The subxiphoid view is obtained by placing the probe under the xiphoid process with the patient in supine positioning. The view is the same as that achieved with a routine assessment with sonography for trauma exams and allows for visualization of the IVC and for presence or absence of pericardial effusions. Rotating the probe counterclockwise opens the view so that the IVC is in its long axis, allowing assessment of its diameter and collapsibility.

Image Interpretation

The information obtained is to be interpreted as a physiologic assessment relative to a given clinical scenario, allowing for the analysis of cardiac function, preload, afterload, and cardiac anatomy:

- Cardiac function can be assessed by evaluating ejection fraction, stroke volume, cardiac output, cardiac index, diastolic function, and right-sided heart function.
- Preload can be analyzed through the calculation of ventricular cavity size, IVC diameter, and diameter change.
- Afterload is estimated with interpretation of systemic vascular resistance and systolic pulmonary artery pressure.

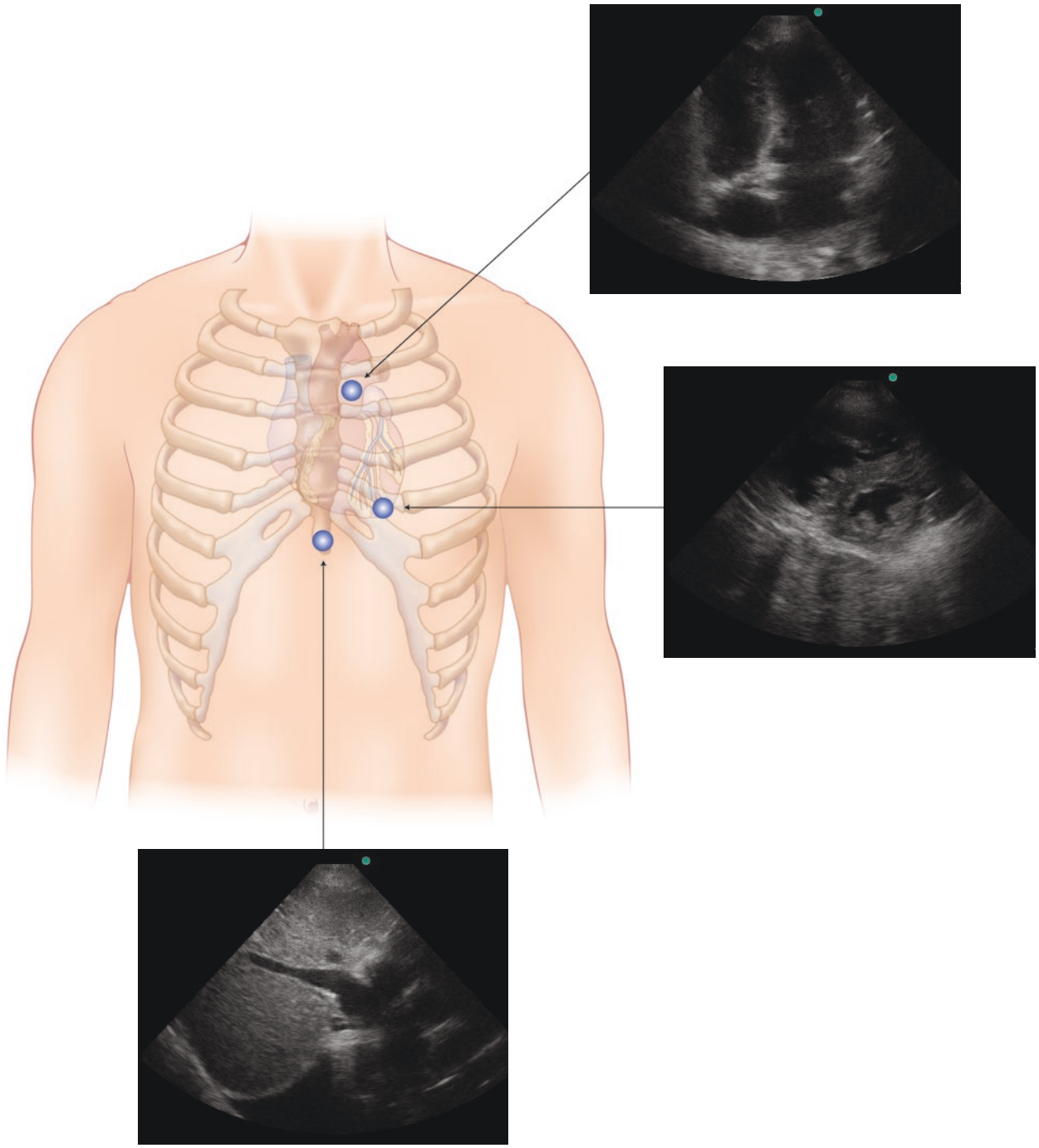

Fig. 8.2 Transthoracic echocardiography probe positions and corresponding views

- Cardiac anatomy such as severe valvular dysfunction resulting in hemodynamic compromise, pericardial fluid, or global wall motion abnormalities can be identified.

Software-driven computations provided by manufacturers of advanced ultrasound devices are imbedded in their individual operating systems which allow for exam findings such as ventricular chamber sized in diastole and systole, to be entered whereupon physiologic data such as CO, CI, EF, SVR, etc., may be generated. IVC diameter and variation can be measured manually and analyzed. Alternatively, the skilled echocardiographer can visually assess for chamber size, variation, and responsiveness to therapy in order to estimate hemodynamic status. The technique of image capture and data point entry for algorithmic analysis for TTE is beyond the scope of this

chapter but is readily available in a variety of well-established teaching modules or manufacture device-specific literature.

Considerations

The TTE examination can be limited by difficulty in obtaining clear images in the presence of subcutaneous emphysema, anasarca or significant edematous states, large patient body habitus, or presence of abdominal wall or thoracic bandages.

A variety of physiologic data can be gleaned from a thorough TEE exam; however, guidelines for provider application have yet to be standardized. IVC size and index of change are currently being applied to hemodynamic monitoring scenarios and studied as a marker for hemodynamic performance. Many researchers and clinicians alike have endorsed the analysis of IVC size and variability of change with therapeutic interventions as a guide for determining fluid needs and responsiveness to therapy [50–52]. Others utilize a composite of all views relative to patient performance and base clinical decisions of measurable data such as computation-derived CO, EF, SVR, as well as other related variables.

Whether computation-driven measurements or visual estimation is utilized is a provider or operator preference. Research is ongoing to identify the validity of both methods as well as domains of intersection. Specific pattern recognition for paradigms of cardiac evaluation relative to shock management is beyond the scope of this chapter but is available through a variety of references and reviews [49].

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is utilized in the management of the critically ill over the last decade due to its accuracy and reproducibility as an assessment tool for cardiac anatomy and performance. However, formal multiplane TEE requires a full-scale TEE module and monitor system, utilizes relatively bulky probes, requires probe reinsertion for each exam, and potentially limits the clinicians' ability to accurately follow changes in cardiopulmonary performance over time. Since the US Food and Drug Administration's approval for the clinical use of a newly developed, miniaturized TEE probe that may remain indwelling in the esophagus for up to 72 h, TEE as an application in the critical setting has become more pervasive. Contemporarily known as hemodynamic TEE or hTEE, this exam modality has the unparalleled advantage of allowing for anatomical and functional assessments of the heart and great vessels in real time for ventilated, critically ill, or injured patients. The ability to continuously monitor and assess for effects of interventions facilitates intensivists by guiding complex resuscitations in order to better tailor therapeutic maneuvers to patient needs and tolerance [53].

Image Acquisition and Interpretation

The hTEE probe is approximately 17 French in size, inserted transorally, and advanced into the stomach. The probe is slowly retrieved where flexion, anteflexion, and gentle rotational torque of the probe facilitate image capture.

The views obtainable with hTEE include (Fig. 8.3):

- Transgastric view: a short-axis view allowing visualization of both cardiac ventricles, permitting measurement of LV size, calculation of LV fractional area contraction, and examination of septal size, shape, and wall motion abnormalities.
- Four-chamber view: a long-axis view providing visualization of the four cardiac chambers and measurement opportunity of LV and RV end-diastolic and end-systolic size and calculation of LV ejection fraction.
- Superior vena cava view: a long-axis view, at the level of the SVC/right atrial junction where examination of the variation in the SVC diameter during the respiratory cycle can be assessed.

Software-driven computations provided by the device manufacturer are embedded in the operating system which allow for exam findings such as ventricular chamber sized in diastole and systole, to be entered whereupon physiologic data such as CO, CI, EF, SVR, etc., can be generated. SVC diameter and variation can be manually measured and analyzed. Alternatively, the skilled echocardiographer can visually assess for chamber size, variation, and responsiveness to therapy in order to estimate hemodynamic status and resuscitation needs. The technique of image capture and data point entry for algorithmic analysis for hTEE is beyond the scope of this chapter but is readily available in a variety of established teaching modules and device manufacturer literature.

Considerations

The simple yet robust TEE images and cardiac performance patterns achieved with hTEE have previously been validated in ventilated patients with septic shock against a more comprehensive and quantitative assessment [53, 54]. The hTEE examination has been demonstrated to provide relevant information for the hemodynamic monitoring of ventilated ICU patients with cardiorespiratory compromise and has proven to be therapeutically impactful in several studies and continues to be applied to various, specific clinical scenarios for more accurate hemodynamic monitoring efforts [53–56].

Through the continuous evaluation of the superior vena cava and the right and LV chambers and their response to therapeutic maneuvers, hTEE can identify the precise cause

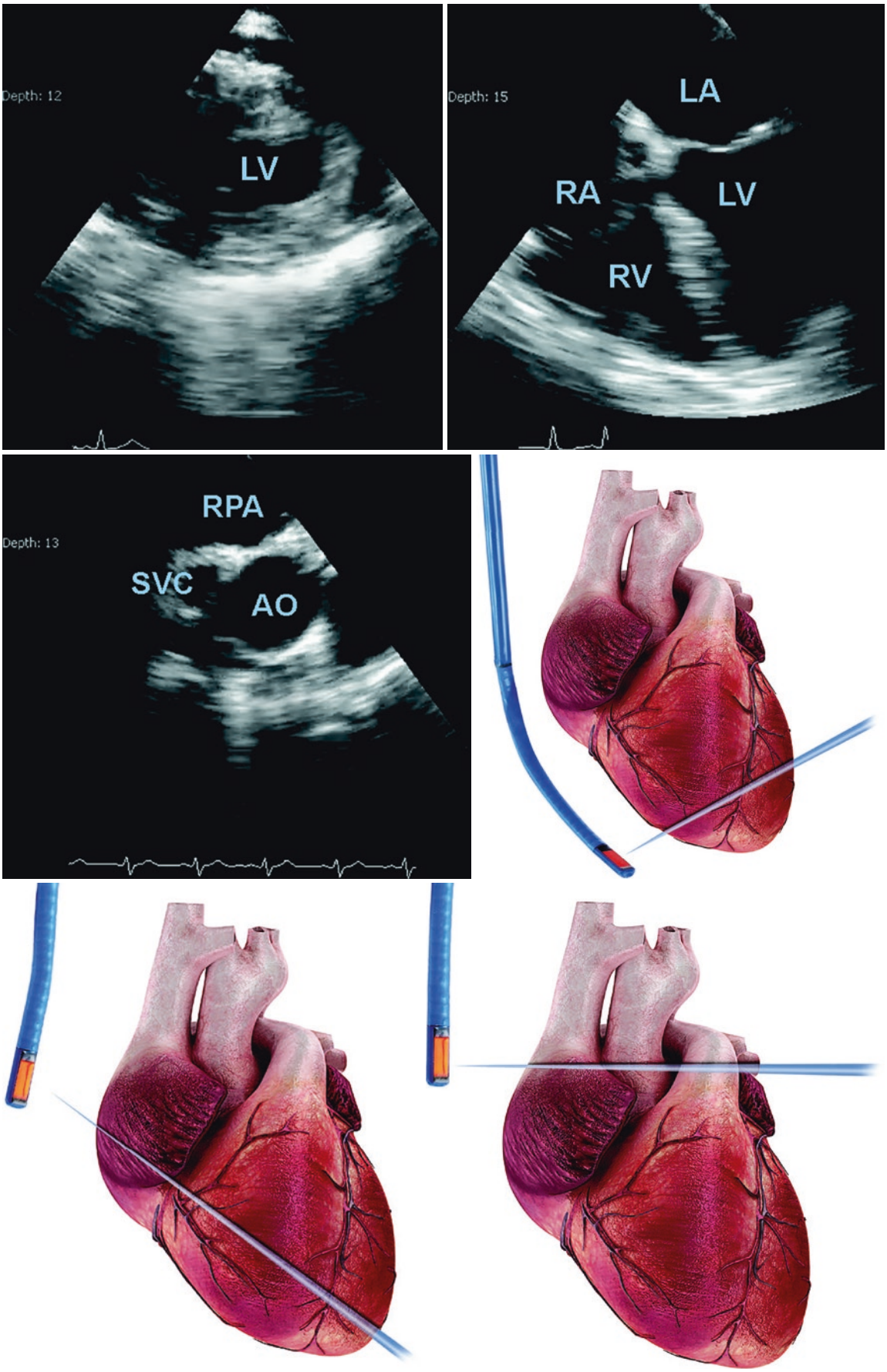

Fig. 8.3 Hemodynamic transesophageal echocardiography probe position and corresponding image (With permission of ImaCor, Inc.)

of hemodynamic instability, which may be hypovolemic, cardiogenic, or distributive. Additionally, SVC collapsibility is proving to be a useful echocardiographic gauge of volume status [55]. An accurate diagnosis is required for an adequate treatment, which may be rapid fluid administration, infusion of an inotropic agent, infusion of a vasopressor application, or a combination therapy approach.

Currently, there are few known limitations to the hTEE examination. The presence of a hiatal hernia can interfere with probe insertion and may preclude the modality's use due to improper conduction, making monoplane image capture impossible. Also, scatter artifact of an indwelling nasogastric tube can also impair acquisition and resolution.

The learning curve required to achieve operator competence in order to proficiently perform an hTEE examination remains to be determined as research regarding hTEE skill acquisition and learning curve establishment are ongoing. Because both the diagnostic capacity and therapeutic impact of any imaging modality are heavily influenced by the experience of the operator, the comfort level of the provider with the technique is key to exam accuracy and utility. Specific pattern recognition for paradigms of cardiac evaluation relative to hemodynamic management strategies is beyond the scope of this chapter but is available through a variety of references and reviews.

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Cardiovascular Emergencies

9

J. Trent Magruder and Glenn J. Whitman

Introduction

Cardiovascular emergencies comprise a major source of morbidity and mortality for the surgical intensive care unit patient. Many of the diagnoses discussed below represent some of the few truly emergent situations in modern medicine in which a delay of literally minutes can hasten an adverse outcome. Moreover, the trend toward surgical intervention on patients who in past years would have been considered too old or ill to undergo surgical intervention dictates that cardiovascular emergencies will remain a challenge for the surgical intensivist. We will discuss several scenarios, including acute myocardial infarction (AMI), pulmonary embolism (PE), cardiac tamponade, tension pneumothorax, aortic dissection, and mechanical complications of myocardial ischemia and infarction. The focus will be on diagnosis and early treatment of these life-threatening conditions.

Acute MI

Diagnosis: *EKG changes + biomarkers*

Therapy: *ASA, beta-blockers, heparin, nitroglycerin, second antiplatelet agent (*e.g., *clopidogrel), revascularization – time matters!*

Following surgery, cardiac complications are a major cause of morbidity and mortality [1]. Each year, it is estimated that at least 500,000 patients experience perioperative cardiac death, nonfatal acute MI (AMI), or nonfatal cardiac arrest [2]. Postoperative MI (PMI) rates have been estimated to be around 1 % for all noncardiac surgery patients and as high as 4–8 % for patients at risk for cardiac disease, with attendant PMI mortality rates in the 15–25 % range [1, 3–6].

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The etiologies for PMI vary and have been debated; traditionally, a major culprit is thought to be an increase in myocardial oxygen demand coupled with stenotic coronary artery disease [7]. This is further supported by the finding that only about a third of postsurgical patients suffering fatal PMI have an intracoronary thrombosis [8, 9]. Other authors have noted that over 50 % of PMI patients have evidence of plaque rupture [10].

Since the complications of PMI can be catastrophic, several risk assessment tools have been developed to stratify patients preoperatively. One such system is the Revised Cardiac Risk Index, which was derived from a population of 2,893 patients undergoing elective major noncardiac surgery and predicts the risk of major cardiac complications (cardiac death, acute MI, pulmonary edema, ventricular fibrillation or cardiac arrest, or complete heart block) [1]. Risk factors identified include performance of a high-risk procedure (vascular or open intraperitoneal/intrathoracic procedures), history of ischemic heart disease, history of heart failure, history of cerebrovascular disease, diabetes mellitus requiring insulin treatment, and a preoperative serum creatinine >2.0 mg/dL. A patient with no risk factors had a 0.4 % chance of a cardiac complication, (1) risk factor was associated with a 1.0 %, (2) risk factors with a 2.4 % risk, and (3) risk factors with a 5.4 % risk. High-risk patients may be referred for further cardiac testing including stress testing, echocardiography, or cardiology consultation.

Postoperatively, the diagnosis of PMI proceeds by the same established criteria as for other MI patients. The phrase "acute coronary syndrome" is used to denote any patient in which there is suspicion of myocardial ischemia and/or infarction. ACS encompasses three clinical entities: unstable angina (UA), ST-elevation MI (STEMI), and non-ST-elevation MI (NSTEMI). For the purposes of surgical patients, we will focus on the latter two categories. Unstable angina is a term used to refer to patients with clinical symptoms suggestive of myocardial ischemia, but who present without a rise in cardiac biomarkers or EKG changes suggestive of ischemia.

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Table 9.1 Diagnostic criteria for acute myocardial infarction

Rise and/or fall of cardiac biomarker (e.g., troponin I), with at least one sample above the 99th percentile upper limit of reference, with one of the following:
Symptoms of ischemia
New significant ST-segment/T-wave changes or new left bundle branch block
Emergence of pathological Q waves on electrocardiography
Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Identification of an intracoronary thrombus by angiography
Or: Stent thrombosis associated with MI (as detected by coronary angiography), in the setting of myocardial ischemia, and associated with a rise and/or fall of cardiac biomarkers with at least one sample above the 99th percentile upper limit of reference

Adapted from Thygesen et al. [11]

The most recent universal definition of myocardial infarction is shown above (Table 9.1) [11]. In brief, an elevated cardiac biomarker coupled with at least one of the following makes the diagnosis of PMI: symptoms of ischemia, new EKG changes (pathological Q waves, left bundle branch block, ST-segment, or T-wave changes), imaging evidence of new loss of viable myocardium, or a new regional wall motion abnormality on echocardiography. Patients with ST-segment elevation are diagnosed with STEMI, while patients with one or more of the above criteria without ST-segment elevation are diagnosed with NSTEMI. Importantly, many of the classical symptoms associated with MI are absent in postoperative patients, thanks to the use of anesthetic and analgesic medications, and most PMIs tend to occur on the day of surgery or the day after [12]. Accordingly, cardiac enzymes should be trended every 6 h until downtrending in patients with a suspected cardiac complication. Troponin I has been shown to be sensitive (94 %) and specific (75 %) in the detection of major adverse cardiac events in postsurgical patients with at least one RCRI risk factor [13].

Management: STEMI

Following diagnosis, goals of STEMI management in the postsurgical patients involve securing the airway, stabilization of hemodynamics (including optimization of myocardial oxygen demand and afterload), pain relief, prevention of further thrombosis, and prompt revascularization. Many postsurgical patients have the added vulnerability of increased bleeding risk, which complicates decision-making in managing an MI.

After attention is paid to securing an appropriate airway, patients suffering from STEMI should be treated with beta-blockade (i.e., metoprolol) if blood pressure permits, statin therapy, narcotic pain medication, and acetylsalicylic acid and anticoagulant therapy if at all possible. Both aspirin and beta-blockers have been shown to durably reduce mortality following MI [14, 15]. Aspirin helps prevent thrombus propagation, while beta-blockers decrease myocardial oxygen demand. Statins, meanwhile, have a scientific rationale for use in acute MI based on their ability to improve endothelial function and reduce inflammation and thrombus formation [16]. Some authors have found that the use of statins in the early post-MI period is associated with a reduction in ischemic events and mortality [17–20], though subsequent meta-analyses have called these results into question [21, 22]. During this period, echocardiography is also indicated to assess the correlation between electrocardiographic and biochemical data and myocardial function.

As much of initial treatment is aimed at halting intracoronary thrombotic processes prior to reperfusion, postoperative patients require specialized decision-making to balance the competing risks of losing myocardium versus inducing life-threatening bleeding. Aspirin, or clopidogrel for aspirin-intolerant patients, should be administered early following PMI diagnosis if the patient is not actively bleeding. In postoperative patients, anticoagulation with unfractionated heparin is preferred because it is quickly reversible. Thrombolytic agents are traditionally considered contraindicated due to bleeding risk; moreover, early postoperative patients have been historically excluded from major thrombolytic trials. Similarly, glycoprotein IIb/IIIA inhibitors are not typically used in postoperative patients due to their high associated bleeding risk.

Unfortunately, precise data on the risk of surgical bleeding induced by treatment of PMI are scarce. In and of itself, major bleeding has been identified as a risk factor for myocardial infarction, which creates difficulties in investigating this relationship [23–25]. Significant surgical site bleeding associated with PMI treatment appears to be relatively uncommon, however. In one study of 120 patients with postoperative ACS (87 % of whom were subsequently fully heparinized), 9.2 % of treated patients experienced clinically significant bleeds, but of these, only three were related to the surgical site, and five were gastrointestinal bleeds [26]. In another series of 48 patients referred for percutaneous coronary intervention (PCI) after experiencing PMI within 7 days of surgery, nine patients (18.8 %) required red blood cell transfusion, but only one (2.1 %) developed bleeding related to the surgical site.

Though bleeding data in surgical populations suffering PMI is rare, several studies have highlighted the risk of continuing antiplatelet therapy in the early perioperative period in all patients. The POISE-2 trial examined continued aspirin use preoperatively and during the early perioperative period and found that this practice had no effect on the composite rate of death or myocardial infarction, but did slightly increase the risk of major bleeding (4.6 % vs. 3.8 % in non-aspirin-treated

controls, $p=0.04$) [27]. These risks were most significantly increased in aspirin-treated patients on postoperative days 0 through 7, with the risks becoming comparable by postoperative day 8. Similarly, another trial of combined clopidogrel and aspirin treatment given within 5 and 2 days prior to coronary artery bypass grafting (CABG), respectively, found this strategy actually increased the risk of both PMI and postoperative bleeding [28].

Reperfusion itself is the most important and lifesaving aspect of MI therapy [29]. As fibrinolytic therapy is typically too risky for the PMI patient given bleeding risks, the first step in this process is percutaneous coronary intervention (PCI), which should be considered in consultation with cardiology for all PMI patients. Though specific data on PMI patients are scarce, data in emergency department populations suggest that each 30-min delay from symptom onset to PCI increases the relative risk of 1-year mortality by 8 % [30]. At the same time, PCI virtually mandates the use of dual antiplatelet therapy, as aspirin and clopidogrel substantially reduce the risks of stent thrombosis within 30 days as well as death, MI, or repeat revascularization within a year [31, 32].

Finally, though primary surgical revascularization is not usually performed due to logistical constraints, STEMI patients may be referred for coronary artery bypass grafting for several indications. These include persistent or recurrent ischemia following PCI, high-risk anatomy such as left main or triple vessel disease, or a mechanical complication of AMI (discussed below). Additionally, patients who can be stabilized and revascularized percutaneously following their MI but who still have significant stenoses may be referred for CABG as well.

Management: NSTEMI

Treatment principles of NSTEMI largely parallel those for STEMI, including early optimization of myocardial oxygen demand, administration of antiplatelet and anticoagulant medications, and cardiology consultation to pursue possible revascularization. However, as opposed to STEMI, both conservative and invasive strategies have been proposed and debated for the management of NSTEMI [33]. The former calls for medical therapy, consisting of aspirin, clopidogrel, and heparin, with angiography only if the patient exhibits evidence of recurrent ischemia. Stabilized patients may undergo noninvasive stress testing (e.g., treadmill, echocardiography, or nuclear) at a later point to assess the need for angiography. Several recent studies suggest that low-risk female patients may benefit from an initially conservative strategy [34–36].

In contrast, the invasive strategy calls for routine angiography early after the diagnosis of PMI. This approach is favored for patients with recurrent angina or ischemia, elevated biomarkers, worsening heart failure, hemodynamic instability, arrhythmia, or other high-risk features [33]. One study of NSTEMI patients found early pretreatment with aspirin, heparin, clopidogrel, and tirofiban plus angiography within 6 h of diagnosis was associated with improved survival as compared to a strategy of pretreatment for 3–5 days prior to MI [37].

Acute Pulmonary Embolism

Diagnosis: *Clinical suspicion, ABG, bedside echocardiography (RV strain), and/or CT-PA*

Therapy: *Heparin (consider empiric treatment for renal insufficiency or clinical urgency); if in extremis, consider thrombolysis or thrombectomy.*

One of the most common complications experienced in surgery is deep venous thrombosis (DVT) and its feared counterpart, pulmonary embolism (PE). Without any form of prophylaxis, DVTs can occur in 10–40 % of medical and general surgical patients and up to 40–60 % of trauma and orthopedic surgery patients [38]. A recent large series of trauma and orthopedic surgery patients found that though only 0.47 % of patients developed PE as diagnosed by computed tomography pulmonary angiogram (CT-PA) scanning, their attendant mortality rate was 15.3 % [39]. One autopsy series of over a thousand patients who died following surgical procedures found that 32 % of these patients suffered a PE; in 29 % of the entire series, PE was determined to be the cause of death [40].

The clinical presentation of PE can vary widely and is suggested by symptoms including dyspnea, pleuritic pain, and cough, particularly in the presence of DVT symptoms (e.g., calf pain, unilateral extremity edema). Hypoxia and hypotension can also be presenting signs of PE, though it is relatively unusual for patients to present in frank shock. Additionally, many surgical patients already have one or more risk factors for pulmonary embolism, such as advanced age, cardiac or respiratory failure, prolonged immobility, the use of central venous lines, and prior DVT [41, 42]. A number of risk scoring systems have been devised to organize such risk factors into a pretest probability. One such clinical decision rule is the Canadian Pulmonary Embolism Score, also known as Wells' Criteria (Table 9.2). As originally studied, patients with a low clinical probability of PE based on a low Wells' score (0–1) and a negative D-dimer test had no further testing, and the diagnosis of PE was considered excluded. All other patients underwent ventilation-perfusion scanning in the original study, with bilateral deep venous ultrasonography performed if the scan was nondiagnostic. This algorithm has been shown to have a negative predictive value of 99.5 % in an emergency department patient population [43, 44].

Table 9.2 Wells' criteria (Canadian Pulmonary Embolism Score)

Risk factor	*Points assigned*
Clinical signs and symptoms of DVT	3
PE is #1 diagnosis or equally likely as another	3
Heart rate >100	1.5
Immobilization for ≥3 days or surgery within the prior 4 weeks	1.5
Previous objectively diagnosed PE or DVT	1.5
Hemoptysis	1
Malignancy within last 6 months	1
Clinical probability of pulmonary embolism	*Score total*
Low (1.3 % chance of PE)	0–1
Intermediate (16.2 % chance of PE)	2–6
High (40.6 % chance of PE)	>6

Adapted from Wells et al. [43]

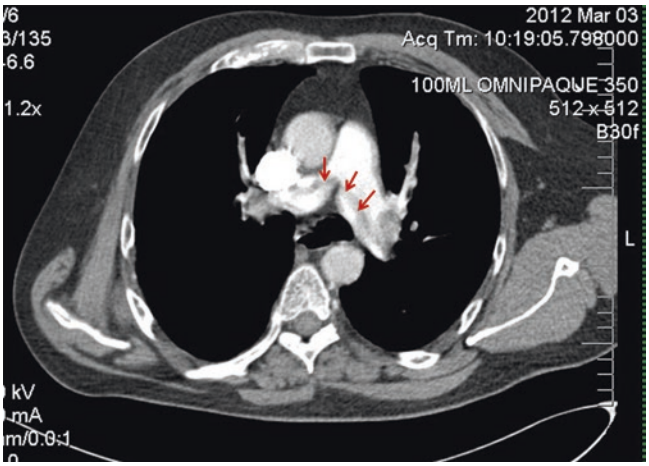

Fig. 9.1 Saddle pulmonary embolus (*arrows*) on computed tomography scanning with intravenous contrast. (Figure courtesy of T. Metkus, M.D.)

For patients who may be safely imaged, the definitive diagnostic test in the modern era is computed tomographic pulmonary angiography (CT-PA) or, less commonly, ventilation-perfusion scanning. CT-PA has been shown to be extremely sensitive and specific with regard to the diagnosis of PE, particularly populations at moderate or high risk of PE (Fig. 9.1). One large series found that CT-PA coupled with venous phase imaging had a sensitivity of 90 % and a specificity of 95 % for the diagnosis of PE, though this population was not exclusively postsurgical [45].

In patients with multiple risk factors who experience a sudden, unexplained change in hemodynamic status – for example, the critically ill bed-bound patient – prompt institution of therapy prior to definitive diagnostic testing may be lifesaving. Empiric anticoagulation and/or thrombolytic therapy is indicated for patients with a high likelihood of having PE in whom definitive testing is dangerous. Ancillary studies such as bedside echocardiography showing right ventricular strain may be helpful in these scenarios.

The standard treatment of PE, after providing respiratory and hemodynamic support as appropriate, is anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH). In surgical patients who are typically deemed at increased risk of bleeding, UFH is usually chosen because it is the shortest-acting agent and can be reversed with protamine sulfate. Additionally, since renal insufficiency can affect the pharmacokinetics of anticoagulation therapy, UFH is preferred in patients with underlying renal disease due to its ease of monitoring. A typical UFH protocol is weight based, with a bolus dose of 80 units/kg given followed by an infusion at 15–20 units/h. The activated partial thromboplastin time (aPTT) is monitored at the beginning of therapy and every 4–6 h thereafter to target a goal range of aPTTs. In our institution, this range is typically 65–80 s for patients not deemed at excessive bleeding risk; the 50–65 s range represents a second choice available to clinicians. Of note, prompt institution of therapy is essential: the risk of recurrent PE may be as high as 25 % when the aPTT is not therapeutic within the first 24 h after heparinization [46].

For patients presenting with massive PE as indicated by persistent hypotension (usually defined as a systolic blood pressure less than 90 mmHg or a decrease of greater than 40 mmHg in systolic pressure from baseline), often with right ventricular dysfunction, thrombolytic therapy may be indicated [47]. Thrombolytic alteplase (Genentech, San Francisco, CA) at a dose of 100 mg infused over 2 h has FDA approval for the treatment of massive PE [47]. Though a mortality benefit to the administration of thrombolytic therapy was seen in a recent meta-analysis (OR 0.53), this came at the cost of a dramatically increased incidence of major bleeding events (OR 2.73) [48]. The same study noted the incidence of major bleeding events to be 9.2 % in patients receiving thrombolysis versus 3.4 % in patients treated with anticoagulation therapy alone, and a 1.5 % risk of intracranial hemorrhage as opposed to 0.2 % in the anticoagulation-only group. Moreover, recent surgery is often considered an absolute contraindication to thrombolytic therapy. A promising option for these patients is catheter-directed thrombolysis, which may offer some of the advantages of thrombolytic therapy without the same systemic exposure. Catheter-directed thrombolysis (CDT) is typically performed using low-profile (<10 French) catheters and may involve mechanical fragmentation or aspiration of emboli, as well as intraclot thrombolytic injection. CDT is reported to have a clinical success rate of 86.5 % (defined as stabilization of hemodynamics, resolution of hypoxia, and overall survival from PE), with a major complication rate of 2.4 % [49], though it has not been well studied in surgical populations.

Finally, pulmonary embolectomy is usually reserved for patients with massive PE and right ventricular strain on echocardiography, with or sometimes without impending hemodynamic collapse [50, 51]. Though the mortality rate

for this procedure has declined over the last few decades, it remains near 20 % [52]. One recent series of 20 patients operated on emergently reported a survival-to-discharge rate of 95 % [53], while another reported that 94 % of emergent patients survived to hospital discharge, with 83 % alive at 3 years [51].

Tamponade

Diagnosis: *Clinical suspicion (Beck's triad, equalization of right & left heart pressures), echocardiography*

Therapy: *Volume, administration, drainage*

Acute cardiac tamponade occurs when fluid under pressure accumulates inside of the pericardial sac. The elasticity of the pericardium is limited to accommodating the physiologic amounts of fluid which normally surround the heart. As excess fluid accumulates, the pericardium stiffens (i.e., compliance decreases) and compression of the heart itself occurs, which impairs cardiac filling. Worsening tamponade is associated with progressively declining preload and a corresponding drop in cardiac output and blood pressure. "Beck's triad" refers to the distended neck veins, muffled heart sounds, and low arterial blood pressure which can be seen in cases of acute tamponade. Additionally, patients with a pulmonary artery catheter in place may exhibit equalization of pressures between right and left sides of the heart.

Tamponade can be seen in a wide range of clinical situations. Etiologies can be subdivided into pericardial effusions, which tend to be medical in nature, and hemorrhage into the pericardium, more often seen in surgical populations. Within this subset, hemorrhage into the pericardium has three major causes: trauma to the myocardium itself, either blunt or penetrating, free ventricular wall rupture following myocardial infarction, or hemorrhage as a result of an aortic dissection.

Tamponade following trauma is a grave event, but it will lead to earlier arrest and better preserved blood volume than injuries that result in hemorrhage and arrest from hypovolemia. The overall survival rate for penetrating cardiac trauma is generally poor, with typical survival figures reported as 10.8 % [54], 14 % [55], or 19.3 % [56] in some series; gunshot wound patients fare less well than those with isolated stab wounds, especially those limited to the right ventricle. One series of 212 patients with penetrating cardiac trauma found that only 96 were even transported to the trauma center (45.3 %). Of those 96, 48 presented with tamponade (22.6 %), and of those, 27 survived (12.7 %) [56]. Though some series have not found that tamponade at presentation is predictive of survival or mortality [57], other series have suggested improved survival among patients presenting with tamponade alone as opposed to those in frank hypovolemic shock [54], highlighting the urgency of rapid intervention. Data indicate that tamponade following blunt trauma is equally serious. Victims of blunt cardiac rupture are unlikely to survival to the hospital, and overall mortality even within those initial survivors lies in the 60–90 % range [58, 59].

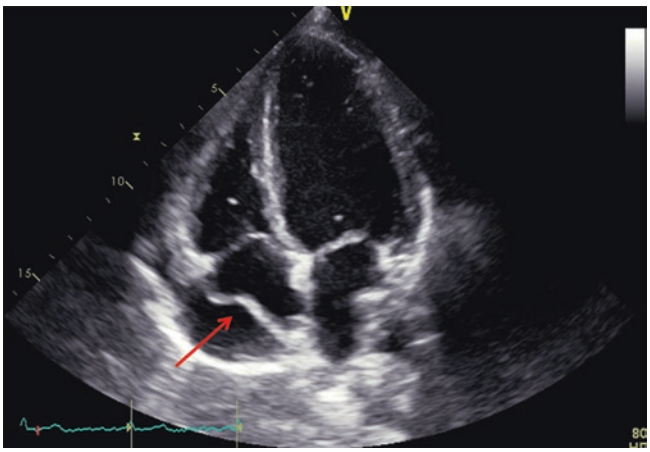

Fig. 9.2 Pericardial effusion with right atrial collapse (*arrow*). (Figure courtesy of T. Metkus, M.D.)

Management of traumatic cardiac tamponade patients follows Advanced Trauma Life Support (ATLS) protocols. In stable patients, hemopericardium may be diagnosed with Focused Assessment with Sonography for Trauma (FAST) ultrasound scanning. Aggressive volume resuscitation is critical to maintaining intracardiac filling pressures but needs to be coupled with rapid definitive hemorrhage control (Fig. 9.2).

In contrast to medical cases of cardiac tamponade arising from pericardial effusions, pericardiocentesis may not always be appropriate for surgical patients because it fails to address the underlying traumatic defect in the myocardium. Pericardiocentesis may be useful as a bridge to definitive surgical therapy, however, and is still taught as part of the ATLS curriculum. A recent review article noted that most studies of pericardiocentesis are biased toward survivors and that the procedure is used as a sole intervention in trauma patients in only 2.1 % of patients [60]. Hemodynamically stable patients presenting with hemopericardium after penetrating chest trauma may be candidates for a subxiphoid pericardial window performed in the operating room; evidence suggests this approach may shorten ICU and hospital stays without any decrement in survival [61]. It is important to note that inducing anesthesia in a patient with significant hemopericardium may worsen hemodynamic compromise. Unstable trauma patients may be taken emergently to the operating room or may undergo emergency department resuscitative thoracotomy should they meet ATLS criteria.

Tamponade can also occur secondary to two primary cardiac events, namely, acute myocardial infarction (MI) or acute aortic dissection. Following MI, weakened myocardium

can rupture, allowing the free passage of blood into the pericardial space. Free wall or left ventricular aneurysm rupture requires emergent operative repair and will be discussed further below. Cardiac tamponade can also complicate acute aortic dissection, occurring in 8.4 % [62] to 18.7 % [63] of all dissection patients in recent series. Tamponade typically complicates an ascending or type A dissection when rupture of the aorta into the pericardium near the aortic root results in hemopericardium under essentially arterial pressures. The presence of cardiac tamponade in acute aortic dissection is independently associated with a higher mortality risk [64, 65], with one series of 674 type A dissection patients reporting mortality of 24.6 % overall and 54.0 % in patients presenting with tamponade [63]. Tamponade as a result of MI or aortic dissection generally requires emergent operative intervention, discussed below. Pericardiocentesis has been suggested to be harmful in cases of acute aortic dissection [66], as it fails to address the underlying disease process.

Finally, no textbook of surgical intensive care would be complete without noting that cardiac tamponade should always be suspected in cardiothoracic surgery patients with declining arterial blood pressure and rising CVP, even in the presence of apparently functioning mediastinal drainage tubes. The intensivist must always be attuned to this possibility, particularly if chest tube output has dropped suddenly. The inadequate placement or failure of these tubes due to clot can lead to inadequate drainage of ongoing bleeding and hemodynamic compromise. Though some advocate "stripping" or "milking" chest tubes to prevent this, a Cochrane Library meta-analysis of chest tube clearance methods found insufficient evidence to support or refute the need for such maneuvers [67]. These patients may require reopening of the chest in the ICU and/or reexploration in the operating room.

Tension Pneumothorax

Diagnosis: *Clinical suspicion (tracheal deviation, decreased breath sounds, jugular venous distension, hypotension), radiography*

Therapy: *Acute decompression*

A tension pneumothorax occurs when air accumulates in the pleural space under pressure. This occurs as a result of a pneumothorax coupled with an impediment to air extravasation from the pleural space – the so-called "one-way-valve" effect. In this manner, air can enter the pleural space, but cannot leave. As air accumulates under pressure exceeding atmospheric pressure, the heart and great vessels are compressed, leading to a decrease in cardiac preload and a drop in cardiac output. Typically, a tension pneumothorax results from a lung laceration (e.g., from a fractured rib or stab wound), though it is theoretically possible to have tension physiology with a chest wall laceration alone as well. Positive-pressure ventilation can create (e.g., the rupture of a lung bleb) or exacerbate situations leading to tension physiology.

Clinically, the classical signs of a tension pneumothorax are decreased breath sounds on the affected side, shift of the trachea away from the affected side (where the tension is building), mediastinal shift away from the affected side, and depression of the affected side's hemidiaphragm. Tension pneumothorax is one of the most common causes of death in battlefield combat injuries and is one of the most common civilian traumatic injuries as well, with a reported incidence of 20 % in patients admitted to trauma centers [68, 69]. Equally important for the intensivist is the fact that tension pneumothoraces may occur insidiously in the intensive care unit patient. The prevalence of positive pressure ventilation as well as invasive procedures such as central line placement can all be complicated by pneumothorax. The classic example is a mechanically ventilated patient who undergoes subclavian central line placement, develops an iatrogenic pneumothorax, and then develops tension physiology due to ongoing positive pressure ventilation coupled with a parenchymal lung injury.

A chest radiograph may be obtained for definitive diagnosis of a pneumothorax; the clinical signs and symptoms mentioned above are useful for determining if tension physiology is occurring. More recently, the increased use of computed tomography (CT) scans in trauma patients has revealed a high incidence of "occult" pneumothoraces which are not appreciated on chest radiology alone. In one series of 230 trauma center patients who were discharged with a diagnosis of pneumothorax, over half (54.8 %) had pneumothoraces missed by presentation clinical examination and chest radiography which were only appreciated following CT imaging [70]; such pneumothoraces are termed occult pneumothoraces.

The treatment for a tension pneumothorax is aimed at relieving the built-up intrathoracic pressure which impairs cardiac preload and therefore cardiac output. Traditionally, tension pneumothorax has been treated by tube thoracostomy, typically performed in the fourth or fifth rib interspaces on the anterior axillary line of the affected side. The tube is directed apically. This allows the escape of pressurized air from the pleural space and insertion of a suitable tube to provide negative pressure suction and therefore reexpand the collapsed lung. For the occult pneumothorax patient – for example, an intensive care unit patient undergoing imaging for another indication – it has been recommended that all patients requiring positive pressure ventilation undergo tube thoracostomy patient to preclude the development of tension physiology. One small randomized trial found that in occult pneumothorax patients requiring positive pressure ventilation, 8 of 21 observed patients progressed to require tube thoracostomy, with three of these developing tension physiology [71]. Another randomized

trial found that 20 % of observed occult pneumothorax patients progressed to require tube thoracostomy, though those who underwent initial tube thoracostomy did not have a survival differential versus those who were observed [72].

Aortic Dissection

Diagnosis: *Clinical suspicion (part of any chest pain differential), asymmetric pulse exam, CT aortography or transesophageal echocardiography. *MUST distinguish type A from type B.**

Therapy: *Negative ionotropy followed by afterload reduction; if type A, immediate surgery. If type B, medical management unless malperfusion, unremitting chest pain, hemorrhagic (left) pleural effusion, continued fall in hemoglobin, uncontrollable hypertension, and rising creatinine (normotensive acute kidney injury).*

Aortic dissection occurs as a result of a tear in the aortic intima, either primary in nature or as a result of an underlying medial hemorrhage. Disruption of the intima allows blood under arterial pressure in the aortic lumen to force its way through the media and thereby separate the intima from the media and/or adventitia, creating a dissection flap and a "false lumen." As blood continues to separate the arterial wall layers, the dissection can spread. Proximally, this may affect the aortic valve and extend into the pericardial interior, resulting in hemopericardium and potentially cardiac tamponade. Distally, dissections of the aorta can involve any of the great vessels to the upper circulation, as well as the visceral vessels. The subsequent potential compromise of blood flow to end organs and resulting ischemia is referred to as malperfusion. Dissections are classified according to their involvement of either the ascending aorta (Stanford type A) or the descending aorta (i.e., distal to the left subclavian artery: Stanford type B) [73]. Alternatively, Debakey's classification describes three types: Type 1, dissections starting in the ascending aorta and extending at least into the aortic arch; type 2, dissections limited to the ascending aorta alone; and type 3, dissections starting in the descending aorta and extending proximally or distally [74].

Aortic dissection is a relatively rare disease, with an incidence of about 3 per 100,000 persons per year, about two thirds of them male [62, 75, 76]. Patients typically are older males, though younger patients are more likely to have a connective tissue disorder (e.g., Marfan syndrome or Loeys-Dietz syndrome), have a bicuspid aortic valve, or have a history of prior cardiac surgery [77]. Cystic medial necrosis, a disorder of large arteries characterized by loss of elastic and muscle fibers in the media, is often present in connective tissue disorder patients presenting with aortic dissection. Presenting individuals may report substernal chest pain or "tearing" or sharp pain in the posterior chest, sometimes radiating to the back. Some patients may experience syncopal episodes as part of their presentation, and a history of hypertension may be present in 72 % of patients [62]. Symptoms of aortic insufficiency may be present if the dissection has propagated proximally to involve the aortic valve or root. If the aortic arch vessels are involved, patients may present with a pulse or blood pressure variation between the right and left arms. Other clues to diagnosis include recent procedural history: in a recent study of 464 aortic dissection patients, 17.9 % were noted to have had prior cardiac surgery, and 2.2 % experienced their aortic dissection secondary to a cardiac catheterization procedure [62].

CT aortography remains the predominant means of diagnosing of aortic dissection, as it is rapid and readily available. CT images can be helpful in assessing not only the anatomy and extent of dissection but also sequelae including intraluminal thrombus and hemopericardium. Sensitivity and specificity of CT are both excellent and have been reported in the range of 98 % and 100 %, respectively [78, 79]. Though slower, MRI is also considered to be highly accurate in the diagnosis of aortic dissection and is better than CT at identifying the dissection's point of origination [78]. Transesophageal echocardiography requires esophageal intubation and the hemodynamic risks of risk of procedure sedation. TEE is quite sensitive but somewhat less specific than CT or MRI (in the range of 77–85 %) [78, 80]. However, advantages to TEE include that it can be performed at the bedside without moving an unstable patient, and it allows the added benefit of assessing any component of aortic regurgitation which may be present in an ascending dissection.

The management of an aortic dissection depends on its anatomic location. Ascending or type A dissections (Debakey classes 1 and 2) are true surgical emergencies and should involve prompt cardiothoracic surgical consultation for operative repair. In contrast, descending or type B dissections (Debakey class 3) are managed nonoperatively unless the patient has evidence of ongoing malperfusion or hemorrhage. Acutely, prior to the consideration of operative intervention, all patients should be admitted to a monitored setting and undergo proper airway management, including intubation in unstable patients and adequate opioid analgesia as needed. Both blood pressure and heart rate must then be controlled in a systematic fashion. In order to minimize the force of left ventricular ejection (i.e., the change in pressure over change in time or "dP/dT"), a beta-blocker such as esmolol or labetalol should be given to lower the blood pressure to a systolic goal of 100–120 mmHg with a heart rate of around 60 [77]. Calcium channel blockers such as diltiazem and verapamil are an acceptable alternative in the rare patient who cannot tolerate beta-blockers. For additional blood pressure control, vasodilating agents are then added, such as sodium nitroprusside.

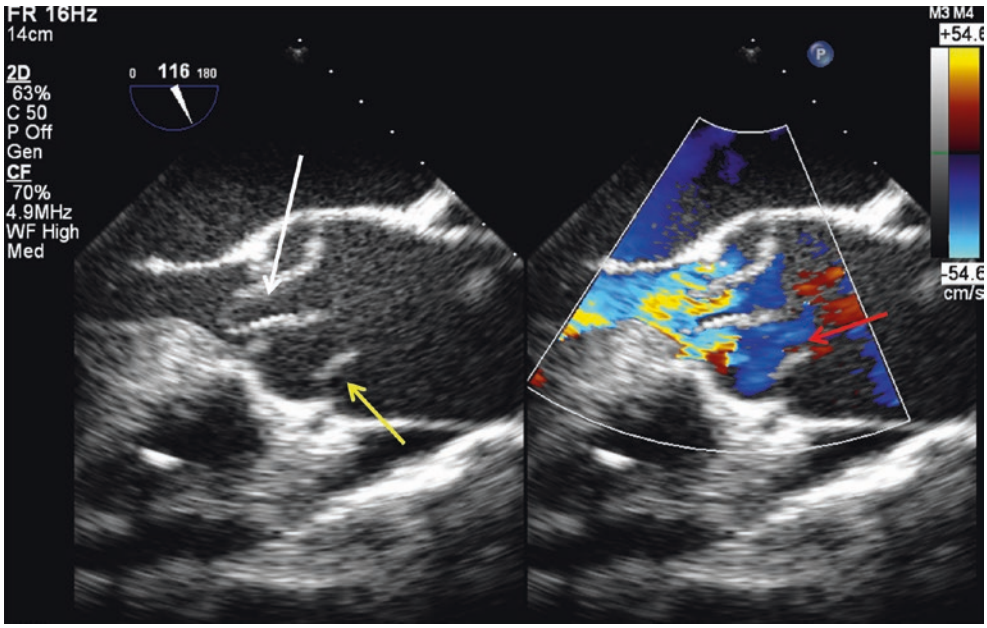

Fig. 9.3 Aortic dissection flap with aortic insufficiency. *White arrow* shows aortic valve leaflets. *Yellow arrow* shows dissection flap. *Red arrow* shows aortic insufficiency arising from flap. (Image courtesy of T. Metkus, M.D.)

Patients who present *in extremis* are exceptionally challenging to manage. These patients may already be in hypovolemic shock from blood loss or extracardiac obstructive shock from cardiac tamponade if the ascending dissection has resulted in hemopericardium. These patients will require emergent intubation and volume resuscitation with blood products. Pericardiocentesis is to be avoided in patients with signs of tamponade, as the patient's increased intrapericardial pressure may be the only factor preventing further bleeding and sudden hemodynamic collapse [66].

Operatively, goals of surgery as originally articulated by Debakey et al., and later by Bahnson and colleagues, involve excision of the intimal tear, removal or obliteration of the point of entry into the false lumen, and aortic reconstruction with a synthetic graft [74, 81, 82]. Cardiopulmonary bypass is used, as well as hypothermic circulatory arrest if circulation to the head vessels must be compromised during repair of the aortic arch. Additionally, if the aortic dissection involves the aortic valve and aortic insufficiency is present, valve replacement is required (Fig. 9.3).

In the series of Hagan et al., 72 % of type A dissections were managed surgically (with some patients not offered surgery due to advanced age or other comorbidities), while only 20 % of type B aneurysms were operated upon [62]. Surgically treated acute type A dissection patients experienced a 26 % in-hospital mortality rate (versus 58 % of type A patients treated medically), while medically treated type B patients had a 10.7 % mortality rate. However, mortality was highest in type B patients who required operation, at 31.4 %. Overall operative mortality for the repair of ascending aortic dissections remains in the 15–35 % range at experienced centers [62, 83, 84].

In recent years, endovascular repair of aortic dissection has been attempted successfully, with or without fenestration of the stent graft. These techniques have been most widely employed for complicated type B dissections (i.e., dissections with the presence of malperfusion or evidence of impending rupture), with some investigators reporting lower rates of paraplegia and mortality as compared to open surgical repair [85]. The VIRTUE trial of endovascular stent grafting for aortic dissection reported 3-year survival of 82 % among patients with an acute type B dissection requiring intervention [86]. Another group reported an 84 % survival rate over a median of 53 months of follow-up [87]. With these results, many surgeons now believe that the endovascular approach is the preferred means of treating complicated type B aortic dissections [88, 89].

Traumatic Aortic Injury

Diagnosis: *Mechanism of injury, CT aortography*

Treatment: *Endovascular or open repair*

No discussion of aortic dissection is complete without mention of the devastating consequences of traumatic aortic injury. Though patients with penetrating aortic injuries typically rapidly suffer exsanguination and death, blunt aortic injury (BAI) may be seen in trauma patients who survive to hospital presentation [90]. Shear forces sustained during rapid deceleration events (e.g., high-speed motor vehicle collisions, airplane crashes, falls from height) are typically implicated in BAI; for example, 73 % of one major commercial airline crash's victims suffered aortic injuries [91]. The most common sites of injury within the aorta are the isthmus,

ascending aortic and arch, and the distal thoracic aorta [92, 93]. As with aortic dissection, diagnosis is most commonly established by CT, and the same initial medical management principles apply, including the use of beta-blockade and aggressive antihypertensive infusions. However, management principles of BAI differ in that other life-threatening injuries are usually stabilized prior to surgical repair of the aortic injury. In a large prospective trial, delayed repair (>24 h after injury) of BAI was associated with improved survival regardless of the presence or absence of major associated injuries [94]. Stent grafts have been employed frequently in the traumatic setting as well and have been associated with relatively favorable outcomes [95, 96].

Mechanical Complications of MI: Ventricular Septal Defect and Free Wall Rupture

Diagnosis: *Physical exam (harsh systolic murmur), echocardiography*

Therapy: *Decrease afterload (consider IABP); hypoxia or shock mandate emergent surgery*

Ventricular septal defects (VSD) have been reported to complicate about 0.2 % of acute MI cases in the modern era and are associated with 30-day mortality rates in the 75 % range [97, 98]. Typically, these occur when an infarct is of sufficient size to result in a large transmural infarction in the septal myocardium. Ruptures may be "simple," in which a straight path is created between the right and left ventricles, or "complex," in which the path of rupture and dissection of blood travels serpiginously through the septum and may result in defects far apart from each other in each respective ventricle. One autopsy series found that simple VSDs tend to be associated with anterior infarcts, while complex VSDs are associated with inferior infarcts [99]. Subsequent left-to-right shunting of blood may impose a marked hemodynamic strain on a struggling heart, depending on the severity of the infarct and resultant VSD.

Traditionally, the classic time period for VSDs and/or free wall rupture to occur is around 5–6 days following acute MI, roughly the time taken for infarcted myocardium to weaken sufficiently [100]. Interestingly, in the modern era of aggressive intervention and revascularization, the median time to VSD occurrence is less than 24 h [101].

Clinical clues to the diagnosis of VSD include increased chest pain, new ST elevations, a pansystolic murmur, or frank cardiogenic shock. VSD can be a sudden event, and acute changes in an AMI patient's condition may alert the clinical to the possibility of VSD. Echocardiography may show the frank septal rupture, left-to-right flow on color Doppler modes, or right ventricular dysfunction in the case of hemodynamically significant VSDs (Fig. 9.4).

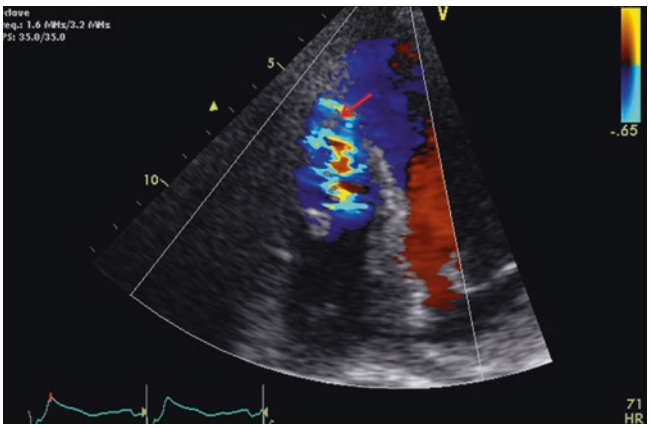

Fig. 9.4 VSD with left-to-right shunting on color Doppler (*red arrow*). (Image courtesy of T. Metkus, M.D.)

Management of the patient with VSD represents a marked challenge, as the few medical therapies available to the clinician are usually already in place at the time of diagnosis. As with the therapy of AMI in general, goals include optimization of coronary and end-organ perfusion, minimization of myocardial oxygen demand, and the reduction of SVR to minimize left-to-right shunting through the VSD. Operative repair remains a mainstay of therapy. Historically, repairs were delayed for as long as 1 month out of concern for the VSD patient's poor hemodynamic condition, as well as the inability of necrotic myocardium to hold sutures. However, since the majority of VSD patients are in cardiogenic shock, survival rates with medical management alone were extremely poor – overall survival in one recent registry found 19 % survival in an operative management group, but only 4 % survival in patients treated medically [101]. Accordingly, with the exception of hemodynamically stable VSD patients whose defects are sufficiently small to allow operative delay, most patients are considered for emergent operations.

Operative repair takes place on cardiopulmonary bypass. A left ventriculotomy is usually performed to gain access to the septum [102]. The surgeon must find myocardium of sufficient strength to hold sutures which will anchor a pericardial patch; this may require not only debridement of necrotic tissue around the defect but also enlargement of the defect itself. The patch must be of sufficient size to minimize tension and preclude the recurrence of a defect. A more recent method of repair, infarct exclusion, involves suturing the pericardial patch to healthy myocardium far from the defect in order to entirely exclude the defect and surrounding tissue from the left ventricular cavity [103]. For example, an anterior VSD would be excluded by suturing the patch to the septum and lateral wall. This method has the advantage of not only closing the defect but also preventing further resection of potentially viable myocardium and preserving left ventricular geometry.

Mechanical Complications of MI: Left Ventricular Aneurysm

Diagnosis: *Echocardiography*

Therapy: *Anti-remodeling therapy, anticoagulation if thrombus present; aneurysmectomy for systemic embolization or refractory symptoms; emergent surgery for rupture*

Left ventricular aneurysms (LVA) result from post-MI healing and scarring and are usually defined as well-delineated, thin segments of the ventricular wall which contain no viable muscle. These aneurysms typically balloon outward paradoxically during systole and are hence termed dyskinetic (or sometimes akinetic). As with VSDs, the incidence of LVA has declined in the modern era of early reperfusion; current figures suggest around 10 % of all AMI patients will develop an LVA. Interestingly, one study found only 7.2 % of patients who underwent revascularization developed LVAs, as opposed to 18.8 % who could not have their infarct-related artery reopened [104]. About three quarters of LVAs occur in the anterior or apical LV walls. Infarct expansion occurs rapidly after AMI via neutrophil-mediated proteolysis [105, 106]. Like VSDs, these lesions are prone to rupture in the early post-MI time period. As ventricular remodeling occurs and scar tissue replaces the infarcted myocardium, the LVAs remain unable to contract and expand appropriately with systole and diastole. These changes, coupled with the compensatory hypertrophy and ventricular dilation which occurs following MI, may further increase myocardial oxygen demand and lead to heart failure.

In addition to worsening heart failure, LVA patients may also present with angina or arrhythmias related to the scar tissue. Mural thrombus has been reported to be present in up to half of patients who undergo surgical correction and seems to be associated with increasing aneurysm size in older reports [107–109]; accordingly, some patients may suffer systemic embolization resulting in cerebrovascular accidents or peripheral arterial occlusion.

Medical therapy for LVA consists of treatment to ameliorate LV remodeling, typically with beta-blockers and angiotensin-converting enzyme inhibitors, and anticoagulation were required for the presence of intraventricular thrombus. Indications for aneurysmectomy include persistent arrhythmias or heart failure refractory to medical therapy, refractory angina, and systemic embolization in patients with contraindications to oral anticoagulation. Typically, revascularization, when indicated, is performed concomitant with aneurysmectomy, since this approach appears to improve survival [110]. Additionally, patients presenting with LVA and/or free wall rupture require emergent surgery.

Mechanical Complications of MI: Papillary Muscle Rupture and Acute Mitral Regurgitation

Diagnosis: *Physical exam (harsh systolic murmur), echocardiography*

Therapy: *Decrease afterload (consider IABP); hypoxia or shock mandate emergent surgery*

Just as infarcted myocardium weakens, resulting in VSD or LVA, so too can the papillary muscles suffer damage during AMI. As these structures control the mitral valve, acute mitral regurgitation can result. The valve leaflets and chordae tendineae are not directly affected by ischemia. However, the posteromedial papillary muscle is usually only supplied by a single artery – the right coronary artery or the circumflex artery – and is therefore at highest risk of an ischemic insult. Meanwhile, the first circumflex marginal and first diagonal arteries both supply the anterolateral papillary muscle, giving it a degree of protection during AMI as compared to its counterpart [111].

Acute mitral regurgitation occurs via two mechanisms. In the first, papillary muscle rupture as a result of infarction and subsequent weakening causes flail mitral valve leaflets. Though an infarction causing total rupture of the papillary muscle common trunk may precipitate prompt hemodynamic collapse, a partial rupture of the trunk or only one head of the muscle may be less severe [112]. Acute mitral regurgitation may also result from poor coordination of the mitral apparatus. Not only may papillary muscle shortening be impaired by infarction but also dysfunction of the LV wall can impede proper valve leaflet coaptation. For example, if the ventricular wall adjacent to a leaflet infarcts, it will dilate and can cause a central leak as the ipsilateral leaflet is pulled slightly away from its proper position.

In the SHOCK trial, moderate or greater mitral regurgitation following myocardial infarction was present in about 40 % of AMI patients who underwent echocardiography, and these patients had poorer survival than AMI patients with mild or no mitral regurgitation [113]. Another study of AMI patients found that about 10 % of AMI patients presenting in cardiogenic shock had clinically significant acute MR [114]. The incidence of papillary muscle rupture is harder to pinpoint, but is thought to account for up to 5 % of all AMI deaths and is usually fatal should a complete rupture occur [115].

Medical management of moderate or severe acute MR follows the same principles as cardiogenic shock following AMI. IABP placement in this setting has been shown, in a calf model, to increase cardiac output while decreasing the degree of MR [114]. Surgical therapy is the only viable corrective therapy for papillary muscle rupture; it carries

high-operative mortality rates (around 20–30 %), but lower mortality rates as compared to medically managed patients [112, 116, 117]. Valve replacement (as opposed to repair) is required in the presence of papillary muscle necrosis. Though survival may be similar between matched patients undergoing repair versus replacement, patients undergoing repair for severe MR following AMI have higher reoperative rates due to mitral valve failure [118, 119]. Notably, in one large series, no survival differences were seen between repair and replacement among high-risk patients [118].

Future Horizons: The Emerging Role of Extracorporeal Life Support in Cardiovascular Emergencies

Though cardiopulmonary bypass is hardly new, the ever-expanding use of extracorporeal life support technologies like extracorporeal membrane oxygenation (ECMO) to maintain patients whose own pulmonary and/or circulatory systems are failing represents a new frontier in medicine. Currently accepted indications for ECMO include potentially reversible causes of cardiopulmonary failure refractory to traditional management, such as hypoxic and hypercapnic respiratory failure, refractory cardiogenic shock, cardiac arrest, failure to wean from cardiopulmonary bypass after cardiac surgery, and as a bridge to heart and/or lung transplantation.

Previously reserved only for highly specialized indications, ECMO utilization has increased dramatically even since the mid-2000s, with a decline in overall mortality rates from above 40 to 33 % in one large series [120]. ECMO has now been shown to be associated with reasonable survival rates in a variety of settings, including acute respiratory distress syndrome, in patients who would otherwise assuredly have nearly 100 % mortality rates [121]. Additionally, new modalities, such as low-flow ECMO for CO_2 removal (extracorporeal carbon dioxide removal or ECCO$_2$R), represent promising new therapeutic options for selected patients.

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Extracorporeal Membrane Oxygenation (ECMO)/Extracorporeal Carbon Dioxide Removal ($ECCO_2R$)

10

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a means of supporting severe pulmonary and cardiac dysfunction. It stabilizes critical derangements of oxygenation and ventilation, allowing time to diagnose, treat, and recover from the underlying cause of organ failure. This technology was first successfully employed by Hill et al. [1] in 1972, who used it to support an injured patient who developed acute respiratory distress syndrome (ARDS). This was quickly followed by successful use of ECMO for cardiogenic shock (1973) and newborn respiratory failure (1975) [2]. Since that time, the technology has matured and been validated as an effective therapy [3]. It is currently used in more than 200 centers around the world to care for over 4,500 neonatal, pediatric, and adult cases per year (Fig. 10.1) [4].

Physiologic Basis of Therapy

Extracorporeal support is employed to guarantee adequate oxygen delivery and carbon dioxide clearance to meet systemic needs. Oxygen delivery (DO_2) is a function of arterial oxygen content (CaO_2) and cardiac output (CO) (Eq. 10.1). Arterial oxygen content, measured in mL/min, is dependent upon the hemoglobin concentration (Hgb), its oxygen saturation percentage (SaO_2), and the partial pressure of the oxygen dissolved in the plasma (PaO_2) (Eq. 10.2). Mathematical review of this equation reveals that oxygen content is largely driven by hemoglobin concentration in contrast to the amount of oxygen dissolved in plasma.

$$CaO_2 = 1.34 * Hgb * SaO_2 + 0.003 * PaO_2 \quad (10.1)$$

$$DO_2 = CaO_2 * CO \quad (10.2)$$

Normal adult human oxygen consumption (VO_2) is 3–5 mL/kg/min. It is decreased by rest, paralysis, and hypothermia and increased with activity, infection, and hyperthermia. It is dependent on tissue metabolism and is independent of the oxygen supply until the supply is very low.

At rest, oxygen delivery is normally five times the oxygen consumption. As consumption changes, normal homeostasis measures attempt to keep this ratio fixed and respond by altering the cardiac output. When compensation fails and the DO_2:VO_2 ratio falls to 2:1, there is increased oxygen extraction, which is evidenced by decreased venous oxygen saturation (SvO_2).

Carbon dioxide production is a by-product of tissue metabolism and is approximately equal to the oxygen consumed per minute. The normal amount of CO_2 dissolved in plasma ($PaCO_2$) is 40 mmHg. The body adjusts the depth and rate of breathing to keep this value constant. Excretion of CO_2 is an efficient process compared to oxygenation and in many cases is achieved even in the setting of severe oxygenation dysfunction.

The Circuit

Components

Three main components make up the extracorporeal cardiopulmonary support circuit:

1. Large-bore cannulae and circuit tubing to provide access to the native circulation
2. An artificial membrane lung to provide gas exchange
3. An active pump, either roller pump or centrifugal pump, to facilitate perfusion

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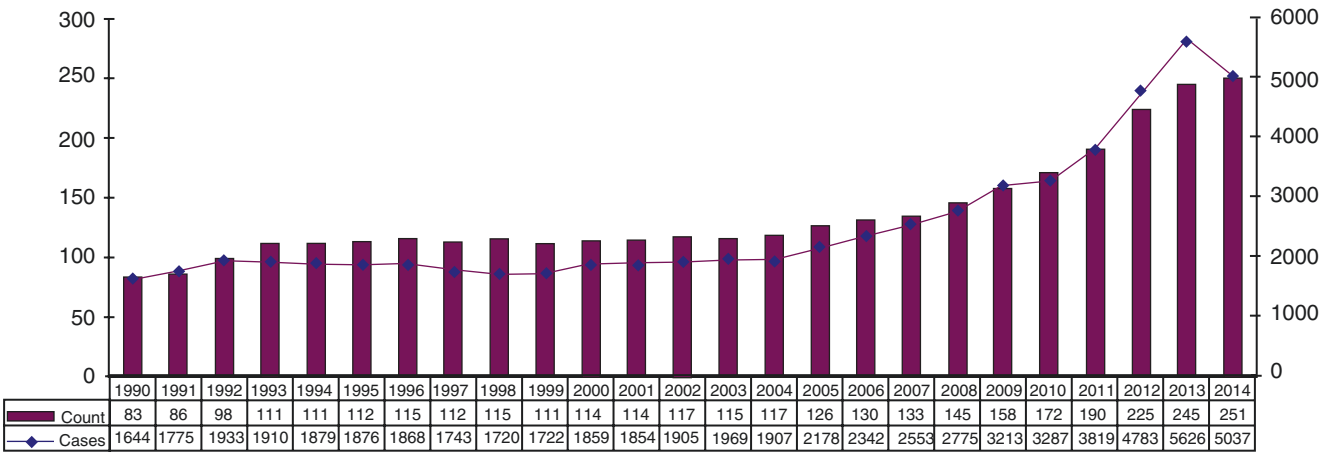

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Count	83	86	98	111	111	112	115	112	115	111	114	114	117	115	117	126	130	133	145	158	172	190	225	245	251
Cases	1644	1775	1933	1910	1879	1876	1868	1743	1720	1722	1859	1854	1905	1969	1907	2178	2342	2553	2775	3213	3287	3819	4783	5626	5037

Fig. 10.1 The number of ECMO centers and annual cases over time as voluntarily reported to the Extracorporeal Life Support Organization registry (From www.ELSO.org, accessed June 2015)

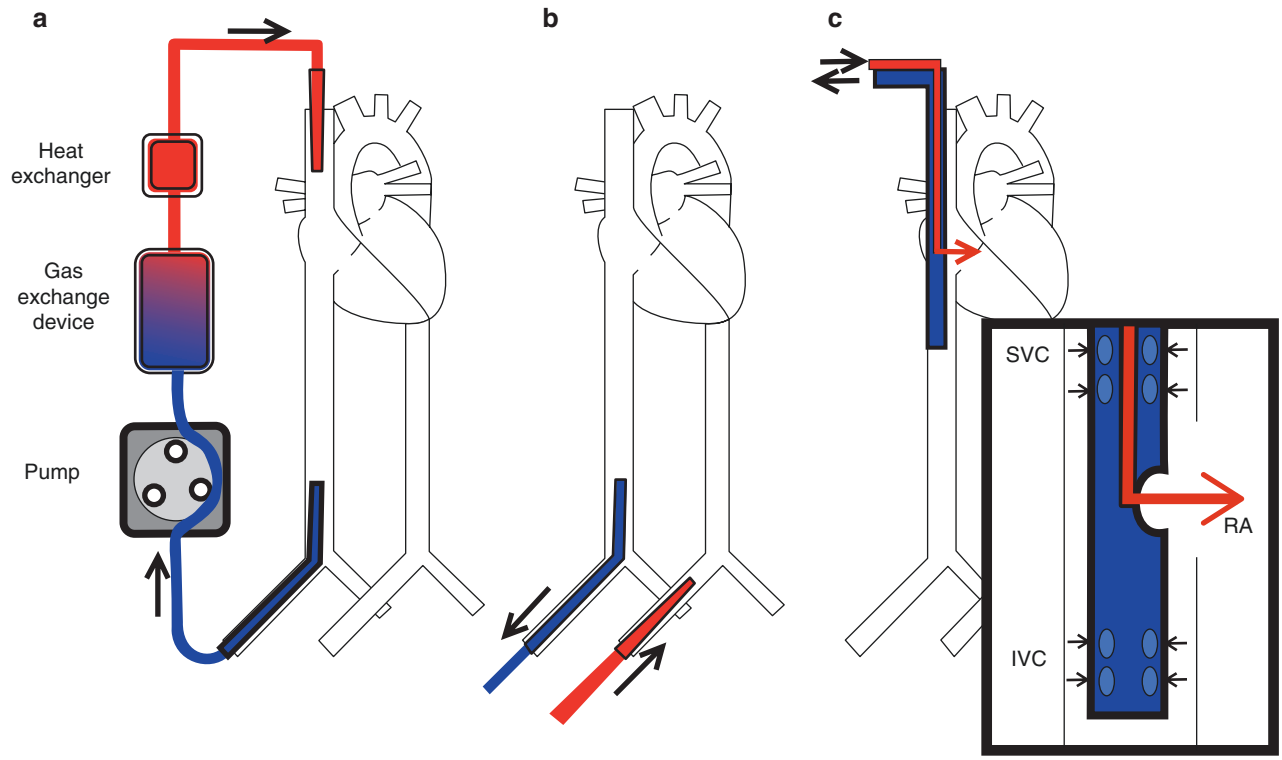

Fig. 10.2 (**a**) Venovenous ECMO support. This circuit drains deoxygenated blood from the femoral vein that is then taken through a pump, gas exchange device, and heat exchanger before returning the oxygenated blood to internal jugular vein. (**b**) Venoarterial ECMO via the femoral vessels. Blood is drained from the femoral vein and, after going through the ECMO circuit, is returned into the femoral artery in a retrograde fashion. (**c**) Venovenous support with a double lumen cannula. Insert shows drainage occurs from both the superior vena cava (*SVC*) and inferior vena cava (*IVC*), while infusion is directly into the right atrium (*RA*)

A schematic of common extracorporeal circuit configurations (venovenous, venoarterial, and single-cannula venovenous) is shown in Fig. 10.2.

Cannulae come in a variety of designs and sizes, but are typically made of polyurethane. Double lumen cannulae have been developed (Fig. 10.2c) that drain from both the superior and inferior vena cava and reinfuse into the right atrium with only a single access site. Cannulation can be performed percutaneously or via cutdown, with percutaneous access being more common. When selecting a drainage cannula for the circuit, the largest appropriate internal diameter should be chosen. This is to maximize flow, which increases by a power of four with increases to the internal radius. In general, 60–80 mL/kg/min of blood flow is needed for

supporting for hypoxemia. Central cannulation of the great vessels is performed in some cases when cervical or femoral access is not possible; it also is utilized for patients that have failed to wean from cardiopulmonary bypass [5].

The gas exchange device, also known as the membrane lung or oxygenator, is the core of the circuit. The patient's deoxygenated blood is distributed onto membrane surfaces, on the other side of which sweep gas flows past; the membrane surface allows for gas exchange between the two flows via diffusion. Oxygenation is increased by increasing blood flood through the device. Carbon dioxide clearance, however, is a function of sweep gas flow: increased sweep gas flow rates remove more CO_2 from the blood. Typically 100% oxygen is chosen as the sweep gas. Increases or decreases in sweep gas rate do not affect oxygenation except at extremely low sweep rates because of the efficiency of the membrane surfaces.

There are two types of pumps that are commonly employed in the extracorporeal circuit, the roller pump and the centrifugal pump. The roller pump is simple in concept; it creates a positive displacement on the circuit tubing, forcing blood forward. It carries a risk of circuit rupture if there is an occlusion downstream of the pump. The centrifugal pump, in contrast, utilizes an impeller design that is coupled with an electric motor to generate flow in a nonocclusive manner that cannot over-pressurize, but can have heating in the pump head that leads to thrombus formation. An important characteristic of all active circulatory drivers is that excessive negative pressure placed on the drainage catheter increases the risk of endothelial damage or air entrapment. While neither type of pump has been shown to be superior to the other [6], the smaller, lighter design footprint of centrifugal pumps has helped to facilitate patient transport on ECMO.

A heat exchanger is often used to maintain normal patient temperature, as blood in the extracorporeal circuit is exposed to ambient temperatures and there is risk of unintentional core cooling. Some companies have combined a heat exchange device with the gas exchange device into a single unit.

Configurations

Naming convention for extracorporeal support is based on the routes by which blood is drained and returned to the corporeal circulation. Venovenous (VV) support refers to venous drainage and venous reinfusion, whereas venoarterial (VA) is configured to reinfuse blood via an artery. VV ECMO support places the circuit in series with the native lung, allowing for total or partial respiratory support. In contrast, in VA ECMO support, the circuit is in parallel with the native lung and heart and allows for both pulmonary and cardiac support.

Pumpless arteriovenous (AV) [7, 8] ECMO takes advantage of native cardiac output to propel blood through the oxygenator, accepting lower flow rates than those achievable with an external pump. Sufficient support of severe hypoxia may not be feasible, but, because of the greater diffusibility of carbon dioxide, satisfactory ventilation with $ECCO_2R$ can be accomplished [9]. Access is most frequently obtained through the femoral artery and femoral vein.

Patient Selection

Patients with acute, potentially reversible, life-threatening respiratory or cardiac dysfunction refractory to conventional therapy are potential candidates for ECMO support. Respiratory support can be considered for hypoxemic respiratory failure, hypercarbic respiratory failure, or as a temporary means to bridge-to-lung transplantation. As a respiratory support modality, ECMO is most appealing for its potential to reduce or eliminate the injurious effects of positive pressure mechanical ventilation. It can minimize or, in some cases, replace mechanical ventilation while maintaining gas exchange, allowing for "lung rest." Cardiac support is used in acutely decompensated patients, including those with persistent shock despite volume administration, inotropes, and vasoconstrictors, failure to wean from cardiopulmonary bypass (postcardiotomy), acute myocardial infarction, and acute myocarditis. ECMO has also emerged as a temporary bridging strategy until cardiac recovery or implementation of definitive therapy such as ventricular assist devices or transplant.

There are no absolute contraindications to ECMO, as each patient should be considered individually with respect to the risks and benefits [7]. There are conditions known to be associated with poorer outcomes and thus are considered to be relative contraindications: mechanical ventilation at a high setting for 7 days or more, major pharmacologic immunosuppression, CNS hemorrhage that is recent or expanding, non-recoverable comorbidity such as terminal malignancy, or baseline advanced organ failure without options for potential salvage or transplantation.

Supporting Literature

Hypoxemic Respiratory Failure

ECMO was adopted into standard neonatal and pediatric practice because of the success of early trials [8, 10]. In contrast, the initial two randomized trials of ECMO support in adult respiratory failure conducted in the 1970s and 1980s failed to show advantage over conventional therapy [11, 12]. These negative results restricted the use of ECMO to a few centers, which continued to find benefit in ECMO support when conventional measures had failed [13–17]. Brogan et al. [18] published a summary report from the Extracorporeal Life Support Organization (ELSO) registry, which included 1,473 adult

patients who received ECMO for respiratory failure between 1986 and 2006. This series had a median patient age of 34 years, median PaO_2/FIO_2 ratio of 57, and overall survival of 50 %. It was not until 2009, when a third randomized controlled clinical trial, the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial [19], was published. This study found a survival advantage for patients referred to a specialized center using a treatment protocol that included ECMO compared to those treated at alternate tertiary care centers (63 % survival without severe disability at 6 months versus 47 %). The study has been criticized, as only 75 % of patients randomized to the ECMO group actually received ECMO and because of lack of a control group receiving standardized mechanical ventilation and ICU care [20]. Nonetheless, it remains the single modern randomized trial available.

In 2009, the H1N1 influenza pandemic renewed the interest of ECMO for respiratory failure. Investigators from Australia-New Zealand described their experience treating suspected or confirmed influenza A patients and reported patient survival of 75 % [21]. Noah et al. [22] reported the UK experience in 80 patients who were referred to the national H1N1 ECMO service. The median age was 36.5 years, the median PaO_2/FIO_2 ratio was 54.9, and the overall survival was 72.5 %. They matched their patients with patients enrolled in a concurrent Swine Flu Triage study who were not referred for ECMO and found the relative risk of death was 0.45–0.51 in the ECMO-referred patients compared with the non-ECMO-referred patients. A severe H1N1 cohort from Utah, however, reported equivalent survival (83 %) without the use of ECMO, calling into question the necessity for invasive therapy [23].

Looking forward, additional controlled trials have been initiated. The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial is an international, multicenter effort begun in 2011 that is comparing survival between rapid initiation of ECMO (within 3–6 h of optimal medical management) to standard low tidal volume ventilation for moderate to severe ARDS patients. A second study, Strategies for Optimal Lung Ventilation in ECMO for ARDS (SOLVE) study, is a pilot trial evaluating mechanical ventilation strategies while on VV ECMO for ARDS. It is anticipated that this study will provide insight into the ventilator-induced lung injury that may occur despite ECMO support.

Hypercarbic Respiratory Failure

Research on extracorporeal carbon dioxide removal ($ECCO_2R$) has primarily focused on hypercarbia occurring in the setting ARDS and lung-protective ventilation. Starting in the 1980s, Gattinoni showed that venovenous $ECCO_2R$ with minimal ventilator settings resulted in lower mortality in an observational study of ARDS patients [24]. Subsequent work was initially reassuring [25] but a randomized control trial in 1994 revealed no survival advantage to this technique [12]. The incidence of device-related complications was high in this study, with clotting seen in 20 %, resulting in discontinuation of therapy. Improvement in circuits and oxygenator design prompted continued $ECCO_2R$ study. Bein et al. used a pumpless system in a series of 90 ARDS patients and achieved rapid normalization of carbon dioxide levels, but most patients required vasopressors to support blood minimum flow through the device and 10 % developed lower limb ischemia [26]. A follow-up randomized trial (Xtravent Study) using $ECCO_2R$ combined with very low tidal volume mechanical ventilation (3 cc/kg) showed improvements in the overall complication rate (8 %) but failed to demonstrate advantage for $ECCO_2R$ in ventilator free days [27]. The SUPERNOVA (Strategy of UltraProtective lung ventilation with Extracorporeal CO2 removal for New Onset moderate to severe ARDS) study will further investigate the value of $ECCO_2R$ in ARDS mortality, morbidity, and ability to reduce ventilator-induced lung injury and is planned to start in 2015.

$ECCO_2R$ use for adult airway disease has not been studied as extensively as ARDS, although the potential population that could benefit from this application is large. Small studies have shown that $ECCO_2R$ may have a role in asthma exacerbations [28] and may avoid or replace ventilation in acute exacerbations of COPD [29, 30]. In a stimulating pilot study, $ECCO_2R$ facilitated both early extubation and ambulation in COPD exacerbations requiring mechanical ventilation [31].

Bridge-to-Lung Transplant

The use of ECMO as a temporary destination therapy for patients with chronic lung disease awaiting transplantation is controversial. The concept is founded by evidence that mechanically ventilated patients prior to transplant have worse survival after lung transplant [32]. Retrospective observation studies using ECMO as a bridge to transplant have been mixed [33–36]. The largest of these was based from the UNOS database and found pretransplant ECMO use resulted in higher rates of retransplantation and was a predictor of mortality posttransplant [35]. Nonetheless, the implication is that many of these patients would have otherwise died without the opportunity to receive an allograft.

Recently there has been a focus on managing ECMO patients awake and spontaneously breathing. This management strategy avoids the complications and drawbacks associated with sedation, intubation, and long-term ventilation, thereby decreasing infectious risk, increasing mobility and strength from being able to participate in physiotherapy, and ability to consume enteral feeds. This strategy has been applied to bridge to transplant patients and appears to have better outcomes.

Fuehner reported a single center experience and found awake ECMO recipients had a higher likelihood of survival at 6 months and shorter posttransplant ventilator course when compared to historical ventilator controls [37]. Furthermore, limited data suggests the survival of these patients may be equivalent to non-supported transplant patients [38].

Cardiac Failure

VA ECMO is one of many therapies available that provide mechanical support for acute cardiac failure. There have not been any controlled trials, however, comparing VA ECMO to other temporizing therapies (intra-aortic balloon pump [IABP] or temporary ventricular assist devices) but several observational studies have shown possible benefit. For patients with acute myocardial infarction, when VA ECMO was combined with coronary revascularization, there appeared to be a survival benefit at 30 days and 1 year compared to those temporized with IABP alone [39, 40]. Favorable survival has also been observed when the cause of failure is fulminant myocarditis [41, 42], sepsis-induced cardiomyopathy [43, 44], and pulmonary-embolism-induced cardiac failure [45]. VA ECMO also provides support for postcardiotomy cardiogenic shock until myocardial recovery or definitive therapy, but mortality in this cohort remains high (67–75%) [5, 46]. ECMO as a bridge to cardiac transplant has been described but has worse survival than those bridged with ventricular assist devices [47]. Larger, randomized trials are needed for this application of ECMO to support its routine application.

VA ECMO has also been used to restore circulation in patients with ongoing cardiac arrest, a strategy known as extracorporeal cardiopulmonary resuscitation (ECPR). The basis for this application is to improve cardiopulmonary support during the resuscitation period prior to emergent myocardial revascularization. Although it has yet to be studied in a randomized fashion, observational studies appear promising [48–50]. One study reported an almost doubled survival of in-hospital cardiac arrest patients resuscitated with ECPR compared to standard CPR (33% vs. 17%) [48]. Some evidence also suggest there may be reduced neurological injury with ECPR patients [50], which is a devastating and common complication in cardiac arrest survivors.

Management of ECMO

Patient Management

The primary goal of ECMO is to permit time for treatment of the underlying lung and cardiac injury; reversible causes should be sought and promptly treated. Supportive ICU therapy should continue concurrently for all patients. Neuromuscular blockade and sedation may be weaned as tolerated. In some cases, commonly the bridge-to-lung transplant setting, ECMO is performed in awake and spontaneously breathing patients. Ventilator settings are managed at low settings to allow for lung rest. Some have advocated for extubation of these awake patients [37]. Hemodynamics often improve after beginning ECMO support, allowing the discontinuation of vasopressors. Fluid shifts and blood product consumption may persist for variable periods, thought to be secondary to blood exposure to the nonbiologic extracorporeal circuit [51, 52]. Continuous renal replacement therapy to assist with volume management can be used concurrently with ECMO, with the dialyzer incorporated directly into the ECMO circuit.

Pharmacokinetics are affected by the ECMO therapy. The circuit increases the overall volume of distribution and many medications are known to adhere to circuit components [53]. The kinetics may additionally be modified by acute kidney injury or continuous renal replacement therapy. Sedation and antibiotic therapies seem to be appreciably affected and often require increased dosing [54]. When available, drug-level monitoring should be performed to ensure adequate dosing and avoidance of toxicity or subtherapeutic concentrations.

Surgical procedures from venipuncture to liver transplantation can be done with success while on extracorporeal support; however, the hemorrhage risk may be substantial. The absolute necessity of every procedure should be questioned to minimize the risk to the patient. Even small procedures, including tube thoracostomy, should be performed with liberal use of electrocautery. When an operation is necessary, anticoagulation may be held and even cautiously reversed, taking into consideration the risk of thromboembolic events and acute, life-threatening circuit failure.

Circuit Management

The extracorporeal circuit can be adjusted to meet gas exchange needs. Oxygenation is primarily proportional to the blood flow rate and the surface area of the membrane lung; it is managed by titrating pump speed. Oximetric measurements from the drainage limb of the circuit may be used as a surrogate for mixed venous saturation and thus provide a measure of the adequacy of oxygenation. In VV ECMO, this measure may be falsely elevated by recirculation (oxygenated blood from the reinfusion cannula crossing directly into the drainage limb rather than entering the right heart). In VA ECMO, oxygenated blood returns retrograde through the aorta so flow dynamics must be monitored closely to ensure adequate cerebral perfusion. The native cardiac circulation may exceed circuit flow, causing only the lower half of the body to be perfused, which is referred to as the Harlequin or North-South syndrome. The retrograde flow may also result

in significant venous admixture and lowered arterial oxygen saturations. In these cases, a high hematocrit target has been advocated to maintain oxygen delivery in the face of relative hypoxemia. Ventilation is managed by titrating the sweep gas flow through the membrane lung. CO_2 clearance can be accomplished at lower blood flow rates, permitting the use of lower flow arteriovenous ECMO or extracorporeal CO_2 removal for patients with hypercarbia.

Systemic anticoagulation is required to prevent circuit clotting. The ideal goal and the best method of anticoagulation monitoring are not known. Regular monitoring of platelet levels is recommended; platelet consumption at the oxygenator interface may necessitate regular platelet transfusion to prevent thrombocytopenia in the anticoagulated patient. Hemolysis can also occur and free hemoglobin should be checked daily. Values greater than 10 mg/dL require further investigation to identify the cause of hemolysis. Circuit-related hemolysis is caused by cavitation that occurs when blood is exposed to significant negative pressure or repeated cycles of transient low flow, known as "line chatter" [55].

Weaning is the strategic decrease in extracorporeal support to assess if a patient can be sustained without it. In VV ECMO, a slow, systematic decrease in circuit flow, sweep rate, or a combination of the two is initiated while monitoring for adequate oxygenation and ventilation. Lung recruitment may be necessary if substantial collapse has occurred. The patient should be monitored for signs of pulmonary fibrosis that may have developed while on ECMO support. This presents as pulmonary hypertension and right-sided heart failure and is fatal. In weaning VA ECMO, the flows are decreased while simultaneously assessing tissue-level perfusion. Echocardiography is used to assess native cardiac function. Inotropes, vasotropes, and vasodilators are typically necessary and their use does not equate to an unsuccessful wean. Trialing is the process of temporarily discontinuing ECMO after the patient has been weaned to less than 30 % of native heart or lung function. Cannulae are removed 24 h after a successful trial off of support.

A concern for futility of treatment should be raised if a patient has been placed on ECMO but the therapy appears to be ineffective or if there is no evidence of recovery. The duration of time after which this determination should be made is unknown and thresholds are rapidly evolving. Historically, respiratory survival was felt to be poor after 2 weeks [56] and cardiac survival after 5 days [57]. More recently, patients have been sustained on prolonged ECMO support [58] and data from the ELSO registry suggest that even after 14 days of support, while survival rates are lower than in shorter runs, they have improved to 48 % over the period from 2007 to 2013 [74]. The potential for late pulmonary recovery is also not known, and the decision to discontinue support for futility should be periodically reevaluated by a multidisciplinary team.

Multidisciplinary Team

A dedicated institutional infrastructure is mandatory for safe ECMO practice. A multidisciplinary team approach to caring for ECMO patients is necessary for the best outcomes [59]. This team includes physicians, nurses, respiratory therapists, pharmacists, dieticians, and care coordinators. Many centers have elected to have a dedicated ECMO team member stationed at the bedside to supervise the circuit who works along side with the bedside nurse providing direct patient care. As ECMO circuits continue to become simpler and easier to manage, the bedside care model will likely continue to evolve, and careful attention must be paid to workload and safety considerations, including alarm fatigue.

The increased use of ECMO in adult patients has led to a proliferation of centers and has brought renewed focus on considerations of training, credentialing, optimal practice, and regionalization of service. A recent position paper on the organization of ECMO programs for adult acute respiratory failure encouraged practice in centers with sufficient experience volume and expertise to ensure safe use [60]. Interpretation of individual center outcomes must be carefully considered; with the absence of clear consensus indications for ECMO, survival reporting is prone to bias from patient selection. Nevertheless, age-specific volume outcome relationships have been demonstrated in registry studies of neonatal and adult, but not pediatric populations [61].

Outcomes

Survival

ECMO has a reported survival of 55 % when used for respiratory support and 40 % for cardiac support [62]. Mortality is associated with many factors including advanced patient age, pre-ECMO arterial pH, increased duration of pre-ECMO ventilation, decreasing patient weight, underlying cause of respiratory failure, the presence of complications, gender, and the initial PaO_2/FiO_2 ratio [13, 18]. To help practitioners stratify the risk of ECMO for individuals with respiratory failure, the Respiratory ECMO Survival Prediction (RESP) score has been developed [63]. This score uses 12 pre-ECMO variables to determine a probability of survival after ECMO (Table 10.1). Unfortunately, no similar score for cardiac failure patients has been developed. A key caveat in using prognostic scores for patient selection is that as they are derived from selected cohorts consisting only of patients who received ECMO, the corresponding outcomes of similar patients who did not receive ECMO cannot be considered.

Table 10.1 RESP score for risk stratification of respiratory failure patients

Parameter		Score
Age, yr		
18–49		0
50–59		−2
≥60		−3
Immunocompromised status*		−2
Mechanical ventilation prior to initiation of ECMO		
<48 h		3
48 h to 7 day		1
>7 day		0
Acute respiratory diagnosis group (select only one)		
Viral pneumonia		3
Bacterial pneumonia		3
Asthma		11
Trauma and burn		3
Aspiration pneumonitis		5
Other acute respiratory diagnoses		1
Nonrespiratory and chronic respiratory diagnoses		0
Central nervous system dysfunction†		−7
Acute associated (nonpulmonary) infection‡		−3
Neuromuscular blockade agents before ECMO		1
Nitric oxide use before ECMO		−1
Bicarbonate infusion before ECMO		−2
Cardiac arrest before ECMO		−2
$PaCO_2$, mm Hg		
<75		0
≥75		−1
Peak inspiratory pressure, cm H_2O		
<42		0
≥42		−1
Total score		−22 to 15
Hospital survival by risk class		
Total RESP score	*Risk class*	*Survival*
≥ 6	I	92 %
3–5	II	76 %
−1 to 2	III	57 %
−5 to −2	IV	33 %
≤−6	V	18 %

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ECMO extracorporeal membrane oxygenation; *RESP* Respiratory ECMO survival prediction; An online calculator is available at www.respscore.com.
* hematological malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.
† diagnosis combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome.
‡ another bacterial, viral, parasitic, or fungal infection that did not involve the lung.

Complications

Complications are a common occurrence in patients supported with ECMO and are associated with increased mortality [18]. Hemorrhage is the most frequently cited complication, occurring in approximately 30–40 % of patients [3, 64]. Cannula sites, surgical sites, and the airway are the most common hemorrhage locations. Hemorrhage on ECMO is managed supportively by transfusing blood products and platelets, decreasing or temporarily discontinuing anticoagulation, and, on occasion, administering antifibrinolytics. The risk of circuit dysfunction, thrombus formation, and embolus must be weighed against the risk of bleeding [65]. Infection is another commonly reported complication. Infection risk has been correlated to the duration of ECMO support [66], but routine surveillance with cultures, however, has not shown to add value, improve outcomes, and is therefore not recommended [67]. Limb-threatening ischemia has been observed in approximately 17 % of cases when the femoral artery is cannulated for VA support. Perfusion of the distal extremity with retrograde posterior tibial catheters or antegrade percutaneous femoral catheters [68] may permit limb salvage while leaving the cannula in situ; however, amputation rates are estimated at 5 %.

Equipment-related failures also contribute to patient complications. While much work has been done to mature extracorporeal technology, circuit failures (rupture, clotting) are estimated to occur in 2–20 % of patients [18]. Oxygenator run time rates vary widely and are a significant contributor to equipment-related complications.

Long-Term Outcomes

Data on long-term outcomes for patients supported with ECMO is limited. Reports on this topic have focused on the pediatric population and on adult ARDS patients. In pediatrics, survivors are reported to have normal lung function and normal growth at an older age, but neurodevelopment problems are often noted [69]. In the adult studies, many had ongoing pulmonary symptoms but these symptoms were less than those of similar but conventionally treated patients [70, 71]. The symptoms, as well as degree of lung fibrosis, appeared to correlate with the duration of ECMO support. Additionally, approximately three quarters of survivors were able to return to their former occupations. Further research in this area remains a priority.

Future Applications

Individual centers continue to apply ECMO technology in unique and innovative ways. Investigations in the areas of ARDS, COPD, resuscitation, and inter-facility transport continue. In transplantation, one such approach is extracorporeal support-assisted organ donation after cardiac death. ECMO has been initiated after pronouncement of death to restore

perfusion of abdominal organs in hopes of improving organ quality [72] and potentially increasing the number of organs available for transplantation. Additionally, researchers have used ECMO in ex situ perfusion of individual organs. The most progress has been made with pretransplant pulmonary perfusion; human lungs donated for transplant have been supported with a modified ECMO circuit for up to 6 h and then successfully transplanted [73]. Further research will be necessary before this technology becomes routinely incorporated into practice.

Conclusion

ECMO remains a promising lifesaving therapy for critically ill adults in acute pulmonary and cardiac failure who have failed conventional management. Since it was first described in the 1970s, its use has grown rapidly and more liberal application has been considered. The components of the circuit have greatly matured, making the therapy more reliable and practical to implement. Complications are still common, and thus further advances, particularly in circuit thromboresistance to reduce the need for anticoagulation, will be critical in minimizing the inherent risks of ECMO therapy. Increased use has also spurred further considerations of optimal practice, credentialing, and regionalization of practice. Additional randomized trials are needed to clarify the appropriate indications and best practices for this lifesaving therapy.

Additional Resources

The Extracorporeal Life Support Organization (ELSO) is an international consortium of healthcare professionals and scientists devoted to the development of life support therapies. ELSO has developed a Web site that contains a member list with contacts, management guidelines [7], references, and training and education materials on ECMO: http://www.elso.org.

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Acute Respiratory Distress Syndrome and Lung Protective Ventilation

11

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Introduction

We begin with a note on terminology. ARDS was first described in 1967 as acute respiratory failure unresponsive to supplemental oxygen but improved with the use of PEEP [1]. Despite that early description, however, research in and clinical diagnosis of ARDS was limited by the lack of a consistent and reproducible definition. In 1994, the American-European Consensus Conference (AECC) attempted to provide a uniform definition, using criteria including a strict cutoff for the level of hypoxemia ($PaO_2/FiO_2 \leq 200$), bilateral infiltrates on chest X-ray, and the absence of left atrial hypertension, as well as describing a milder entity of acute lung injury (ALI) [2]. However, confusion remained regarding the lack of an explicit time frame for "acute," variable PaO_2/FiO_2 ratios depending on ventilator settings, poor reliability of chest X-ray interpretation, and difficulties in assessing left atrial hypertension [3, 4].

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More recently, a novel approach combining consensus discussion with empiric evaluation of patient data was used to revise and update the criteria for ARDS, resulting in the Berlin Definition in 2012 [3]. This definition describes three mutually exclusive categories of mild, moderate, and severe ARDS based on PaO_2/FiO_2 ratios of 201–300, 101–200, and ≤100, respectively (eliminating the term ALI). The Berlin Definition, upon empiric analysis, provided better predictive validity for mortality than the AECC definition and demonstrated a significant association with the duration of mechanical ventilation (see Table 11.1) [3].

Additionally, a period of less than 7 days was used to define "acute" onset, and the previous requirement of pulmonary artery occlusion pressure (PAOP) was removed. Clinical judgment in characterizing hydrostatic pulmonary edema was deemed sufficient, unless there is no apparent risk factor for ARDS (in which case an objective evaluation is required). A PEEP value of ≥5 cm H_2O was added to the definition, though no additional levels of PEEP and FiO_2 were included (as these effects were less relevant to outcome with increasing severity of ARDS). In a post hoc analysis, static respiratory compliance ≤20 mL/cm H_2O and corrected expired volume per minute ≤13 L/min did identify a subset of patients with severe ARDS with higher mortality; however, these variables were not included in the definition [3].

The Berlin Definition for ARDS provides a valid and reliable tool for clinicians and researchers alike. But despite increasing clarity in diagnosis and definition, ARDS remains a heterogeneous syndrome with varying etiologies and pathophysiologic responses [5]. Surgical patients are particularly susceptible, due to the development of alveolar instability associated with operative and injury-related changes, and concomitant predisposing conditions such as shock, sepsis, traumatic brain injury (TBI), and multiple fractures [6–8]. Moreover, the morbidity and mortality associated with ARDS continues to have substantial impact on health-care expenditure and public health, despite advances in intensive care unit (ICU) management and an overall decline in incidence of ARDS in recent years [9–11].

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Table 11.1 Predictive validity of AECC vs. Berlin Definition for outcomes in ARDS

		Berlin Definition		
Outcome	AECC	Mild	Moderate	Severe
Mortality, percent (95 % CI)	37 % (35–38)	27 % (24–30)	32 % (29–34)	45 % (42–48)
Duration of mechanical ventilation, median days (IQR)	7 (4–14)	5 (2–11)	7 (4–14)	9 (5–17)

Modified from ARDS Definition Task Force et al. [3]

The authors of this chapter are intensivists with diverse backgrounds (anesthesiology, family medicine, pulmonology, and surgery), reflecting the multidisciplinary approach necessary for the optimal treatment and understanding of such an indiscriminate disease. Herein, we provide a comprehensive review of current strategies for MV, pharmacologic and non-pharmacologic adjuncts to MV, and special situations pertaining to the surgical patient population. This is not intended to be a basic chapter on pulmonary physiology and MV – with information that can be found in other critical care texts – but rather an in-depth discussion of current debates, evidence-based guidelines, and critical care principles as they apply to ARDS.

Approach to MV in ARDS

The pathophysiologic manifestations of ARDS result in impaired oxygenation and reduced lung compliance, making MV the mainstay of treatment [5]. However, potential harm from ventilator-induced lung injury (VILI) may worsen outcomes via multiple mechanisms, including barotrauma, alveolar overdistention (volutrauma), repeated cycles of alveolar collapse and reopening (atelectrauma), and release of inflammatory mediators (biotrauma) [12–16]. Furthermore, the release of inflammatory mediators that potentiates the pathophysiology of ARDS may also contribute to the development of multi-organ dysfunction [17, 18]. Thus, a balanced approach to MV – achieving *adequate* (not necessarily *normal*) gas exchange, while minimizing the risk of further lung injury – must be undertaken [12].

In 1992, B. Lachmann proclaimed "Open up the lung and keep the lung open" in an editorial regarding optimal ventilatory strategies in ARDS [19]. The examination of various treatment modalities that followed led to the current "open lung" strategy of lung protective ventilation, which combines the avoidance of high peak inspiratory and plateau pressures, use of low V_T, and lung recruitment with *appropriate* levels of PEEP, and has demonstrated survival benefit in patients with ARDS [20–24]. While this has become the de facto standard of care, there remains some uncertainty regarding the evidence for each of these individual aspects of ventilatory management [25–27].

In ARDS, due to edema, atelectasis, and consolidation, only a small area of relatively unaffected (and more compliant) lung is available for ventilation and gas exchange [5]. The term "baby lung" has been used to describe this phenomenon, with the implication that patients with ARDS should be managed according to this smaller lung area, in order to prevent further lung injury [28]. Judicious management of V_T and airway pressures, therefore, would seem to be important in considering the most appropriate lung protective strategy. We examine each of these in the following paragraphs.

The avoidance of volutrauma in lung protective ventilation strategies was studied in the seminal ARDS Network trial, which became very influential in the treatment of patients with ARDS [20]. This multicenter, randomized controlled trial (RCT) compared V_T of 6 mL/kg ideal body weight (IBW) and plateau pressures (Pplat) <30 cm H_2O, with more traditional V_T of 12 mL/kg IBW and Pplat <50 cm H_2O. The trial was stopped early when interim analysis demonstrated significantly lower mortality, 31.0 % vs. 39.8 %, $p = 0.007$, for the low V_T group [20]. Several additional studies and meta-analyses have confirmed a reduction in mortality for patients with ARDS using pressure and volume-limited ventilation [21–23, 29, 30].

Despite the significant impact of the ARDS Network trial, it remains difficult to parse out the respective influence of pressure and volume limitation in lung protective ventilation. Any discussion of pressure variables is further complicated by the question of which pressure to manage and in what way: peak inspiratory pressure (PIP), Pplat, mean airway pressure (mPaw), PEEP, etc., or in fact some other variable such as driving pressure (ΔP) [27].

High peak inspiratory and plateau pressures can result in hemodynamic compromise and were initially thought to cause barotrauma [31–33], a well-known complication of ARDS which manifests as extra-alveolar air (resulting clinically in pneumothorax, pneumomediastinum, subcutaneous emphysema, or air embolism). However, subsequent investigations demonstrated a correlation of barotrauma only with high levels of PEEP and not with peak, mean, or plateau pressures [34–36]. While barotrauma may no longer be ascribed to high PIP or Pplat, subsequent studies have continued to limit them as part of a lung protective strategy. In

fact, limiting these pressures has demonstrated a protective effect (in combination with other variables) in humans, as noted in the ARDS Network trial and others, though the mechanism is unclear [20, 21].

Interestingly, the same animal studies that indicted high PIP and Pplat as putative causes of barotrauma also provided the first suggestions of a protective effect of PEEP [31, 37]. The effect of PEEP in humans (in the setting of low V_T ventilation for all patients) has been studied in three rigorous clinical trials, which individually did not demonstrate a survival advantage for higher levels of PEEP but did demonstrate lower rates of refractory hypoxemia and decreased use of rescue therapies [38–40]. Meta-analysis of these trials did, however, show a decreased mortality rate for the higher PEEP group, in patients with $PaO_2/FiO_2 \leq 200$ (now defined as moderate to severe ARDS), of 34.1 % vs. 39.1 % (adjusted RR 0.90; 95 % CI 0.81–1.00; $p = 0.049$) [24].

In addition to keeping the lung open with PEEP, recruitment maneuvers (RMs) have been used to reopen collapsed alveoli in attempts to increase the lung volume available for gas exchange [41, 42]. While multiple techniques have been described, RMs generally involve a sustained high-pressure inflation of 30–50 cm H_2O for 20–40 s, which may be followed by an increase in PEEP to potentiate the effect [41, 43]. The potential benefit of (at least transient) improvements in oxygenation, however, must be weighed against the risk of overdistention of healthy alveoli and possible hemodynamic effects of increased transpulmonary pressure and is not routinely recommended other than on an individualized basis [26, 42]. One caveat to this, though, may be in the intraoperative setting, as discussed further below.

It is certainly worth noting that a consequence (while not necessarily a deliberate strategy) of pressure and volume-limited ventilation is permissive hypercapnia [44–47]. In fact, there has been some suggestion that hypercapnic acidosis in ARDS may have an intrinsic protective effect beyond its associated ventilation strategies [48, 49]. However, surgical patient populations with concomitant cardiovascular disease or traumatic brain injury may suffer from the negative inotropic effects or increased intracranial pressure associated with hypercapnia, which should be avoided in these groups (either through ventilator strategies or medical management with buffering agents, to produce an offsetting metabolic alkalosis) [47].

Investigations of the effect of mPaw, which can potentially minimize both overdistention and atelectasis, have been most common in the study of high-frequency oscillatory ventilation (HFOV) and APRV – further discussion of mPaw follows in the section on alternate approaches to MV.

As we continue to try to determine the relative importance of these various modalities with respect to survival in patients with ARDS, recent data has emerged that the most relevant ventilation variable may be ΔP [27]. Using multilevel mediation analysis, the data from 3,562 patients with ARDS from nine previously reported RCTs was retrospectively analyzed. This demonstrated that ΔP was the variable most strongly associated with survival and may help explain some of the conflicting results seen in previous trials – since reductions in V_T or increases in PEEP in this analysis were beneficial only if they were associated with decreases in ΔP [27]. While this study does not establish causality, it does promote a better understanding of the potential impact on outcome when one variable affects another (e.g., when Pplat is affected by PEEP) and provides intriguing evidence that may be used to design additional clinical trials.

Alternate Approaches to MV

While the open lung strategy, based largely on the ARDS Network trial using volume-controlled ventilation (VCV) [20], has garnered the most supportive evidence in patients with ARDS, there is little data available regarding actual patterns of use of various modes of ventilation [50]. It is the authors' experience, however, that practice patterns vary widely by hospital and by region, based on familiarity and training. While generally termed "alternate" or "rescue" strategies, modes of ventilation other than VCV have also been a focus of research in patients with ARDS, most notably, high-frequency oscillatory ventilation (HFOV) and APRV [25, 26]. The use of nonventilatory adjuncts as rescue therapies is discussed later in the chapter.

HFOV delivers *very* small tidal volumes (~2 mL/kg ideal body weight) around a relatively constant high mPaw, at frequencies of 3–15 Hz (a respiratory rate >>100 breaths per minute), oscillating a bias gas flow in the airway [51–53]. In theory, HFOV addresses the pathophysiology of ARDS and mechanisms of injury associated with VILI while maintaining adequate gas exchange and has thus sparked interest in its clinical application [12]. Early data suggested an improved survival associated with HFOV [54, 55]. However, two long-awaited, larger multicenter RCTs (Oscillation for ARDS Treated Early, OSCILLATE, and OSCillation in ARDS, OSCAR) [56, 57], as well as subsequent meta-analysis [58], failed to show improvement in mortality with HFOV compared to conventional lung protective ventilation. The OSCILLATE trial was, in fact, stopped early due to higher mortality in the HFOV group, 47 % vs. 35 % (RR 1.33; 95 % CI 1.09–1.64; $p = 0.005$) [56]. While these results may have been impacted by issues of patient selection and details of study protocol, caution must be used in the application of HFOV in patients with ARDS [59].

APRV was first described in 1987 [60], and although its use continues to increase, it is still relatively unfamiliar to

many clinicians [61]. APRV is a pressure-limited, time-cycled mode of ventilation that alternates between two airway pressures (P high and P low), with the majority of the total cycle time spent at P high (T high), in order to prevent atelectasis and promote alveolar recruitment and stability, thus allowing for more efficient diffusive ventilation [26, 52, 61, 62]. As a result of the extended duration of this continuous positive airway pressure (CPAP) phase, APRV produces a minimal dynamic strain component on the lung (which is known to be injurious) [63]. A brief intermittent pressure release to P low retains end-expiratory lung volume and allows for convective alveolar ventilation and exchange of CO_2. Unlike pressure-controlled inverse ratio ventilation (PCIRV), APRV allows for spontaneous breathing during the entire respiratory cycle, which has demonstrated multiple benefits including improved organ perfusion, cardiac performance, patient comfort, and reduced need for heavy sedation [64–69]. In addition, APRV provides precise and individualized control of the duration of both the P high and P low phases, rather than using a fixed inspiratory/expiratory (I/E) ratio. Furthermore, given the high mPaw achieved with APRV, and subsequent alveolar recruitment, hypoxic pulmonary vasoconstriction (HPV) is greatly reduced [64, 70, 71].

With respect to clinical outcomes, APRV has demonstrated improved oxygenation and gas exchange, with an equivalent safety profile, compared to more conventional modes of ventilation [72–74]. As such, it would seem an attractive mode for patients with ARDS. However, the clinical evidence in humans has been relatively limited to date and is comprised of retrospective cohort studies and small RCTs [64, 72, 74–77]. Only one RCT (with 63 patients enrolled) has compared APRV with a low V_T ventilation strategy and did not demonstrate any significant difference in mortality [74].

In contrast, individual institutions with extensive knowledge and wide use of APRV have demonstrated that *early* application of APRV (rather than as a rescue mode) may help to prevent ARDS and reduce mortality in high-risk trauma patients, both in longitudinal data, as well as compared to similar patient populations undergoing conventional ventilation at other institutions [75, 78]. This is further supported by animal data showing that APRV may prevent VILI (and subsequently ARDS), thus making it more efficacious as a preventive strategy [79–82]. Definitive evidence of improved patient outcome for APRV, in well-designed and adequately powered RCTs, however, is still lacking.

Nonventilatory Adjuncts to MV

While MV is the cornerstone of support for patients with ARDS, various adjunct therapies have been utilized when hypoxemia persists, in attempts to achieve better patient outcomes. These include NMBA, conservative fluid management, corticosteroids, inhaled vasoactive medications, prone positioning, and ECLS (see Table 11.2). Many of these strategies continue to stimulate debate and fuel ongoing research regarding their effectiveness. As a result, individual institutions and practitioners must carefully weigh the risks and benefits when deciding whether or not to implement these treatments.

Table 11.2 Adjuncts to mechanical ventilation

Adjunct	Recommendations
NMBA	Short (48 h) course in early ARDS, with train-of-four and blood gas monitoring
Conservative fluid management	Goal net even fluid balance (note contraindications listed)
Corticosteroids	Long (14 days) course, started within 72 h of diagnosis, followed by gradual weaning
Inhaled nitric oxide (iNO)	May be used as short-term bridge in life-threatening hypoxemia
Prone positioning	Early proning (within 48 h of diagnosis) for ≥16 h/day, up to 28 days
V-V ECMO	Referral to ECLS center should be considered for patients who have failed despite optimized MV and adjuncts

NMBA have been widely studied in the management of patients with ARDS, though their implementation and monitoring is variable [83–85]. Three prospective RCTs have demonstrated improved oxygenation in patients with moderate to severe ARDS with the use of NMBA, although the mechanism for this remains unclear [86–88]. The largest and most recent RCT (the French ARDS et Curarisation Systematique or ACURASYS) demonstrated that patients treated with a short course (48 h) of NMBA early in the onset of ARDS were found to have reduced duration of MV and improved 90-day mortality (31.6% compared to 40.7%, $p=0.08$), with no increase in critical illness myopathy (CIM) [88]. These results were confirmed in subsequent reviews and meta-analysis [89–91]. The beneficial effects of NMBA are thought to be multifactorial: improved patient-ventilator synchrony, improved chest wall compliance, and decreased oxygen consumption secondary to decreased work of breathing [88, 92, 93]. One study even demonstrated decreased pulmonary and serum concentrations of inflammatory markers in patients being treated with NMBA [87]. This may seem to contradict the demonstrated benefits of spontaneous breathing in patients with ARDS, but it is important to note that patients in the ACURASYS trial were transitioned to the weaning process (using pressure support and promoting spontaneous breathing) immediately following the period of initial NMBA infusion [94]. Additionally, despite some early concerns, there was no association demonstrated between NMBA and CIM [88, 90, 92].

There has also been substantial interest in the role of conservative fluid management strategies in the treatment of patients with ARDS. The state of increased microvascular permeability present in ARDS potentiates pulmonary edema that may be caused by increased hydrostatic pressure associated with fluid administration [95, 96]. In 2006, the ARDS Network published a comparison of conservative and liberal strategies of fluid management [97]. There was no significant difference in 60-day mortality, but the conservative strategy demonstrated improved oxygenation and decreased duration of MV [97]. In patients with ARDS who are also hypoproteinemic, albumin administration in conjunction with diuretics in a conservative fluid management strategy may also improve oxygenation but is not associated with improved survival [98, 99]. In surgical and trauma patient populations, however, the role of conservative fluid management is usually limited, since it is not recommended for patients who are hypotensive, are oliguric, have recently received vasopressors, or have a central venous pressure (CVP) <4 mmHg [91, 97, 100, 101].

Corticosteroid utilization to address the fibro-proliferative and inflammatory response in ARDS continues to generate debate. Yet another ARDS Network trial examined the use of methylprednisolone in established courses of ARDS (at least 14 days after onset) and, despite improvements in oxygenation and reduced duration of MV, showed a significant increase in 60- and 180-day mortality [102]. Conversely, a later study suggested a trend toward decreased mortality, but patients in this study received corticosteroids *early* (within 72 h of being diagnosed with ARDS) [103]. Meta-analysis has confirmed a trend toward, and in some cases a statistically significant, reduction in mortality with the use of early corticosteroids, without any increase in infectious or CIM complications [104, 105]. As a result of the current evidence, a long course (at least 14 days) of methylprednisolone administration, followed by gradual weaning, may be considered in patients with early severe ARDS [106, 107].

Inhaled nitric oxide (iNO) improves oxygenation due to selective pulmonary vasodilation, which improves ventilation perfusion (V/Q) mismatch and decreases pulmonary arterial pressure [91]. It has been shown in multiple trials and meta-analyses to improve short-term oxygenation in patients with ARDS but without any impact on duration of MV or mortality [108–115]. The use of iNO should be limited to short-term rescue for life-threatening hypoxemia [25, 91]. Inhaled prostacyclins have been investigated as alternatives to iNO, due to their lower cost and similar effects on oxygenation, though evidence to support their use is lacking [91, 110, 116].

Another strategy to improve outcomes in patients with severe refractory hypoxemia in ARDS is prone positioning. The mechanism of improvement is again multifactorial, including increased alveolar recruitment and ventilation in the dorsal pulmonary segments, decreased shunt physiology, and decreased pulmonary compression by the heart [117, 118]. Early studies consistently showed prone positioning to improve oxygenation and gas exchange; however, mortality benefits were not shown [119–122]. Subsequent meta-analysis, though, demonstrated improved mortality in patients with severe ARDS [123, 124]. This prompted further investigation in the Proning Severe ARDS Patients (PROSEVA) trial, an RCT that showed significant reduction in mortality in patients with $PaO_2/FiO_2 < 150$ who were proned within 48 h of diagnosis of ARDS, for at least 16 consecutive hours/day up to 28 days (16.0 % vs. 32.8 %, $p < 0.001$), with no increase in complications compared to patients who were supine [125].

ECLS has been perhaps the most controversial adjunct to MV in patients with severe ARDS. ICUs that offer ECLS are specialized centers with focused providers. The goal is to allow for complete gas exchange by means of an extracorporeal membrane oxygenation (ECMO) circuit while minimizing VILI by using minimal settings on the ventilator, thus allowing "lung rest"[126]. Veno-venous ECMO (V-V ECMO) is most commonly used in isolated respiratory failure and employs large central venous catheters (via jugulofemoral or bifemoral placement) to remove blood from the body, circulate it through an oxygenator that allows for gas exchange, and return oxygenated blood to the patient [127, 128]. For years, the only data showing positive results for ECMO in adults were retrospective studies [129–132]. However, most recently, a multicenter prospective RCT (Conventional ventilation or ECMO for Severe Adult Respiratory failure, or CESAR) compared referral to an ECMO center to conventional treatment and showed improved 6-month mortality (63 % vs. 47 %; RR 0.69; 95 % CI 0.05–0.97; $p = 0.03$) [133]. Interestingly, only 75 % of the patients referred were actually placed on ECMO, which begs the question whether the survival benefit was due to ECMO per se or simply transfer to a facility with greater resources and expertise. Despite criticisms of the CESAR trial, it has sparked new debate regarding the advantages of ECMO. Especially relevant to the surgical patient population are reports of its successful use in patients with TBI and multiple injuries, in which heparin-bonded circuits may be used in order to forgo systemic anticoagulation [134–137]. However, restraint is still advised, as the optimal techniques and clinical indications for ECLS continue to be clarified [138, 139].

In summary, many adjuncts to MV have been used in the treatment of ARDS and continue to undergo rigorous investigation. While some have demonstrated improvements in mortality, all the adjuncts discussed here have demonstrated improvements in oxygenation. As a result, these therapies may be considered in the setting of life-threatening hypoxemia despite optimized MV.

Intraoperative MV: A Setup for Disaster?

Although lung protective ventilation is the standard of care in ICU patients with ARDS, it is still not widely practiced in the operating room (OR) – in fact, the use of high V_T and zero PEEP is still commonplace, with fewer than 20 % of patients receiving protective ventilation in routine anesthetic practice [140, 141].

Early studies that investigated *intra*operative factors associated with *post*operative pulmonary complications (PPC) focused primarily on patient variables (age, smoking, arterial-alveolar differences, and pulmonary function tests (PFTs)), surgical events (estimated blood loss and transfusion volumes), and types of procedures (vascular, cardiac, abdominal), rather than the impact of MV itself on outcomes [142–144]. Even in a trial designed specifically to define risk factors for postoperative morbidity, parameters for MV during surgery were not examined [142]. Though there are currently no standardized guidelines for intraoperative MV, it is becoming increasingly clear that lung protective ventilation is one of the many important modalities associated with postoperative outcomes [145–147].

General anesthesia can result in both atelectasis and decreased pulmonary blood flow [148]. Intra-abdominal surgery can induce atelectasis due to the direct pressure of the operative field onto the (basilar) lungs. Atelectasis may also be present with lateral positioning, Trendelenburg, lithotomy, or intra-abdominal insufflation – even in patients who are previously healthy. Within 5 min of induction of anesthesia, increased densities have been shown in the dependent regions of both lungs [149]. Furthermore, pulmonary blood flow may be reduced for several reasons: systemic vasodilation, high V_T ventilation, patient position (blood flow may be decreased to nondependent areas), or HPV. HPV occurs when the partial pressure of oxygen in a given lung region falls, and vascular smooth muscle in the pulmonary circulation contracts in an effort to maintain V/Q matching. Vasodilators (including inhaled anesthetics) inhibit HPV [150] and may thus contribute to an increase in the shunt fraction; conversely, intravenous anesthetics do not have this effect [151].

Evidence supporting intraoperative lung protective ventilation strategies to improve oxygenation and respiratory mechanics, and to decrease PPC, has now been shown in several studies [152–156]. One prospective RCT in patients undergoing open abdominal surgery compared protective MV (V_T 7 mL/kg, PEEP 10 cm H_2O with RMs) to "standard" ventilation (V_T 9 mL/kg, zero PEEP): patients in the protective MV group had improved oxygenation, better PFTs, and fewer alterations in chest X-ray (CXR) postoperatively [145]. Recent meta-analysis also demonstrated an association between lower V_T and decreased rates of PPC (2.0 % vs. 4.7 %; RR 0.40; 95 % CI 0.22–0.70) [146].

To further confirm this finding in a large RCT, the Intraoperative Protective Ventilation (IMPROVE) investigators studied patients undergoing major abdominal surgery, with risk factors for PPC [147]. During anesthesia, patients were randomized to protective ventilation (V_T 6–8 mL/kg, PEEP 6–8 cm H_2O with RMs) vs. non-protective ventilation (V_T 10–12 mL/kg, zero PEEP, and no RMs). Over the 7-day postoperative study period, 5.0 % of patients in the protective group compared to 17.0 % of patients in the non-protective group required noninvasive ventilation (NIV) or intubation (RR 0.29; 95 % CI 0.14–0.61; $p = 0.001$). The protective ventilation group also demonstrated a significantly shorter hospital stay (mean difference −2.45 days; 95 % CI −4.17 to −0.72; $p = 0.006$) [147].

Once again, however, parsing the relative contributions of V_T and PEEP has not been straightforward. Several meta-analyses have shown a beneficial effect of higher PEEP: it has been associated with decreased rates of PPC (1.4 % vs. 4.9 %; RR 0.29; 95 % CI 0.14–0.60) [146] and reduced postoperative atelectasis [157]. However, this was not confirmed in the large PROtective Ventilation (*PROVE)* Network trial comparing high vs. low PEEP in the OR [158]. In 30 centers across Europe, North, and South America, patients at high risk of PPC undergoing abdominal procedures were randomized to high (12 cm H_2O) or low (≤2 cm H_2O) PEEP, using a consistent V_T of 8 mL/kg. PPC were seen in 40 % of patients in the high PEEP group and in 39 % in the low PEEP group; furthermore, patients in the high PEEP group had more hypotension and required more vasoactive medications [158].

The largest and most recent meta-analysis sought to clarify the role of intraoperative PEEP and the frequency of PPC [159]. As previously demonstrated, rates of PPC were lower in patients assigned to low V_T – but there was no statistical difference between low V_T/high PEEP and low V_T/low PEEP (8.9 % vs. 12 %; adjusted RR 0.93; 95 % CI 0.64–1.37; $p = 0.72$) over the 2,127 patients analyzed. Furthermore, there was no dose-response relationship found between rates of PPC and level of PEEP ($R^2 = 0.08$) [159]. The optimal level of PEEP in intraoperative ventilation, therefore, remains unclear.

It is worth noting that many of the studies referenced above refer to specific types of surgery (neurosurgery, thoracic surgery, oncologic surgery, general surgery) and to patient populations with an increased risk of PPC due to preexisting comorbidities. The healthy patient undergoing elective surgery is not well studied with regard to optimal ventilator settings, and it is unknown if V_T or PEEP impacts their postoperative outcomes. Finally, there is also a paucity of data on the intraoperative management of trauma and acute care surgery patients – who may have been healthy prior to their precipitating event but then develop an inflammatory response and/or hemodynamic instability *before* they

reach the operating room. Given the increased mortality and substantial economic burden of PPC, further research on their prevention could have a great impact [160].

Summary

ARDS and PPC in surgical patients contribute substantially to mortality and to the economic burden on the health-care system – although progress has been made, and ARDS has shown recent declines. The Berlin Definition for ARDS will help clarify populations of interest in future studies. At present, the standard of care in MV for patients with ARDS remains an open lung protective ventilation strategy, with low V_T and relatively higher PEEP. A more nuanced understanding of the effect of pressure settings is beginning to emerge and may further delineate the most beneficial aspects of MV. Additionally, as further evidence accumulates, the *prevention* rather than the *treatment* of both ARDS and VILI may ultimately prove to be most efficacious, with strategies such as early APRV holding great promise. Finally, in the comprehensive management of critically ill surgical patients, the lines between ICU and OR often blur – making recent investigations of intraoperative lung protective strategies all the more important. Despite the already vast literature, there is more work to be done.

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Noninvasive Ventilation in the Perioperative Period

12

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Introduction and Physiology

Noninvasive ventilation (NIV) is defined as ventilatory support that is delivered in a spontaneously breathing patient without establishing an endotracheal airway [1]. Instead, noninvasive ventilation is delivered through a tight-fitting mask applied to the face.

Like mechanical ventilation via endotracheal intubation, the goals of positive pressure noninvasive ventilation are the same: correct the underlying respiratory abnormality by improving oxygenation, ventilation, or both. To accomplish this task, patients who have an indication for NIV are connected to a ventilator circuit via a nasal mask or face mask. Depending on the clinical scenario, the ventilator is then either set to a volume-controlled setting or a pressure-controlled setting. Earlier noninvasive ventilators used volume ventilation settings that allowed for the delivery of a specific volume during the inspiratory cycle and were shown to be associated with improvement in acute respiratory failure [2, 3]. However, this mode is more difficult to tolerate for patients, and as the ventilator automatically adjusts airway pressures to achieve a specified volume, it can result in high inspiratory pressures and air leaks around the face or nose mask [4].

Since the early 1990s, pressure-controlled settings have been more commonly utilized, and their success has been demonstrated across levels of care and a variety of indications. Specifically, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) are the two most commonly used modes of noninvasive ventilation both of which can be delivered either by standard ICU ventilators or portable ventilators. Almost every mode of ventilation that can be delivered invasively can also be delivered noninvasively. However, certain modes are used more frequently. Here we will discuss BPAP and CPAP modes, but it is important for the provider to be aware that alternative modes of ventilation can be utilized (pressure support ventilation, assist control, proportional assist ventilation). The use of noninvasive ventilation in the medical population with acute COPD exacerbations and acute cardiogenic pulmonary edema is well established and beyond the scope of this chapter. Here we will focus our review on the physiology, rationale for use, equipment, indications, contraindications, and complications of NIV in the preoperative, intraoperative, and postoperative populations.

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Continuous Positive Airway Pressure (CPAP)

CPAP applies a fixed amount of positive pressure to be delivered continuously throughout the respiratory cycle and as such is a constant pressure but variable flow mode. This mode increases the functional residual capacity without increasing the tidal volume resulting in decreased atelectasis and reduced work of breathing [5–9]. Since CPAP does not provide additional pressure during inspiration, it technically does not directly support ventilation, but it does exert some effects that can indirectly improve ventilation. For example, by mitigating against atelectasis through increased alveolar recruitment, CPAP decreases the ventilation-perfusion mismatch caused by non-ventilated alveoli and improves hypoxemia. However, because CPAP cannot increase tidal volume, it is not indicated in the treatment of hypercapneic respiratory failure.

Bilevel Positive Airway Pressure (BPAP)

BiPAP, on the other hand, delivers variable positive pressure assistance to the patient at different phases of the respiratory cycle, in contrast to a set pressure applied continuously

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throughout the respiratory cycle as in CPAP mode. The terms "BiPAP" and "BIPAP" are often used incorrectly to refer to NIV in the BPAP mode. "BiPAP" refers to the BPAP mode of ventilation delivered by a specific portable ventilator manufactured by Respironics Corporation. Similarly, "BIPAP" stands for biphasic positive airway pressure and refers to a time-cycled, pressure-controlled mode that is also a constant pressure variable flow mode with a period of flow cessation for CO2 clearance available on ventilators produced by Draeger Medical, Inc. These are just two of the many ventilators that can deliver BPAP. Once this mode of NIV has been selected, the provider must then select the inspiratory positive airway pressure (IPAP) value and the expiratory positive airway pressure (EPAP) value. Unlike CPAP, BPAP will vary the pressure support delivered during inspiration and expiration and therefore must use a sensor which triggers alternation between the two pressures. This trigger is usually a flow or volume trigger that detects flow, volume, or pressure at the proximal airways.

Once the ventilator detects that a patient is exhaling, it will maintain positive pressure assistance equal to the EPAP value. When inspiration is detected, the ventilator delivers positive pressure assistance equal to the IPAP value in addition to the EPAP, which is continuously delivered. For instance, if a ventilator were set to an EPAP of 5 cm H_2O and an IPAP of 10 cm H_2O, the machine would maintain 5 cm H_2O of positive pressure during expiration and deliver gas flow to establish 15 cm H_2O during inspiration. Commonly, inspiratory positive pressure assistance lasts until the ventilator detects a 25 % decrease in peak inspiratory flow or 3 s elapses, whichever comes first [5].

Like CPAP, BPAP increases the functional residual capacity and can recruit atelectatic lung segments, thereby decreasing shunting. Unlike CPAP, however, the addition of extra inspiratory pressure increases tidal volume. Augmentations in tidal volume subsequently cause increases in minute ventilation and thus give BPAP the ability to treat hypercapneic respiratory failure in addition to hypoxemic respiratory failure. Finally, the addition of IPAP also decreases the work of breathing and total lung resistance, which is particularly beneficial in patients who require BPAP for an acute or severe indication [5].

Rationale and Epidemiology

The most important advantage that NIV offers is avoidance of invasive endotracheal intubation and the associated deleterious effects including airway injury, sedation, and ventilator-associated infections and conditions. Unlike intubated patients, noninvasively ventilated patients have the ability to be liberated from the ventilator intermittently, which promotes progressive mobility, pulmonary toilet/coughing, eating, and speaking.

There is abundant high-quality evidence to recommend the use of NIV in specific medical conditions, including acute cardiogenic pulmonary edema, obstructive sleep apnea, and acute COPD exacerbations [10–12]. These indications allowed NIV to gain significant popularity and expand its applicability to medical patients over the last two decades. Increasingly, NIV is being applied to specific populations of surgical patients with similar improvements in outcomes as outlined later in this chapter.

Respiratory dysfunction in the postoperative patient represents a complex clinical challenge that differs from the medical patient. Intensive care providers must take into consideration several factors before using NIV for a postoperative patient including clinical status, surgical procedures performed including anatomic and physiologic alterations, and the potential for further surgical intervention.

Although supplemental oxygen administration and incentive spirometry are effective in treating mild postoperative hypoxemia, endotracheal intubation and mechanical ventilation may be required in 8–10 % of patients who develop acute postoperative respiratory failure [13]. The use of endotracheal intubation and invasive mechanical ventilation has been shown to increase the risk of nosocomial infections, utilization of critical care resources, prolong length of hospital stay, and increase overall morality [14]. There is compelling evidence that demonstrates the benefits of NIV for both the patient and health-care utilization through avoidance of invasive ventilation [12]. Additionally, increased recognition of postoperative patients' exceptional vulnerability to hypercapnia due to incisional pain, opioid agents, and unrecognized sleep apnea has led to increased use of NIV in the perioperative period.

Equipment

NIV can be delivered by standard ICU ventilators or portable ventilators. Modern ICU ventilators can provide higher inspiratory flow rates, have separate inspiratory and expiratory tubing which minimizes carbon dioxide rebreathing, are capable of delivering a higher fraction of inspired oxygen (F_iO_2), and have more appropriate monitors and alarms [15].

Interface

The ideal interface is one that minimizes air leakage and is most comfortable, thus promoting efficacy and compliance. The most commonly used interface in the critical care setting is the oronasal mask [16]. Other available interfaces include nasal prongs (pillows), a full-face mask (covers the mouth, nose, and eyes), a nasal mask, and a helmet. Regardless of the interface chosen, they should be properly fitted, comfortable, effective, and minimize leakage to maximize efficacy.

Equipment Complications

Patient discomfort and thus compliance with NIV is a limiting factor in its clinical applicability and contributes significantly to NIV failure rate. The most common complications of NIV equipment include air leakage, pressure ulceration, and patient-ventilator dyssynchrony.

Pressure Ulceration

Facial skin lesions, including ulceration and necrosis, are pressure-related lesions that result from prolonged contact with tight-fitting masks and predominantly develop on the bridge of the nose. Their development is directly related to the duration of NIV therapy. Factors that have been associated with formation of nasal skin lesions, and must be considered at initiation of NIV therapy, include progressive tightening of the harness, increasing the air volume in the mask cushions, and increasing inspiratory pressures [17].

Patient-Ventilator Dyssynchrony

Dyssynchrony occurs when the phases of ventilator-delivered breaths do not match with the patient's. This results in poor tolerance of NIV and can be alleviated by using an alternative ventilator mode (pressure support ventilation allows the patient to trigger each breath and may be more comfortable for some patients) or minimizing mask leaks [18]. Air leakage increases the time required for the ventilator to reach its pressure target, thus prolonging inspiration and causing discomfort.

Patient Selection

Prior to discussing the indications for NIV, it is important to understand the constituents of appropriate patient selection and the contraindications to NIV. Patient selection and continuous monitoring are critical to recognizing and reducing NIV failure. In general, the most important factors to consider when selecting patients for NIV are patient cooperation, ability to protect the airway, and their unique risk of aspiration. NIV should not be used in patients with altered mental status, severely agitated or obtunded patients, hemodynamically unstable patients, and those suffering from claustrophobia either due to an inability to cooperate or an impaired ability to protect their airway. Patients with obvious respiratory distress, proximal gastrointestinal hemorrhage, active emesis, facial trauma or burns, and those with neuromuscular dysfunction are at an increased risk of aspiration and should avoid NIV. These patients warrant prompt endotracheal intubation and mechanical ventilation. Similarly, patients with impending respiratory failure due to copious secretions that they are unable to clear are poor candidates for NIV.

Early Recognition of NIV Failure

Improvement in respiratory status is usually apparent within the first 1–2 h after initiation of NIV. The absence of improvement in a patient's respiratory status is a strong indication to promptly proceed with intubation. Delays in recognition of NIV failure and postponing invasive ventilation result in increased morbidity and mortality and should be avoided. Predictive factors associated with an increased risk of NIV failure include advanced age, high-acuity illness score at admission, presence of ARDS, sepsis, or multisystem organ failure (MSOF). In ARDS patients, an arterial oxygen tension/inspired oxygen fraction (P_aO_2/F_IO_2) ratio <175 mmHg drawn 1 h following initiation of a NIV trial accurately predicts failure [19].

NIV should be initiated and continuously monitored in a critical care setting with a multidisciplinary team familiar with this therapy and advanced airway techniques; NIV as rescue therapy is generally not appropriate for ward care. There is no established consensus on NIV failure criteria; however, general recommendations including failure to clinically improve, unrelieved dyspnea, worsening P_aO_2/F_IO_2 ratio, and increasing oxygen or pressure requirements should prompt transition to invasive ventilation. Should the provider anticipate failure, it is essential to promptly proceed to intubation while the patient is still able to adequately preoxygenate, allowing a safe window of time to perform endotracheal intubation. Patients requiring 100 % F_IO_2 on BPAP are prone to respiratory arrest due to a lack of pulmonary reserve and rapid desaturation during intubation. High-flow NC O2 may be used as an aid in maintaining oxygenation in the period between removing the BPAP mask and establishing a definitive airway.

Protocol for Initiating NIV

Parameters to be set upon initiation of NIV will be guided by the mode of ventilation chosen. Currently, there is not a universally accepted established protocol for initial NIV settings; however, general recommendations can be made. It is imperative to tailor the ventilator mode and settings to each clinical scenario and adjust parameters as needed to alleviate respiratory distress. Table 12.1 presents some commonly recommended settings for initiation of BPAP [16].

Specific Indications and Patient Considerations

NIV is now generally regarded as safe in most surgical patients and provides the most benefit to patients with rapidly reversible physiology (atelectasis, acute pulmonary edema, etc.) and patients with an oropharynx prone to

Table 12.1 Protocol for initiation of BPAP in the ICU

Ensure patient is an appropriate candidate for NIV
Patient is located in a monitored unit with, at a minimum, continuous pulse oximetry, blood pressure, and heart rate being monitored frequently
Elevate head of bed to at least 30°
Provide education and reassurance to patient and family members prior to application of interface to reduce patient anxiety and improve compliance
Apply a well-fitting mask, secure straps to patient's head
Turn on ventilator, select desired mode (BPAP, pressure-limited, flow-triggered) used in this example). Recommended initial settings: IPAP 8–12 cm H_2O, EPAP 4–5 cm H_2O
Respiratory rate: BPAP is a spontaneously triggered mode and can be set with or without a backup rate. If a backup rate is chosen, ensure it is lower than the patient's intrinsic respiratory rate to reduce discomfort. An initial rate of 8–10 breaths/min is usually appropriate
Supplemental oxygen: set the F_IO_2 at a level adequate to maintain oxygen saturations >90 %. Initial setting F_IO_2 of 0.35–0.40 is recommended
Monitor patient comfort, air leakage, and respiratory status. Draw an arterial blood gas within 1 h of NIV initiation. Failure to improve or reverse acute respiratory distress warrants intubation and invasive ventilation

This table describes one example of initial BPAP settings for noninvasive ventilation in perioperative patients with acute respiratory distress that do not require intubation. Initial pressures are set low to facilitate patient acceptance and compliance, but they can be titrated up to alleviate respiratory distress. Avoid pressures in excess of 20 cm H_2O

F_IO_2 fraction of inspired oxygen, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *NIV* noninvasive ventilation, *BPAP* bilevel positive airway pressure

obstruction. Below, we outline the use of NIV in the preoperative, intraoperative, and postoperative settings.

Preoperative NIV

NIV has been used preoperatively to successfully reduce postoperative pulmonary dysfunction after pulmonary resection [20, 21]. For OSA patients maintained on PAP therapy preoperatively, it is recommended to continue patients on their home PAP regimen preoperatively if clinically appropriate with regard to the surgical procedure [22].

NIV for Pre-oxygenation During Anesthetic Induction

Compared to high-flow oxygen administration by oronasal mask, the addition of positive pressure noninvasive ventilation, specifically CPAP, has been shown to improve pre-oxygenation prior to intubation of both hypoxemic patients in the intensive care unit and clinically severely obese patients in the operating room [23]. Increasing the duration of apnea without desaturation allows for a greater window of time for tube placement in the event of a difficult intubation. Prior to induction of general anesthesia, pre-oxygenation with supplemental oxygen for 3 min (or until fraction of excreted oxygen, F_eO_2, is >90 %) is considered sufficient to maintain adequate arterial oxygen saturations during the apneic period of endotracheal intubation. However, application of low-pressure CPAP (5–7 cm H_2O) plus 100 % F_iO_2 for 3 min prior to induction maintained higher arterial oxygen saturations during intubation and lower arterial carbon dioxide levels immediately following intubation suggesting improved oxygenation and ventilation [23].

Postoperative NIV

Abdominal Surgery

Increased recognition that postoperative patients are exceptionally vulnerable to hypercapnia due to incisional pain, opioid agents, and unrecognized sleep apnea has led to the increased use of NIV in the postoperative period [23]. Atelectasis is common after major abdominal surgery and can usually be managed successfully with supplemental oxygen and incentive spirometry. However, approximately 10 % of acutely hypoxemic patients currently require intubation and mechanical ventilation [24].

Recent clinical trials suggest a decrease in intubation rates with the use of CPAP for the treatment of atelectasis-induced acute hypoxemia following elective major abdominal surgery [24]. The proposed mechanism of atelectasis-related hypoxemia after abdominal surgery is the impairment of the pulmonary ventilation-perfusion ratio due to loss of functioning alveolar units caused by the recumbent position, high oxygen concentration, temporary diaphragmatic dysfunction/poor diaphragmatic excursion, impairment of pulmonary secretion clearance, pain, and potentially the absence of PEEP during intra-op mechanical ventilation [24].

As previously mentioned, administration of continuous positive airway pressure increases functional residual capacity, improves gas exchange, and promotes alveolar recruitment resulting in improved oxygenation. It is important to note that these benefits are not applicable to patients with any relative or absolute contraindication to NIPPV, and intubation should never be delayed in the setting of persistent respiratory failure. For the treatment of acute hypoxemia early in the postoperative period following major abdominal surgery, the use of CPAP in the ICU has been demonstrated to decrease the risk of pneumonia and re-intubation rates and

improve oxygenation faster compared to supplementation oxygen and chest physiotherapy alone [25].

Foregut Surgery

Application of postoperative NIV in patients with proximal foregut anastomoses remains a controversial topic. Despite emerging data strongly supporting the safe and effective use in this population, there remains a large resistance for acceptance and incorporation into clinical practice due to trepidations for excessive anastomotic stress and resulting leak [26]. These concerns stem from the *theoretical* risk that pressurized air applied to the oropharynx will be distributed between the lungs and the GI tract causing inflation of the stomach and proximal intestine. Thus, many surgeons have chosen to avoid NIV in this population given the morbidity and mortality associated with an anastomotic leak.

With increasing recognition that NIV decreases complications, length of stay, infections, and cost compared to invasive ventilation, this theoretical risk merits critical reappraisal. CPAP has been demonstrated to be safe in the immediate postoperative period following bariatric surgical procedures including Roux-en-Y gastrojejunostomy for use in their patients with preoperative OSA without increasing the risk of anastomotic leak or major postoperative complications [27, 28].

Most interestingly, a recent study using a porcine esophagectomy model captured in vivo esophageal pressures during NIV and the minimum esophageal pressures required to induce an anastomotic disruption. Esophageal pressures increased as more pressure was applied; however, the luminal pressures were profoundly lower than the minimum threshold required for the occurrence of an anastomotic leak in their model [29]. The spectrum of pressure applied to the oropharynx was 20–40 cm H_2O, and the corresponding median transmitted esophageal pressures detected were 5 cm H_2O, 11 cm H_2O, and 15 cm H_2O, respectively. The minimum esophageal pressure needed to induce a leak, in vivo, was 46 cm H_2O, demonstrating that the esophageal anastomosis can tolerate considerably higher pressures than is transmitted by NIV.

Several limitations apply to the aforementioned data and further investigation is needed before generalizability is applied, but this is an important foundation to suggest the safety of NIV in patients with a proximal foregut anastomosis. While anastomotic disruption is unlikely, gastric insufflation is a more common concern in these patients and can be limited by keeping the applied positive pressure less than 20 cm H_2O and judicious use of nasogastric tube decompression. In addition, large tidal volumes (800 mL–1,200 mL), high airway resistance, low respiratory system compliance, and short inspiratory time all increase airway pressure and promote gastric insufflation and should be limited when possible [19].

There is a paucity of data that demonstrate an increased risk of anastomotic complications from NIV in this population. With the accumulating human and laboratory evidence to suggest its safety and the lack of data to demonstrate NIV being harmful, the use of NIV has the potential to become more widely accepted in the postoperative management of foregut surgery [19, 26–29].

Thoracic Surgery

Patients undergoing lung volume reduction surgery (LVRS) or pulmonary transplantation represent a selected group of patients with advanced chronic respiratory disease and are at high risk of preoperative and postoperative complications. Respiratory distress requiring re-intubation in this patient population portends a very poor prognosis. Attempts are made to avoid endotracheal intubation with the use of BPAP, which has been demonstrated to be beneficial in both decreasing re-intubation rates and increasing hospital survival in several clinical trials [24, 30, 31]. BPAP is a useful adjunct in improving the postoperative course of lung surgery patients. Thus, noninvasive ventilation should be considered in selected postoperative patients at high risk of pulmonary complications or with frank respiratory failure, especially in the setting of underlying COPD or pulmonary edema.

Injured Patients

Several small studies have demonstrated that application of NIV following blunt thoracic trauma (flail chest, rib fractures, pulmonary contusions) results in lower intubation rates [32, 33], improves oxygenation, decreases endotracheal intubation rates, and lowers ICU length of stay [34]. However, caution must be exercised with the use of positive pressure ventilation in the setting of a preexisting pneumothorax. The potential for progression to a tension pneumothorax warrants treatment with tube thoracostomy decompression prior to initiation of positive pressure ventilation. Data is less clear with regard to progression to a clinically evident pneumothorax, when the pneumothorax is occult (visible only on CT but not plain radiography).

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a syndrome characterized by repetitive partial or complete upper airway obstruction occurring during sleep, resulting in recurrent self-arousal to restore airway patency. This cycle of disturbed sleep with frequent apneic episodes results in nocturnal oxygen desaturation and hypercarbia and is exacerbated in the perioperative patient due to the plethora of the aforementioned factors that impair level of consciousness and the integrity of the pulmonary system [22]. Postoperative patients are particularly prone to sleep apnea because of the changes in respiratory dynamics as a result of general anesthesia, opioid agents, and incisional pain [23].

In theory, the widespread use of supplemental oxygen via the nasal cannula in the immediate postoperative period may

blunt the respiratory drive of patients who have a hypoxic respiratory drive (as opposed the normal medullary proton concentration driven respiratory drive) and delay recognition of hypoventilation, putting these patients at further risk of postoperative pulmonary complications. In the perioperative and critical care setting, OSA represents a significant clinical challenge. It is crucial for the health-care team to have a better understanding of potential perioperative complications specific to these patients with the goal of improving morbidity and mortality.

Perioperative OSA Risk Assessment

Ideally, preoperative evaluations for elective operations would be completed in advance. This would allow for appropriate in-laboratory polysomnography confirmatory testing and therefore initiation of CPAP preoperatively. Rather, the majority of undiagnosed OSA patients are not recognized until postoperatively [22]. Untreated OSA patients are known to have a higher incidence of difficult intubation and postoperative complications, increased intensive care unit admissions, and greater duration of hospital stay [22]. Thus, identifying OSA patients preoperatively and initiating appropriate postoperative therapies are crucial for reducing perioperative morbidity and mortality.

The STOP-Bang questionnaire (Fig. 12.1) is a validated screening tool used to identify suspected OSA patients and risk stratify them into low, intermediate, and high risk for OSA based on an eight-question evaluation [35]. A score of 3 or more is indicative of intermediate risk and a score of 5 or more indicates high-risk for OSA. This stratification allows for appropriate management by the anesthesiology team in all phases of the perioperative setting.

The American Society of Anesthesiology Task Force recommends that known OSA patients previously on PAP therapy should be encouraged to be compliant with PAP therapy postoperatively, and PAP therapy should be ordered in the postoperative period [22]. High-risk, suspected OSA patients who develop recurrent apnea and hypoxemia in the postoperative recovery unit (PACU) should be monitored in a critical care setting and initiated on PAP therapy if the surgical procedure does not prohibit PAP use [22].

Immunocompromised Patients

Immunocompromised patients represent a population of critically ill patients who benefit significantly from NIV for treatment of acute respiratory failure. Avoidance of endotracheal intubation in this population dramatically reduces the risk of nosocomial infections and reduces ICU mortality. This benefit has been demonstrated in several different immunocompromised populations including solid organ transplant recipients [36], patients with hematologic malignancies [37], and acquired immunodeficiency syndrome (AIDS) patients with *Pneumocystis carinii* pneumonia [38].

Post-extubation Respiratory Failure

The use of NIV in post-extubation patients critically depends on two factors: patient selection and timing. Patients who are prone to atelectasis, fatigue requiring intermittent augmentation of work of breathing, and those with known OSA are most likely to benefit from NIV post-extubation [39]. It is important to note however that the data supporting this benefit is highly dependent on the timing of NIV initiation. There is a clear benefit in the prophylactic use of NIV immediately upon extubation in high-risk patients, prior to the development of acute respiratory failure post-extubation [40]. The use of NIV to treat established post-extubation respiratory failure, as opposed to prophylactic application, results in the delay of re-intubation and increased mortality [22, 41, 42].

Palliative NIV

As NIV gains popularity, there has been increased interest in the use of NIV for patients who have declined invasive life support measures. The utility of NIV in patients with acute respiratory failure who refuse intubation (DNI) or have chosen comfort measures only remains controversial. Palliative NIV is effective and should be considered in relieving symptoms of dyspnea, improving the patient's ability to communicate, and prolonging life to allow for affairs to be arranged [43, 44]. However, NIV can reverse nonterminal acute respiratory failure and therefore may be considered inappropriate when patients have chosen to limit life support near the end of their lives. It is important to consider noninvasive ventilation as an option when discussing comfort care measures with patients and family members. The decision to use palliative NIV should be guided by clear delineation of the patient's goals of care and may be optimized in conjunction with planned palliative care medicine consultation.

STOP-Bang Questionnaire

☐ Yes	☐ No	**Snoring?** Do you **snore loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
☐ Yes	☐ No	**Tired?** Do you often feel **tired,fatigued,or sleepy** during the daytime (such as falling asleep during driving)?
☐ Yes	☐ No	**Observed?** Has anyone **observed** you **stop breathing** or **choking/gasping** during your sleep?
☐ Yes	☐ No	**Pressure?** Do you have or are being treated for **High Blood Pressure?**
☐ Yes	☐ No	**Body Mass Index more then 35kg/m^2?**
☐ Yes	☐ No	**Age older then 50 years old?**
☐ Yes	☐ No	**Neck size large?(Measured around Adams apple)** For male, is your shirt collar 17 inches or larger? For female, is your shirt collar 16 inches or larger?
☐ Yes	☐ No	**Gender=Male?**

Scoring Criteria

Low Risk of OSA: Yes to 0 to 2 questions

Intermediate Risk of OSA: Yes to 3 to 4 questions

High Risk of OSA: Yes to 5 to 8 questions

Fig. 12.1 STOP-Bang questionnaire for preoperative OSA risk assessment. *OSA* Obstructive sleep apnea (Adapted with permission from Chung et al. [35])

Conclusion

Noninvasive positive pressure ventilation has been shown to reduce the need for endotracheal intubation, decrease rates of nosocomial infections, and decrease length of ICU stay in a variety of medical and surgical critical care populations including major abdominal surgery, immunocompromised patients, thoracic injury, and high-risk postextubation patients. More data will be needed, but emerging evidence suggests NIV can be safely used in patients with proximal foregut anastomoses, which has previously been regarded as a relative contraindication due to concerns for anastomotic leak risk. The success and efficacy of NIV relies heavily on several notable factors including proper patient selection, timing of NIV initiation, interface fit and comfort, patient compliance, and appropriate physiologic monitoring. Most importantly, the use of NIV should never delay endotracheal intubation in a patient whose clinical condition requires invasive ventilation for salvage. Noninvasive positive pressure ventilation is an important adjunct in our expanding

repertoire of therapies for respiratory dysfunction and, when properly applied, may improve perioperative patient outcomes in the critical care setting.

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Care of the Surgical ICU Patient with Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension

13

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Chronic Obstructive Pulmonary Disease

Overview and Epidemiology

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease characterized by airflow limitation that is frequently progressive and associated with respiratory impairment. As the fourth leading cause of death in the United States and Europe, COPD results in a substantial and ever increasing economic and social burden [1]. Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are frequently encountered in the intensive care unit (ICU). Although there is no standardized definition, AECOPD are characterized by a significant change in patient symptoms from baseline accompanied by overall increased airway resistance [2]. These exacerbations carry a significant risk to patients, with 10 % in-hospital mortality and 1-year and 2-year all-cause mortality rates of 43 % and 49 %, respectively, in patients with hypercapnic exacerbations [3]. Other studies note in-hospital mortality rates as high as 30 % with worse outcomes associated with older age, severity of respiratory and non-respiratory organ dysfunction, and hospital length of stay [4]. Given that patients transferred to the ICU with AECOPD are at high risk for complications and adverse outcomes, early diagnosis and management are critical to improve patient outcomes and survival in this population.

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Pathophysiology and Etiology

AECOPD are the result of increased airway resistance as a consequence of inflammation and/or increased airway secretions. Data suggests that 50–70 % of AECOPD are due to respiratory infections, with greater than 50 % being due to bacterial pathogens. The most commonly isolated organisms include *Haemophilus influenza*, *Streptococcus pneumonia*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. Gram-negative rods are isolated less frequently but are more common in patients with advanced disease and more severe exacerbations as well as those with diabetes. Patients may be chronically colonized with bacteria in the respiratory tract, but it is unclear whether asymptomatic colonization leads to exacerbations caused by the same bacterial strains or predisposes to new bacterial growth. Atypical bacteria such as *Mycoplasma pneumonia* may be responsible for up to 14 % of exacerbations [2, 5].

Viral infections are estimated to cause 20–40 % of exacerbations. However, many patients with documented bacterial infections report a viral prodrome, making the true prevalence of viral illness difficult to estimate. Estimates indicate that rhinovirus (17–25 %), influenza (5–28 %), parainfluenza (5–10 %), and respiratory syncytial virus (5–10 %) are among the most common viral pathogens in AECOPD. Adenovirus, human metapneumovirus, and coronavirus are also potential but less common culprits. In many cases the exact precipitant of an exacerbation may never be identified [2, 5–7].

Initial Evaluation

Clinical Symptoms and Physical Exam

Acute exacerbations are typically defined by worsening dyspnea, cough with or without increased sputum production, wheezing, and a subjective sense of chest tightness and may be accompanied by pain [1, 7]. It is important to appreciate the severity of underlying airflow limitation, comorbid conditions, duration of worsened symptoms, current outpatient treatment regimen, and previous exacerbations including any

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Table 13.1 Indications for ICU admission in patients with COPD exacerbations

Severe dyspnea that responds inadequately to initial emergency therapy
Changes in mental status (confusion, lethargy, coma)
Persistent or worsening hypoxemia (PaO_2 <40 mmHg) and/or severe/worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and noninvasive ventilation
Need for invasive mechanical ventilation
Hemodynamic instability and/or need for vasopressors

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Note: Indications will vary by institution and ability to do noninvasive ventilation outside of the ICU

Table 13.2 Estimated mortality and intubation risk according to the BAP-65 risk score

Class	Score	Mortality (%)	Need for mechanical ventilation (%)
I	0	0.5	2.1
II	1	1.4	2.2
III	2	3.7	8.4
IV	3	12.7	30.1
V	4	26.2	54.6

prior need for mechanical ventilation. Patients with severe exacerbations presenting to the ICU will often have signs of increased work of breathing including accessory muscle use, paradoxical chest or abdominal wall movements, cyanosis, altered mental status, and hemodynamic instability [8]. A focused cardiopulmonary exam is recommended with close attention to work of breathing including use of accessory respiratory muscles, ability to speak in complete sentences, degree of air movement and adventitious lung sounds on auscultation, evidence of volume overload including jugular venous distension (JVD) and peripheral edema, presence of cardiac arrhythmias, and cyanosis. The patient's mental status and hemodynamic stability should also be assessed.

Indications for ICU Admission

The severity of AECOPD varies greatly. Mild exacerbations may be managed as an outpatient whereas others with the most severe presentations will require close monitoring in the ICU setting. Table 13.1 summarizes indications for ICU admission.

The BAP-65 is a novel scoring system developed to risk stratify the need for mechanical intubation and mortality rate of hospitalized patients with AECOPD (see Table 13.2). Although useful as a risk stratification tool, the decision to admit a patient to the ICU should be based on individual patient presentation and treatment center capabilities. The assessment is based on the presence of any of the following, with increased scores portending a worse prognosis [10]:

- BUN >25 (1 point)
- Altered mental status (1 point)
- Pulse >109 beats/min (1 point)
- Age >65 (1 point)

Differential Diagnosis and Diagnostic Workup

The initial evaluation of a patient with suspected AECOPD admitted to the ICU should be focused on assessing severity of illness, need for possible ventilatory support, and exclusion of other possible causes for respiratory distress. For all patients admitted to the ICU with suspected AECOPD, we recommend the following diagnostic elements [8]:

- Continuous pulse oximetry
- Arterial blood gas (ABG)
- Chest radiograph
- Electrocardiogram
- Basic metabolic panel (BMP)
- Complete blood count (CBC)
- Sputum culture (consider induced sputum sample for patients with minimal sputum production)

This initial workup may be useful in differentiating COPD from other cardiac and pulmonary causes of respiratory failure. Important differential diagnoses in patients with severe dyspnea and/or impending respiratory failure include congestive heart failure, acute coronary syndrome, pulmonary embolism, cardiac arrhythmia, pneumothorax, pleural effusion, acute infectious processes such as bacterial or viral pneumonia, and exacerbations of other underlying pulmonary conditions such as interstitial lung disease. These conditions may coexist with or precipitate AECOPD. Thus, it is important to pursue a thorough diagnostic workup in tandem with ongoing therapeutic interventions. Additional diagnostic measures including chest computerized tomography (CT), echocardiography, cardiac biomarkers, brain naturetic peptide (BNP), and respiratory viral molecular testing should be considered in the appropriate clinical setting. Spirometry during an acute exacerbation is not recommended as it is likely to be both difficult for the patient to perform and provide an inaccurate assessment of lung function.

Pharmacotherapeutic Management

Glucocorticoids

Systemic glucocorticoids are considered a cornerstone of therapy in AECOPD, particularly in patients ill enough to warrant ICU admission. Although the optimal formulation, duration, and dosage of treatment remains unclear, studies have shown that systemic steroids accelerate improvement in airflow, gas exchange, and symptoms in addition to reducing the rate of treatment failure [11]. A trial by Niewoehner

and colleagues demonstrated that there was no benefit of 8 weeks of steroid treatment compared to 2 weeks [12]. Although some studies in patients with AECOPD suggest that a 5-day regimen of 40 mg of prednisone may be superior to 14 days, no trials have clearly defined the optimal regimen for patients with severe exacerbations requiring ICU admission [13]. In general, we recommend intravenous steroid administration with 0.5–1.0 mg/kg methylprednisolone every 6 h for 24 h with tapering to twice daily and then daily over the course of 2–3 days as tolerated for patients with severe exacerbations admitted to the ICU. In general, the duration of treatment should not exceed 14 days. Oral steroids are likely equivalent to intravenous formulations if the patient can take pills by mouth. Careful monitoring for side effects including alterations in cognition, hyperglycemia, insomnia, fluid retention, and peptic ulcer formation is essential; routine H2 receptor antagonist or proton pump inhibitor prescription should accompany steroid therapy in those admitted to the ICU [14].

Bronchodilators

There are no controlled trials documenting efficacy of these agents. However, in general, combination short-acting inhaled beta-2 agonists (albuterol) with or without short-acting anticholinergics (ipratropium) every 2–4 h are recommended for the treatment of AECOPD [1, 8]. There is no evidence to support combination therapy, although albuterol and ipratropium are frequently used concurrently, particularly in patients requiring ICU admission [15]. For non-intubated patients admitted to the ICU, we recommend these medications be administered in nebulized form as inhaler use is difficult for patients with significant respiratory distress. Metered-dose inhalers should be used for patients requiring mechanical ventilation. As there is no evidence to support the addition of methylxanthines during an exacerbation, routine use is not recommended [8, 15].

Antibiotics

Given that the majority of AECOPD are thought to be due to bacterial infections, the empiric administration of antibiotics in patients with COPD exacerbations has been frequently studied [15]. Antibiotic use during COPD exacerbations reduces treatment failures, need for mechanical ventilation, risk for readmission, as well as mortality when administered in the inpatient setting [16–18]. A study by Anthonisen et al. showed that patients with increases in sputum production or changes in sputum color experienced a greater benefit from antibiotics [19]. In addition, a study of patients with AECOPD requiring mechanical ventilation showed that administration of a fluoroquinolone reduced mortality and the need for additional antibiotics when compared to placebo [20]. Therefore, antibiotics are recommended for patients admitted to the ICU, particularly those requiring mechanical ventilation [1, 8]. The choice of antibiotic should be based on local bacterial resistance patterns and cover the common pathogens associated with exacerbations (*H. influenza*, *S. pneumonia*, *M. catarrhalis*). Antibiotic selection varies based on whether or not an exacerbation is considered complicated as these patients may be at risk for *P. aeruginosa*, gram-negative enteric *Bacilli*, or other resistant bacterial strains. Complicated AECOPD is defined as:

- Age >65 years
- FEV_1 <50 % predicted
- >4 exacerbations/year
- Presence of other comorbid conditions

In uncomplicated patients, a beta-lactam, macrolide, or tetracycline antibiotic may be used [8]. For most ICU patients, we recommend a respiratory fluoroquinolone, third- or fourth-generation cephalosporin, or piperacillin/tazobactam. Coverage for atypical bacteria with a macrolide or fluoroquinolone is also recommended if the patient lives in the community. Broader coverage for nosocomial pathogens is recommended for patients residing in health-care settings and those who have had recent or repetitive contact with the hospital environment or therapeutic courses of antimicrobial agents. Combination therapy is often necessary [1, 14, 15]. See Table 13.3 for antibiotic recommendations. In general, a total duration of 7 days of antibiotics is usually appropriate. Coverage may be tailored based on sputum culture results and sensitivities.

Ventilatory Support

Airway Clearance Techniques

There is no data to support the routine use of pharmacologic adjuncts or bronchoscopic mucus clearance techniques, although efforts to clear secretions via pulmonary toiletry and chest physiotherapy (e.g., percussion and postural drainage) are reasonable [15].

Oxygen

Oxygen supplementation is frequently necessary in AECOPD. In order to maintain adequate cellular oxygenation while avoiding hypercapnia, careful monitoring and avoidance of over-supplementation is prudent. The goal is to maintain a PaO_2 >60 mmHg or SpO_2 of 88–92 %. Values significantly above this provide little added benefit while potentially promoting CO_2 retention in this at-risk population. ABGs should be checked frequently to identify any potential interval worsening of respiratory acidosis; VBGs may be a reasonable alternative to ABG analysis when the focus of inquiry is pH-pCO_2 balance as opposed to oxygenation [1].

Table 13.3 Recommended antimicrobial therapy for patients with acute exacerbations of COPD admitted to the ICU

Pathogens	Uncomplicated AECOPD	Complicated AECOPD
H. influenza	Macrolide (e.g., azithromycin, clarithromycin)	Respiratory fluoroquinolone (e.g., levofloxacin, moxifloxacin)
S. pneumoniae		
M. catarrhalis	Trimethoprim/sulfamethoxazole	Third-generation cephalosporin (ceftriaxone)
H. parainfluenza	Doxycycline	
	Second- or third-generation cephalosporin (cefuroxime, ceftriaxone)	
	Respiratory fluoroquinolone (e.g., levofloxacin, moxifloxacin)	
P. aeruginosa (or other gram-negative rods)		Fluoroquinolone (levofloxacin has enhanced antipseudomonal activity)
		Fourth-generation cephalosporin (cefepime)
		Piperacillin/tazobactam
Atypical bacteria	Azithromycin or fluoroquinolone	Azithromycin or fluoroquinolone
Mycoplasma pneumonia		
Chlamydia spp.		
Methicillin-resistant staphylococcus aureus (MRSA)		Vancomycin

Table 13.4 Contraindications to use of NPPV in AECOPD

Recent facial, upper airway, or gastroesophageal surgeries
Active vomiting/high aspiration risk
Poor mental status, inability to protect the airway, severe confusion or agitation
Recent upper gastrointestinal surgery
Copious secretions
Bowel obstruction
Life-threatening hypoxemia
Hemodynamic instability

Noninvasive Ventilation

Many patients with AECOPD will require respiratory support beyond supplemental oxygen. Although endotracheal intubation may be required in severe cases, noninvasive positive-pressure ventilation (NPPV) is a first choice treatment for patients with hypercapnic respiratory failure in severe AECOPD and when there are no contraindications to noninvasive ventilation (see Table 13.4). Patients with clinical signs of respiratory muscle fatigue and/or increased work of breathing should also be considered for early NPPV initiation. The success rate of NPPV in randomized controlled trials of patients with severe AECOPD has been documented as 80–85 %, with improvements in acute respiratory acidosis, tachypnea, work of breathing, and decreases in ventilator-associated events [8, 21]. Previous studies demonstrated that the use of NPPV was associated with a reduction in the overall need for endotracheal intubation, lower cost, reduced ICU length of stay, and decreased overall ICU mortality for patients placed on NPPV [22, 23].

NPPV may not be efficacious in all patients with AECOPD. In particular, patients with Glasgow Coma Scale score <11, acute physiology and chronic health evaluation (APACHE) score ≥29, respiratory rate ≥30, and admission pH <7.25 have a failure rate of that exceeds 70 %. Close monitoring while on NPPV is necessary and rapid clinical improvement is expected if NPPV is likely to be of benefit. Studies have shown that if the pH after 2 h of NPPV remains <7.25, there is a high likelihood of failure (70–90 %), and endotracheal intubation should be considered. Conversely, if the pH and/or the $PaCO_2$ improve within the first few hours of NPPV, there is a significant probability of success [24].

Therefore, frequent monitoring with ABGs and serial clinical exams is critically important. When interpreting ABGs, the acuity of any respiratory acidosis should be considered given that many patients with COPD have underlying chronic hypoxemia and/or hypercapnia. Prior ABGs or serum bicarbonate measurements during previous periods of stability may be useful for comparison. In addition, consideration of other coexisting acute or chronic conditions that might impact on acid-base balance (e.g., acute kidney injury or chronic kidney disease stage III or greater) is also important to successful ABG interpretation and clinical application.

Mechanical Ventilation

Although NPPV can rescue many from respiratory failure, invasive mechanical ventilation may be necessary in patients with particularly severe exacerbations. Intubation should be considered in patients with NPPV failure or contraindication, severe acidosis and hypercapnia (pH <7.25 and/or PCO_2 >60 mmHg), life-threatening hypoxia, or tachypnea with impending evidence of acute respiratory failure [1]. Table 13.5 summarizes indications for invasive mechanical ventilation.

In general, assist-control volume-cycled ventilation is recommended for patients with severe obstructive lung disease. This allows for careful control of minute ventilation, tidal volume, inspiratory flow rate, and expiratory flow time given the predisposition for this patient population to experience dynamic hyperinflation and ventilator-induced lung injury. Specific recommendations for ventilator parameters are summarized in Table 13.6.

It should be noted that no specific trials have been performed to determine optimal ventilator settings in patients with AECOPD. It is likely that every patient will respond differently depending on the severity of underlying lung disease, existence and severity of other comorbidities, and degree of ventilator synchrony. Careful titration and adjustment of ventilator settings at the bedside is often necessary given the dynamic nature of respiratory failure in this patient population. Consultation with a pulmonologist with specific expertise in COPD management may be necessary in select, severe cases in which ventilator management is a challenge.

Table 13.5 Indications for invasive mechanical ventilation

Intolerance of NIV or NIV failure
Respiratory or cardiac arrest
Diminished consciousness or severe psychomotor agitation
Respiratory pauses
Massive aspiration
Severe bradycardia
Hemodynamic instability without adequate response to fluids or vasoactive medications
Severe ventricular arrhythmias
Life-threatening hypoxemia

Adjustments should not be made solely on the basis of gas exchange from ABG results, rather in conjunction with close monitoring of the clinical exam including patient-ventilator synchrony, work of breathing, and hemodynamic parameters. Sedation and analgesia are also important to successful ventilator management.

Dynamic Hyperinflation and Auto-PEEP

Auto-PEEP is an important consideration in patients with severe obstructive lung disease. Positive end-expiratory pressure (PEEP) is the pressure in the alveolus at the end of exhalation. In patients with COPD, increased airway resistance may result in incomplete deflation of the lungs prior to initiation of the next breath, causing the intra-alveolar volume and therefore pressure to remain elevated above that which is desired. This dynamic hyperinflation creates auto-PEEP (in contrast to the intentional application of extrinsic PEEP via mechanical ventilation). The presence of auto-PEEP is important as it can increase the work of breathing, trigger patient-ventilator dyssynchrony, and worsen gas exchange. Auto-PEEP may result in misinterpretation of clinical data such as central venous or pulmonary arterial catheter measurements and lead to unnecessary treatments such as higher doses of sedative medications [25].

Auto-PEEP may also provoke hemodynamic compromise by increasing intrathoracic pressure that results in decreases in right and left ventricular preload, ultimately leading to arterial hypotension. Misdiagnosis of the etiology of shock in this setting may lead to unnecessary fluid and vasopressor administration; failure to recognize and correct auto-PEEP may result in hemodynamic collapse and death. For this reason, any mechanically ventilated patient with COPD and new onset hypotension should be assessed for the presence

Table 13.6 Recommended initial ventilator settings for patients with AECOPD

Ventilator parameter	Recommendation	Other considerations
Ventilator mode	AC/VC	Weaning generally performed with PSV. AC/PC generally avoided. SIMV may be used in select patients
Respiratory rate	Initial rates should be set to mirror the pre-intubation respiratory rate with a typical range of 12–25 breaths/min	Further titration should be based upon ABG results with goal minute ventilation target to achieve a pH >7.25 and patient tolerance while allowing adequate time for expiration[a]
Tidal volume	6–8 cc/kg although lower tidal volumes if tolerated are recommended	Patients with ARDS should have Vt of 4–6 cc/kg based on ideal body weight
Applied PEEP	5–10 cm H_2O	Higher levels of PEEP may be necessary if significant auto-PEEP is present
FiO2	Set to maintain PaO_2 >60 or SaO_2 >92 %	
Inspiratory flow rate	Set at least 60 L/min although higher flow rates (up to 100 L/min) may be necessary in order to shorten the inspiratory phase and prolong the expiratory phase	Presence of significant auto-PEEP should prompt adjustment of flow rate, pending patient tolerance
I/E ratio	Sufficient expiratory flow time to achieve complete exhalation prior to the next ventilated breath (e.g., expiratory flow rate reaches zero)	Increase expiratory time as necessary to minimize breath stacking

[a]Minute ventilation requirements will vary by patient, and settings for tidal volume and respiratory rate will need to be considered on an individual basis. High respiratory rates may provoke a shortened expiratory phase and lead to air trapping, auto-PEEP, and hemodynamic compromise

of auto-PEEP. If hemodynamic compromise from auto-PEEP is present, disconnection from the ventilator circuit for 10–20 seconds should facilitate a release of air from the patient's pulmonary tree and improve hemodynamics. Auto-PEEP can be monitored on the ventilator through the use of the end-expiratory hold maneuver (although accurate measurements require that the patient have no active respiratory effort) [25]. Auto-PEEP may also be identified by monitoring the flow-time trace where the exhilatory trace fails to return to baseline prior to the start of the next breath.

Significant auto-PEEP may be treated by careful ventilator management aimed at increasing the expiratory time to allow adequate emptying of the lungs. Maneuvers include increasing the inspiratory flow rate and decreasing the respiratory rate or tidal volume. Other methods for minimizing auto-PEEP include reduction of spontaneous ventilatory demand through the administration of sedation, analgesia, and occasionally paralytics. Similarly, reducing flow resistance with larger bore endotracheal tubes, frequent suctioning, and bronchodilator administration may also reduce auto-PEEP by reducing resistance to gas flow. Expiratory flow limitation can also be counterbalanced with the application of applied (external) PEEP to match the intrinsic (auto) PEEP [25].

Ventilator Weaning, Consideration of Tracheostomy, and Palliative Care

Patients with severe underlying COPD and exacerbations with resultant respiratory failure may experience difficulty weaning from the ventilator. Goals of care discussions regarding tracheostomy, possible chronic mechanical ventilation needs, and advanced care planning may be necessary; palliative care consultation may be invaluable in this process. In general, patients with failure to progress in weaning toward possible extubation by the end of the second week of mechanical ventilation should be considered for tracheostomy as prolonged endotracheal intubation can result in upper airway injury. In patients with advanced COPD, weaning from mechanical ventilation may require several weeks.

Strategies for ventilator weaning vary but typically consist of steadily increasing time on pressure support trials admixed with periods of assist-control volume-cycled ventilation for rest. The weaning process may be augmented by tracheostomy placement given the ability to perform tracheostomy collar trials with intermittent ventilator support rather than proceeding directly to extubation and independent ventilation. Tracheostomy is also generally more comfortable for patients, thereby reducing sedation and analgesia needs that may accelerate weaning. NPPV may also be an important salvage mode of ventilation for patients who initially fail extubation and only require intermittent ventilatory support.

Clinical decision-making regarding tracheostomy versus palliative extubation should be based on individual patient and family preferences. Prognostication in this patient population is often challenging and complex but early involvement of palliative care consultants, where available, is recommended. An episode of respiratory failure should prompt discussions of patient care goals and values for both short- and long-term advanced care planning. When appropriate, formal hospice referrals should be considered. In all cases, sufficient treatment of dyspnea and pain should be provided.

Pulmonary Hypertension

Background and Classification

Pulmonary hypertension (PH) refers to a complex group of clinical conditions defined by abnormal elevation of blood pressure in the pulmonary circulation. It is further defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest on right heart catheterization (RHC) [26]. Typically PH is discussed in the context of true pulmonary arterial hypertension (PAH) resulting from pressure elevations in the pulmonary arterial system or pulmonary venous hypertension (PVH) occurring secondary to pressure elevations in the pulmonary venous and capillary systems. PVH is typically seen in the setting of elevated pulmonary artery occlusion pressures (PAOP) resulting from volume overload in left ventricular (LV) failure. This distinction becomes important in understanding the pathophysiology of the disease and in treatment decisions.

The World Symposium on Pulmonary Hypertension updated its classification in 2013 to incorporate five groups of disorders (Table 13.7) [27]. The diagnostic evaluation and treatment of PH in the clinically stable patient is a separate topic and will not be addressed here. Rather, the focus of this discussion will be on the pathophysiology, diagnostic evaluation, and treatment of PH and resulting right ventricular failure (RVF) as this is most commonly observed in the intensive care unit (ICU) setting.

Pathophysiology of Right Ventricular Failure

Pulmonary hypertension results from increases in pulmonary vascular resistance (PVR) present in both acute and chronic PH. Rising pulmonary pressures create increases in afterload that are difficult for the RV to overcome. The right heart attempts to compensate for rising pressures by dilating acutely and hypertrophying chronically. However, these compensatory mechanisms are maladaptive, and the resulting volume overload that ensues as cardiac output declines

Table 13.7 Updated classification of pulmonary hypertension

Group 1: pulmonary arterial hypertension
Idiopathic PAH
Heritable PAH
Drug and toxin induced
Systemic disorder associations with:
Connective tissue disease
HIV
Portal hypertension
Congenital heart disease
Schistosomiasis
Group 1': pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Group 1": persistent pulmonary hypertension of the newborn (PPHN)
Group 2: pulmonary hypertension due to left heart disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3: pulmonary hypertension due to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive/obstructive pattern
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases
Group 4: chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5: pulmonary hypertension with unclear multifactorial mechanisms
Hematologic disorders
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
Metabolic disorders
Other

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ultimately leads to RVF. As the RV fails, stroke volume and cardiac output drop further, leading to cardiogenic shock. In the ICU setting, RVF is typically acute but occasionally may be due to worsening of underlying chronic PH [28, 29].

Additional elements that may contribute to impaired cardiac function include compromised filling of the right coronary arteries due to elevated right-sided wall tension leading to myocardial ischemia, tricuspid valvular insufficiency, and bowing of the interventricular septum which impinges on LV diastolic filling (enlargement of the right heart due to increased pressure and volume displaces the interventricular septum toward the LV). Because the heart functions in a fixed space within the pericardium, this displacement of the interventricular septum impedes LV filling, causing a further decrease in systemic stroke volume and cardiac output. This may result in hypotension and ultimately hemodynamic collapse [28, 29].

Etiology and Prognosis

In general the outcome for patients with PH admitted to the hospital with RV failure is poor, with an estimated mortality of 30–40 % for those requiring ICU admission [30, 31]. The majority of patients admitted to the ICU with PH will have disease that is a result of underlying critical illness rather than preexisting PH. Although not impossible, it is uncommon to diagnose de novo PH as the primary reason for ICU admission except in the setting of acute pulmonary embolism. Many triggering factors causing or aggravating RV failure include infection, anemia, injury, surgery, pregnancy, medical therapy nonadherence, pulmonary embolism, and arrhythmia. However, it is frequently the case that the exact trigger for decompensation is never identified. Identification of an infection in this patient population at any time during the ICU stay generally portends a poor prognosis [31, 32].

Clinical Presentation

Acute RVF typically clinically presents with systemic congestion and/or low cardiac output. This usually manifests as chest pain, dyspnea, lightheadedness, syncope, altered mental status, cool extremities, and acute kidney injury. On exam, the jugular venous pressure will most often be elevated. Other overt signs of volume overload include hepatomegaly, peripheral edema, ascites, and crackles on pulmonary auscultation. Cardiac exam may reveal a RV heave, a tricuspid regurgitant murmur, an accentuated P2, and/or an S3 or S4 gallop. In the ICU, patients may present in extremis with tachycardia, tachypnea, hypoxia, hypotension, and shock as a result of inadequate cardiac output and elevated filling pressures [26, 33].

Diagnostic Evaluation

The initial diagnostic workup of any patient admitted to the ICU with known underlying PH with suspected decompensation or a possible new diagnosis of undifferentiated RVF should include the following:

- Infectious workup including chest radiograph and cultures of the blood, urine, and sputum when clinically indicated
- Basic laboratory evaluation including complete blood count (CBC) and comprehensive metabolic panel (CMP) to assess renal and hepatic function

- Electrocardiogram
- Transthoracic echocardiography (TTE)
- Possible right heart catheterization

Ongoing monitoring of end-organ perfusion including renal, hepatic, and neurological function is necessary. In addition, acute pulmonary embolism should be excluded in any patient with decompensated or acute RVF [32].

In general, noninvasive testing and assessment of cardiac function are preferred prior to RHC. Therefore, transthoracic echocardiography (TTE) remains the cornerstone of the diagnostic evaluation in patients with suspected PH. Assessment of both the pulmonary arterial systolic pressure (PASP) and RV structure and function is an important parameter in this evaluation. Right atrial enlargement, pericardial effusion, low tricuspid annular plane systolic excursion (TAPSE), and septal displacement are poor prognostic indicators. In general, patients with an estimated PASP >40 mmHg or a peak TR jet velocity ≥3 m/s are likely to have PH confirmed by RHC. However, RHC is the gold standard for confirming diagnosis of PH. Invasive hemodynamic monitoring remains key to the ongoing evaluation and therapeutic management of these patients [28].

Management Considerations

In patients with confirmed or suspected PH and/or RV failure, a thoughtful, systematic, and multidisciplinary approach to medical management should be pursued. Early consultation with an expert in pulmonary hypertension is advised as patients are often misdiagnosed and referred late for consideration of advanced therapies. Consultation with PH experts may also be necessary to discern PH and RV failure from other causes of clinical decompensation. Collaboration between local medical centers and PH specialty centers to facilitate referral and patient transfer when necessary is advised [26].

Clinical Monitoring

Careful monitoring of cardiac, renal, neurologic, and hepatic function is essential in the care of the patient with PH and/or RV failure. Urine output, laboratory data (liver function tests, serum creatinine, lactate, troponin), and hemodynamic parameters obtained either from a central venous catheter (e.g., central venous pressure (CVP) and central venous saturation ($ScVO_2$)) or PA catheter (right atrial pressure, cardiac index, mean PA pressure, PVR and mixed venous saturation (SvO_2)) are useful in making management decisions. Given their complexity, the use of RHC and ongoing invasive hemodynamic monitoring is recommended for patients with evidence of RV failure requiring ICU admission, particularly in the setting of vasoactive agent titration [32].

Table 13.8 Directed therapies for specific etiologies of RV failure

Acute pulmonary embolism	Surgical or percutaneous embolectomy
	Systemic- or catheter-directed thrombolysis
Acute respiratory distress syndrome	Lung-protective ventilation
CTEPH	Pulmonary thromboendarterectomy
Endocarditis	Antibiotics and surgery if indicated
Left ventricular dysfunction	Percutaneous coronary intervention or thrombolysis
	Mechanical circulatory support
	Cardiac transplant
Right ventricular infarct	Percutaneous coronary intervention or thrombolysis
Congenital heart disease	Surgical or percutaneous repair
Valvular heart disease	Surgery if indicated

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In general, management of acute RVF and severe PH in the critically ill patient focuses on optimization of RV preload, afterload, and contractility while also carefully controlling oxygenation, ventilation, and cardiac rhythm. The search for potentially reversible causes of decompensation is critical. If a specific cause of RV failure is identified, management should include consideration of one of the directed therapies listed in Table 13.8. Consideration of acute PE is important in this population; however, its specific management will not be discussed here.

Preload Optimization

Careful attention to and evaluation of fluid status are critical in the management of PH. Assessment based on clinical exam, CVP, and invasive hemodynamic monitoring with RHC may aid in accurate determination of volume status and fluid management. Occasionally patients may be hypovolemic and require fluid administration. However, even in the case of suspected sepsis, overly judicious administration of fluids may have detrimental hemodynamic effects in patients with compromised RV function. Thus, cautious administration is advised. A reasonable fluid challenge for a patient with acute RV dysfunction or acute PH is 500 ml of a normotonic fluid over 15–20 min, with a general goal CVP target of 10–12 mmHg [26, 29, 33].

More often than not, patients with RVF will be hypervolemic and require administration of intravenous (IV) diuretics or acute hemofiltration for volume removal. IV loop diuretics, potentially in the form of a continuous infusion to avoid abrupt swings in filling pressures, are preferred. Extracorporeal fluid removal via ultrafiltration may be necessary in the presence of the cardiorenal syndrome and

Table 13.9 Vasodilatory medications available for treatment of acute severe PAH necessitating ICU admission

Medication	Route of administration	Notes	Side effects
Nitric oxide	Inhaled	Rapid onset and short half-life	Risk of rebound PH after drug withdrawal
Epoprostenol (Flolan®)	Inhaled or IV	First line, preferred agent in the ICU and for post-op PH	Hypotension, bradycardia, headache, nausea/vomiting, thrombocytopenia, and flushing; potential for worsening hypoxemia owing to V/Q mismatch
		Only agent to demonstrate improved survival in PAH [34]	
		Short half-life (6 min)	
Treprostinil (Remodulin®)	SQ or IV	Half-life of 4 h	
		Typically used for chronic rather than acute therapy	

diuretic resistance. However, either of these generally portends a poor prognosis [33].

Afterload Optimization

Afterload reduction with the use of pulmonary vasodilators remains an important consideration in severe PH and RV failure. However, systemic PAH-specific therapies are discouraged in patients with PH of unknown etiology. Pulmonary vasodilators may be considered in cases where immediate reduction of PVR is necessary [33]. Both IV medications with selective effects on the pulmonary vasculature and inhaled agents delivered directly to the lungs are available for this purpose. See Table 13.9 for a summary of available vasodilatory medications for PAH in the ICU setting. Oral agents including PDE-5 inhibitors and endothelin receptor antagonists (ERAs) are typically not appropriate for use in the acute ICU setting (except in selected treatment-naïve PAH patients who have been stabilized with IV prostanoids) and thus will not be covered in this chapter.

It is important to note that treatment with PAH-specific drugs has only been associated with improved outcomes in outpatients with chronic PAH. Given that few critically ill patients with PH and or RV failure will have underlying PAH, many of these PAH-specific drugs may not be warranted. In addition, no studies have demonstrated clinical superiority of one agent [29, 32, 33]. One should also recall that systemic acidosis results in pulmonary arterial vasoconstriction. Therefore, abrogation of acidosis may be a useful therapeutic goal using either augmented minute ventilation or intravenous fluids that influence pH such as those constructed entirely of, or supplemented with, sodium bicarbonate or sodium acetate (especially when $NaHCO_3$ is in short supply).

Vasoactive Therapies

A variety of vasoactive drugs may be used in patients with RV failure and critical illness including vasodilators, inotropes, and/or vasopressors. The goal of therapy is to maintain end-organ perfusion through reduction in PVR without compromising systemic mean arterial pressure and increasing cardiac output. The selection of specific therapies or combinations thereof should be tailored to each patient, taking into account their hemodynamic, respiratory, and volume status. Patients requiring initiation and titration of these therapies should have a pulmonary artery (PA) catheter placed for ongoing management optimization; while other hemodynamic monitoring techniques are available, none directly measure PA pressures.

A combination of overstretching, derangements in cellular metabolism, and insufficient oxygen delivery lead to decreased RV contractility in the setting of critical illness. Dobutamine, dopamine, and milrinone are the agents most commonly used for inotropic support in this patient population. See Table 13.10 for a summary of the hemodynamic effects of commonly used vasoactive drugs. There is debate as to the first-line agent for inotropic support, but in general, dobutamine is preferred over dopamine for acute inotropic support in unstable patients in the ICU, especially since dopamine is strongly pro-arrhythmogenic at higher doses. Milrinone is also often strongly considered, particularly in patients with biventricular failure. However, caution should be exercised given the vasodilatory properties of both agents (dobutamine and milrinone) and their potential to provoke systemic hypotension.

In some cases, concomitant administration of a vasopressor may be necessary to maintain systemic precapillary arteriolar sphincter tone, mean arterial pressure, and cardiac output. Adequate systemic blood pressure is necessary to maintain coronary perfusion and cardiac function, and thus vasopressors may be a necessary first-line or adjunct therapy [32]. As with inotropic support, careful selection of the most appropriate vasopressor will vary depending on the clinical scenario. The increased risk of tachyarrhythmias with all vasoactive agents is an important consideration given the potential hemodynamic impact on myocardial oxygen consumption, coronary artery flow demand, and RV filling time.

Table 13.10 Summary of vasoactive agents and hemodynamic effects

Agent	Class	Action	PVR	SVR	CO	Notes
Inotropes						
Dobutamine (DBA)	β1/β2 agonist	Inotropy	↓↔	↓↔	↑↑	Preferred in primary RV dysfunction (e.g., RV infarct)
						Generally preferred over dopamine for inotropic support in unstable patients
						Less tachycardia than dopamine but more hypotension
Dopamine	β1/dopa agonist	Inotropy	↑	↑	↑	Risk of arrhythmias, tachycardia
Milrinone	PDE-3 inhibitor	Inotropy, pulmonary vasodilation	↓↓	↓	↑↑	Less tachycardia than DBA but risk of arrhythmias
						Preferred for RVF, particularly if normotensive or post-op PH
						Possible hypotension given vasodilating effects
Vasopressors						
Epinephrine	α1/β1/β2 agonist	Inotropy, vasoconstriction	↑	↑	↑↑↑	Beware of tachycardia, arrhythmias, lactic acidosis
Norepinephrine	α1/β1 agonist	Vasoconstriction, limited inotropy	↑	↑	↑	First line with severe hypotension
						↑SVR > PVR
Phenylephrine	α1 agonist	Vasoconstriction	↑↑	↑	↑↔	Reflex bradycardia, generally avoid in RV failure
Vasopressin	V1 agonist	Dose-dependent pulmonary and systemic vasodilation/vasoconstriction	↓	↑	↔	May work well in conjunction with norepinephrine

Rhythm Control

The presence of atrioventricular synchrony is critical for optimal RV filling and maintenance of cardiac output. The presence of atrial arrhythmias (e.g., atrial fibrillation, atrial flutter, and supraventricular tachycardia) and electrical conduction delays (e.g., complete heart block) is associated with worse outcomes given that the RV is highly dependent on atrial contraction to maintain adequate filling. Rate control alone is not typically sufficient and rhythm control is recommended. Electrical cardioversion for tachyarrhythmias and atrioventricular (AV) pacing for bradyarrhythmias are the first-line treatments for unstable patients. Amiodarone is the recommended first-line medication for most tachyarrhythmias due to its lower risk of hypotension and comparatively fewer negative inotropic effects. The use of beta-blockers and calcium channel blockers is generally avoided given that both classes of agents may impair RV contractility as well as AV nodal conduction [32, 33].

Oxygenation and Ventilatory Support

Hypoxemia and hypercapnia place additional strain on the heart by inducing hypoxic vasoconstriction with resultant increases in PVR and RV afterload. Therefore, maintenance of normoxia (peripheral O_2 saturation >90%) and normocapnia ($PaCO_2$ of 35–40 mmHg) is recommended. Any other impedance to adequate oxygen delivery to the tissues should be corrected, including anemia if present (goal Hgb >10 g/dL) [32, 33].

In the setting of respiratory decline, every effort should be made to avoid invasive mechanical ventilation if possible. The risk for systemic hypotension and hemodynamic collapse during intubation as a result of sedative administration is significant. Ongoing ventilator support with positive-pressure ventilation may also have untoward effects as the positive pressure increases intrathoracic pressure and may result in decreased venous return and hypotension. Therefore, noninvasive ventilation should be considered prior to intubation if the patient's clinical condition is stable enough

for a trial. However, if intubation is necessary, etomidate is the preferred drug for induction of general anesthesia given its minimal effect of cardiac contractility and vascular tone. One should recognize that controversy exists regarding the effects of etomidate on later adrenal function, and alternative agents should be considered dictated by provider training and agent availability. Preemptive administration of vasopressors and or inotropes prior to intubation to offset the commonly induced hypotension should also be considered [32, 35].

Advanced Therapies

In select patients with medically refractory PH and/or RVF, advanced therapies including mechanical circulatory support and bilateral lung transplantation may be considered.

Right ventricular assist devices may be used as a bridge to durable mechanical support or as a bridge to recovery. They have been successfully used in the treatment of RV failure due to myocardial infarction, cardiopulmonary bypass, left ventricular assist device implantation, and cardiac transplant [29].

Extracorporeal membrane oxygenation (ECMO) has been used successfully to treat RV failure due to massive PE, chronic thromboembolic pulmonary hypertension (CTEPH), and PAH as a bridge to endarterectomy or lung transplantation. Typically venoarterial (VA) ECMO is utilized to unload the RV while maintaining systemic oxygenation. In patients with PAH, it may also be used to support the RV during initiation of pulmonary vasodilator therapy. However, complications including hemorrhage, infection, anemia, thrombocytopenia, thromboembolism, and neurologic sequelae are possible [28].

Percutaneous interventions such as balloon atrioseptostomy (BAS) may be used as either a bridge to lung transplantation or as palliative therapy. The procedure works by creating an atrial level right-to-left shunt that bypasses the obstructed pulmonary circulation, allowing for improved LV filling, systemic oxygenation, and blood flow. However, its use as an emergent rescue therapy is not recommended given the high risk for fatal complications in patients with markedly elevated RV filling pressures and/or low oxygen saturations [32, 33].

Lung and or heart-lung transplantation is an important treatment option for patients with progressive PH, particularly in the presence of RV failure. Bilateral lung transplantation may be considered in select cases with dual heart-lung transplant reserved for selected patients with severe irreversible PH and concomitant severe cardiac disease. Indications and contraindications for transplant will not be reviewed herein as its consideration is complex and uncommon in the typical ICU setting [32, 33].

Palliative Care and End of Life

Patients with end-stage RVF who are refractory to medical therapy and not candidates for advanced therapies have a poor prognosis and are unlikely to survive cardiac arrest. Therefore, in patients with PH and RV dysfunction, early conversations regarding patient preferences and goals of care are essential, particularly in the ICU setting. Recommendations for limiting life-sustaining therapies may be appropriate. Palliative care and hospice should be considered in the correct setting.

Pre-, Peri-, and Postoperative Management Considerations

Patients with pulmonary hypertension have significantly elevated morbidity and mortality associated with surgery and anesthesia, in large part due to fluid shifts, mechanical ventilation, and inflammatory mediator release that results in the setting of surgical interventions [33, 36]. Both cardiac and noncardiac surgical patients with PH have higher incidences of postoperative congestive heart failure, hemodynamic instability, sepsis, respiratory failure, and in-hospital death. Given the associated risks, nonemergent surgeries should generally be avoided in the setting of PH-induced RV failure [37–39].

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Diagnosis and Management of Acute Kidney Injury

14

Neesh Pannu and Matthew T. James

Introduction

Over the last decade, there has been a paradigm shift in our understanding of acute renal failure or acute kidney injury (AKI). Initially described and defined as a complete loss of kidney function, it is now widely recognized that lesser degrees of kidney injury have important implications for health. As currently defined, AKI represents a heterogeneous clinical syndrome with multiple etiologies rather than a specific disease. However whether it occurs in critically ill patients with multisystem organ failure or in isolation, AKI is associated with high costs and adverse clinical outcomes including excess mortality, increased length of hospital stay, the development and/or progression of chronic kidney disease (CKD), and requirement for chronic dialysis in survivors [1–4]. In its most severe form (requirement for acute dialysis), AKI is associated with mortality ranging from 15 % in patients presenting with isolated AKI to as high as to 80 % in critically ill patients [5].

The principles of management of acute kidney include early recognition of the problem, identification and correction of the underlying cause, and steps to avoid further renal injury. Once acute kidney injury is established, the therapeutic options are limited, and mortality remains high despite recent technological advancements. Nonetheless, regional and temporal variations in mortality among hospitalizations for acute kidney injury suggest that several elements of management, including supportive care, management of complications, and use of renal replacement therapy, may influence outcomes. This chapter focuses on the management of early or established acute kidney injury due to prerenal azotemia or acute tubular necrosis.

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Epidemiology of AKI

The incidence of AKI using serum creatinine (Scr) and urine output-based consensus definitions (see Table 14.1) has been best characterized in critically ill populations where lab and urine output data are frequently measured. Despite the use of common definitions for AKI in these populations, multicentre studies have reported the incidence of AKI to be between 10 and 67 %, likely reflecting case mix differences between health-care systems and countries [6–9]. The incidence of AKI managed with renal replacement therapy in critically ill patients is somewhat more consistent at 6–12 % [10].

Causes of AKI

As our knowledge of AKI has expanded, so too have recognized causes. These diverse etiologies include toxin, flow, sepsis, and contrast-mediated AKI. Sepsis is the most common cause of AKI and accounts for 25–50 % of AKI seen in critically ill patients [11]. AKI is also commonly seen in patients with circulatory shock, burns, trauma, and

Table 14.1 KDIGO AKI definition (a) and staging (b)

(a) AKI definition		
Increase in SCr by ≥0.3 mg/dL within 48 h or		
Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or		
Urine volume <0.5 ml/kg/h for 6 h		
(b) AKI staging		
AKI stage	**Serum creatinine**	**Urine output**
Stage 1	1.5–1.9 × baseline	<0.5 ml/kg/h for 6–12 h
	or increase ≥0.3 mg/dL (≥26 umol/L)	
Stage 2	2–2.9 × baseline	<0.5 ml/kg/h for × 12 h
Stage 3	3 × baseline	<0.3 ml/kg/h for × 24 h OR Anuria for × 12 h
	or serum creatinine ≥4 mg/dL (353 umol/L)	
	or requiring dialysis	

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postoperatively (esp. cardiac and vascular surgery) [12]. Potentially modifiable causes of AKI include exposure to radiocontrast and other nephrotoxic medications including nonsteroidal anti-inflammatories, ACE inhibitors, angiotensin receptor blockers, diuretics, and chemotherapeutic agents. The causes of AKI in hospitalized albeit not critically ill patients have not been well characterized; however several smaller studies have reported toxin and flow-based causes as the etiologies responsible for the majority of cases [5]. Non-modifiable risk factors common to all populations which increase susceptibility to AKI are presented in Table 14.2. Despite awareness of these factors, risk prediction models that accurately predict the occurrence of AKI remain elusive.

Table 14.2 Patient-specific risk factors for AKI

Patient-specific risk factors for AKI
Age
Gender (male)
Chronic kidney disease
Proteinuria
Diabetes
Congestive heart failure
Sepsis
Volume depletion
Chronic liver disease

Early Recognition and Initial Management

Timely detection and recognition of AKI may allow for prompt implementation of interventions to reverse early AKI and avoid the development of severe kidney injury and its complications. AKI is usually identified based on an increase in serum creatinine and a decrease in urine flow. Antiquated definitions identified AKI only after large changes in baseline Scr such as doubling or an absolute value >2 g/L. These definitions are inadequate for a host of reasons. Since Scr reflects muscle mass, those with little mass, such as the aged, will have a low baseline (i.e., baseline Scr = 0.6 g/L) and may have sustained extensive injury and decrements in renal function by the time Scr reaches 2 g/L. In contrast, those with CKD who start at a baseline of 1.8 g/L will have little change at 2.0 g/L and very little residual function by the time they reach 3.6 g/L. Moreover, the opportunity for early intervention may be lost awaiting such triggers to be met.

Small changes in Scr early in the course of AKI (as little as a change of 0.3 g/L) may represent large changes in glomerular filtration rate. The recently published international consensus Kidney Disease Improving Global Outcomes (KDIGO) guidelines propose a diagnosis and staging system for AKI based on changes in serum creatinine and/or urine output using a volume and time metric (Table 14.1). The KDIGO guidelines also incorporate stage-based management recommendations (Fig. 14.1) [12].

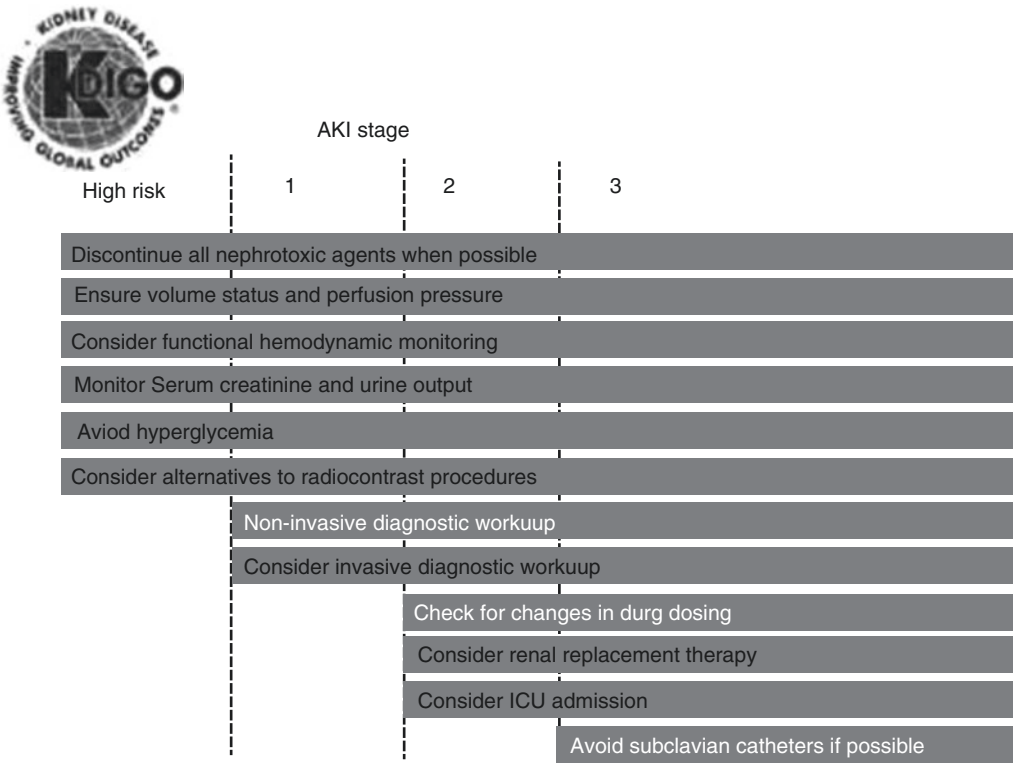

Fig. 14.1 KDIGO stage-based management of AKI. Shading of *boxes* indicates priority of action: *solid shading* indicates actions that are equally appropriate at all stages, while *graded shading* indicates increasing priority as intensity increases. *AKI* acute kidney injury, *ICU* intensive care unit (From Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group [57])

While these definitions of AKI show consistent associations with hard end points such as mortality and hospital or ICU length of stay, the role of these definitions in the clinical management of AKI has not been established. Recently published observational data in critically ill patients suggest that using a combination of both serum creatinine and urine output criteria may provide the best prognostic information about AKI patients both with respect to requirement for dialysis and mortality [13]. Several novel biomarkers for acute kidney injury have been identified in recent years, including NGAL and cystatin C, kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18). While attractive, these tests are not yet widely used in clinical practice and remain the focus of ongoing studies to determine their appropriate role in guiding management of patients at risk of, or impacted by, AKI.

Investigations

Once acute kidney injury has been identified, the etiology should be determined through further clinical assessment, investigations, and interventions as necessary. A thorough history and examination aids in identifying potential causes of AKI. In particular, a search for indicators of prerenal and postrenal causes should be performed as their correction can lead to rapid recovery of kidney function. A number of urine studies have been described that supplement data from the history and physical examination including the urine sodium concentration, fractional excretion of sodium, and fractional excretion of urea. Unfortunately, all of these tests have limitations in their diagnostic performance and interpretation is dependent on the clinical context.

Clinical examination to determine volume status may benefit from more precise assessments of volume status especially in those with preexisting cardiopulmonary dysfunction such as reduced ejection fraction, COPD, and pulmonary hypertension, for example. Rapid assessment may be augmented using bedside complete or limited echocardiography evaluating chamber size, chamber and IVC collapsibility during the phases of respiration, as well as ejection fraction.

AKI due to hypovolemia may be rapidly reversible by plasma volume expansion. However, not all episodes of AKI due to hypovolemia (i.e., hemorrhagic shock) respond to restoration of plasma volume. This may be especially true where plasma volume is expanded using media that provide little free water leading to hyperoncoticity which is strongly associated with AKI [14]. Fluids known to cause hyperoncoticity when used in large quantity for plasma volume expansion as the sole volume expander include hyperoncotic albumin, hyperoncotic starch, and hypertonic saline.

A host of toxins have been identified including a broad range of renally cleared medications such as aminoglycosides, vancomycin, angiotensin converting enzyme inhibitors, angiotension receptor blockers, statins, and nonsteroidal anti-inflammatory agents. Hydroxyethyl starch in limited volume appears at least in observational studies to not impact renal function, but in a key trial using an appropriate comparator fluid, HES demonstrated a definitive negative influence on renal function in those with severe sepsis or septic shock [15]. Why this effect is so clearly pronounced in those with infection remains unclear but may relate to the subcellular cascade of events that occurs with AKI (see *Subcellular Events* below). Radiocontrast (iodinated compounds) have been associated with AKI (contrast-induced AKI (CI-AKI)) but there is conflicting data, even in the elderly [16]. In general, dehydration and diabetes are believed to render one more susceptible to CI-AKI; the only well-described effective mitigation strategy is restoration of a plasma volume deficit prior to contrast exposure. Naturally occurring toxins such as that found in concentrated cherry juice behave similarly to NSAIDs [17]. Exposure to bioartificial membranes also appear to impact renal function, principally through their impact on hepatocyte growth factor [18]. Perhaps the best model for endogenous toxin-mediated AKI is hepatorenal syndrome where hepatic failure compromises renal function in the absence of structural renal abnormalities. The clinician should be aware that hyperchloremia and hyperchloremic metabolic acidosis is also associated with reduced GFR; chloride intake management should be considered. Such efforts are associated with reduced time to pH normalization, reduced fluid administration, reduced ICU length of stay, and reduced cost although the effects of such strategies on clinically relevant outcomes remains under investigation [19].

Mechanical causes of AKI should also be considered and take one of three general forms. The most commonly identified is lower urinary tract obstruction with bladder distension with or without concomitant ureteral dilatation. Common etiologies include benign prostatic hypertrophy, clot after bladder or ureteral instrumentation or renal trauma, and indwelling bladder catheter obstruction. Detection strategy includes physical examination, bladder scan, and flushing or removal and/or replacement of an existing indwelling bladder catheter. Selected use of renal ultrasound is useful for identifying hydroureter and/or hydronephrosis indicative of a postrenal cause and may be of particular use in the postoperative setting after procedures where there is the potential for ureteral injury and obstruction although it is important to note that hydronephrosis may not be universally present in the setting of acute obstruction. CT scanning may be required as a complementary tool when there is no hydronephrosis to evaluate for ureteral laceration (as opposed to obstruction) with a surrounding urinoma. Bladder catheterization can effectively relieve lower urinary tract obstruction, while nephrostomy tubes or ureteric stents can be used to treat upper urinary tract obstruction. Reconstruction of a lacerated ureter is beyond the scope of this chapter.

Postrenal obstruction also occurs with intra-abdominal hypertension. In this setting, the postrenal component is relative, and increasing extrinsic renal vein compression leads to reduced flux of blood across the renal vasculature. Experimental data creating renal vein hypertension by external compression demonstrates reproducible decreases in renal blood flow, urine flow, and GFR, as well as increases in aldosterone and renin and the development of proteinuria. Moreover, in the experimental setting, these findings are reversible with relief of renal vein hypertension [20]. In a related fashion, raising intra-abdominal pressure to 20 mmHg with induced pneumoperitoneum creates physiology that mimics the abdominal compartment syndrome with concomitant decreases in RBF, urine flow, and Scr [21]. However, unlike relief of renal vein compression, relief of intra-abdominal hypertension does not lead to reversed physiology but instead has only partial recovery of urine flow and a further increase in Scr. Interestingly, this model also demonstrated systemic impact on pulmonary and GI mucosal histology consistent with ischemia and reperfusion as well. These data also support a toxic effect of functional hypovolemia that may be explained in part by induced changes in mitochondrial function and the elaboration of damage or pathogen-associated molecular patterns [22].

The third setting in which postrenal obstruction may occur is with intracapsular hypertension – a less common condition after injury where there is renal parenchymal injury but intact Gerota's fascia. Extravasated blood that cannot escape the capsule creates intrarenal hypertension and leads to renal venous compression in advance of renal arteriolar compression. Renal recovery has been described in an experimental model with Gerota's fascia incision [23].

Intrinsic etiologies are diverse but may impact the vasculature, parenchyma, or collecting system and span the gamut of infectious, inflammatory, immune-mediated, malignant, thrombotic, and embolic events. Regardless of etiology, investigation benefits from a combination of imaging to determine the presence of structural and flow abnormalities – generally as an ultrasound often complemented by a CT scan with IV contrast as appropriate based on the patient's intrinsic renal function. Urinalysis and urine microscopy provide important information about intrinsic renal causes of acute kidney injury, although may be of limited value in catheterized and critically patients. The findings of granular casts or renal tubular epithelial cells are associated with an increase in the likelihood of tubular injury and help to predict patients at highest risk of worsening renal function, the requirement for renal replacement therapy, or death. The findings of hematuria and proteinuria in the absence of risk factors for ATN should prompt further investigations for causes of glomerulonephritis, while white blood cell casts should prompt a careful assessment for causes of interstitial nephritis, including a review of medication exposures. Acute interstitial nephritis is likely underdiagnosed and can be associated with urine eosinophils as an allergic manifestation.

Subcellular Events: Current Theories

It is increasingly clear that our knowledge of clinical conditions is rapidly expanding as we come to understand the molecular underpinnings of the host response to injury or illness; similar events have occurred for AKI. Since septic AKI predominates in high acuity ICUs, it provides an excellent platform from which to develop insights into commonalities between the different etiologies of AKI at the subcellular level. Central to AKI are the interwoven effects of altered microcirculation, inflammatory mediators, and their downstream effects, as well as energy metabolism impacting mitochondrial alterations in productivity or survival. Interweaving these three domains into a coherent whole has crafted a unifying theory of AKI triggers and the functional consequences as the cellular and subcellular levels [24]. Key to sepsis is the circulation of pathogens, pathogen products (pathogen-associated molecular patterns (PAMPs), e.g., lipopolysaccharide), and cellular response elements to cellular injury (damage-associated molecular patterns (DAMPs), e.g., nuclear protein high-mobility group box 1) [25]. These various triggers initiate a variety of host responses including the well-described cytokine cascades associated with the host response to injury or inflammation.

Each of these elements is in turn filtered by the glomerulus leading to exposure to vascular and tubular elements of the renal parenchyma and predictably leads to a local inflammatory response that alters microcirculation, reduced net flow, and enhances the exposure time of the vascular endothelium to these modulators. Endothelial activation and WBC recruitment follows in the wake of endothelial triggering. These events lead in turn to the elaboration of alarmins, DAMPs that are released by dying cells that drive further inflammation, perhaps most notably at the distal tubule, and may act in concert with mediators such as TNF-α in reducing tubular function. As a result, cell homeostasis is distorted; toxic O_2 mediators are created establishing cell lipid bilayer and molecular machinery oxidant damage, triggering mitophagy as a bioenergetic adaptive response. Mitophagy then leads to cell cycle arrest, reducing energy utilization and perhaps providing time for host defense recovery and then in turn renal recovery. Supporting that AKI may be functional and not structural is the series of observations in one experimental *E. coli* sepsis model using sheep, where net renal blood flow increased during the period of peak AKI (as judged by peak Scr) but was unaccompanied by significant histopathological changes despite intense cortical immune responses such as nitric oxide synthase isoforms and hypoxia inducible factor-1 expression during the peak period of AKI

[26]. At present, it remains unclear how to modify these recently articulated host responses to mitigate against the AKI phenotype outlined above.

Supportive Care and Medical Management of Complications

Once acute kidney injury is established, management focuses on preventing further extension of kidney injury and providing supportive care while awaiting potential renal recovery. Attempts are usually made to avoid further exposure to nephrotoxic agents to the greatest extent possible without compromising management of other comorbidities. Doses of renally cleared medications should be adjusted for the level of kidney function. This can be particularly important for antimicrobial agents in order to maintain appropriate therapeutic levels in patients with sepsis while avoiding further nephrotoxicity. The involvement of a PharmD focused on critical care may be helpful.

Supportive care in patients with established acute kidney injury requires continued interventions to maintain fluid, electrolyte, and acid-base balance. Disorders of sodium and water handling, metabolic acidosis, and hyperkalemia are common complications of acute kidney injury. Hyponatremia may result from impaired free water excretion in excess of sodium or solute intake, while hypernatremia is common in patients with impaired free water intake, hypotonic fluid losses, or in those who have received large volumes of intravenous saline for resuscitation. These abnormalities may be corrected by modifying free water intake or the composition of intravenous fluids. It is appropriate to also evaluate the water content of supplemental medications such as antibiotics and vasoactive infusions as water intake may be substantial, especially with vasoactive agents prepared in low concentration solutions.

Acid generation can be reduced by dietary protein restriction as is common for those with CKD in the outpatient setting, although this is undesirable in hypercatabolic patients such as those after septic shock, severe sepsis, or severe injury, especially traumatic brain injury. Often overlooked acid sources such as chloride intake are also appropriate to evaluate be it in the form of intravenous fluids for maintenance or oral or IV nutritional support formulae [19]. In particular, those with AKI who also need mechanical ventilation benefit from having a reduced need for minute ventilation to buffer iatrogenically induced acidosis. Multiple correction strategies have been articulated including the administration of alkalinizing intravenous fluids such as those supplemented with sodium bicarbonate (or sodium acetate) may be provided to correct metabolic acidosis. Of course, when physiologic limitations prevent the administration of additional IV fluid, renal replacement techniques can also restore acid-base balance.

Hyperkalemia is a common complication of AKI and has multiple etiologies spanning excess administration in oral or IV form, infusion of aged blood in large quantity, rhabdomyolysis, and a host of others. Hyperkalemia therapy has three goals: (1) elimination of potassium intake, (2) preservation of myocardial conduction, and (3) potassium elimination [27]. For those with preserved renal function, forced diuresis using IVF and furosemide generally is sufficient to repair hyperkalemia. Preservation of myocardial conduction in the presence of ECG changes such as peaked T-waves is supported by calcium chloride ($CaCl_2$) infusion instead of calcium gluconate as the calcium in $CaCl_2$ is immediately bioavailable as Ca^{2+}, and Cl^- are strong ions and remain dissociated from one another at physiologic pH in an aqueous milieu; Ca gluconate needs to undergo degluconation via hepatic processing and has a therefore less rapid bioavailability. Supplemental therapy may also include beta-agonists, insulin, and glucose; these agents help to shift K from the extracellular space in to the intracellular one principally relying on the ability of insulin to drive this process. Glucose administration is required to avoid iatrogenic hypoglycemia.

Potassium elimination for those with AKI or CKD may be ineffective via the urine and, therefore, alternative methods are required. One common method is to use Na-K cation exchange resin administration via the upper or lower GI tract. Mixed in sorbitol to draw potassium-rich fluid into the GI tract to interact with the resin, dosing is guided by the initiation of diarrhea and has a relatively slow onset. Usage of these exchange resins has been associated with intestinal necrosis or perforation in certain circumstances [28]; therefore, this approach is generally supplemental in nature rather than stand-alone therapy and is unlikely to be adequate in patients with severe hyperkalemia associated with life-threatening dysrhythmia. When medical management of these abnormalities is unsuccessful or medical interventions cannot be tolerated by the patient, renal replacement therapy is usually necessary. In those with anuria and dialysis requiring CKD at baseline who have life-threatening hyperkalemia, dialysis is a first-line therapy. While marshaling the appropriate resources for either IHD or CRRT, volume loading to dilute the potassium concentration, administration of potassium displacing agents, and $CaCl_2$ may require concomitant airway control and mechanical ventilation to preserve oxygenation and manage work of breathing from the induced extravascular lung water.

Other common complications include volume overload, hyperphosphatemia, and increased work of breathing related to acidosis. Each of these is manageable using some form of RRT to reduce total body water, adjust electrolytes, and reduce metabolic acid load.

Intravenous Fluids and Hemodynamic Support

Hypotension is a common contributor to the initiation of acute kidney injury and renal perfusion may be further diminished once acute kidney injury is established because autoregulation is impaired and unable to maintain constant blood flow with changes in systemic blood pressure, in particular, mean arterial pressure. Early correction of hypovolemia and hypotension cannot only reverse many prerenal causes of acute kidney injury but is likely also important to avoid extension of an existing injury. Strategies to maintain hemodynamic stability include the use of intravenous fluids, vasopressors/inotropic medications, as well as protocols that involve hemodynamic monitoring to guide use of these therapies. While more aggressive use of intravenous fluids early in the initial phase of illness may be beneficial when acute kidney injury is volume responsive, excessive fluid repletion in oliguric patients with established AKI may have adverse effects, including prolonged mechanical ventilation, initiation of secondary abdominal compartment syndrome, anastomotic leak, and mortality in a variety of studies [29–31].

Isotonic crystalloids are the principal intravenous fluid used for plasma volume expansion of patients with AKI with 0.9 % NSS predominating globally. Observational data suggest that buffered crystalloids may be associated with a decreased risk of AKI and of death as compared to saline [32–34]. The presumed toxicity of saline is attributed to the high chloride content of the solution, which may decrease glomerular filtration rate due to tubuloglomerular feedback from excessive chloride delivery to the distal tubule. A recent systematic review and meta-analysis of high vs low chloride content fluids in perioperative and critical care fluid resuscitation found no association between fluid chloride content and mortality but a weak association of high chloride solutions with AKI – primarily identified in the observational studies [35]. In contrast, a recent randomized controlled trial of high vs. low chloride solutions in a heterogeneous group of critically ill patients found no difference between groups with respect to mortality or acute kidney injury although the total fluid volume received in each group over the course of the study was 2 L, perhaps insufficient to definitively determine an effect. Further study in patients with or at high risk of AKI is warranted.

Colloid solutions such as albumin and starches are theoretically attractive alternative fluids for intravenous volume expansion given their oncotic properties; however, their appropriate use remains controversial. No differences in the incidence or duration of renal replacement therapy were observed in a randomized trial of critically ill patients comparing treatment with 4 % albumin in 0.9 % saline with isotonic saline alone [36]. However, a recent systematic review of randomized trials concluded that the use of hyperoncotic albumin solutions reduced the risk of acute kidney injury and may be appropriate for some patients including those with ascites, spontaneous bacterial peritonitis, burns, or following surgery but not as the sole resuscitant given concerns of hyperoncoticity [37]. Hydroxyethyl starch is an alternative colloid solution; however, when compared to crystalloids, hyperoncotic hydroxyethyl starch has been associated with a higher incidence of acute kidney injury [38, 39] and features of renal tubular injury (termed osmotic nephrosis) on kidney biopsy, suggesting these solutions may be harmful. As colloids have not been shown to consistently reduce mortality when compared with crystalloids across all populations who are at high risk of acute kidney injury, these solutions are usually reserved for selected patients or in those with continuing large fluid requirements. In light of the 6S trial that identified an increase in AKI frequency with starch resuscitation, starch solutions are generally avoided in those with severe sepsis or septic shock [15].

Distributive shock is a common contributor to acute kidney injury in patients with sepsis, anaphylaxis, liver failure, and burns. Aggressive fluid resuscitation remains of paramount importance in these patients; however, once intravascular volume has been repleted, vasopressors such as norepinephrine and vasopressin may be required to maintain hemodynamic stability. On the basis of a single-center trial, protocol-based fluid, vasopressor, and blood component transfusion strategies for the resuscitation of those with severe sepsis or septic shock gained widespread prominence [40]. However, three separate randomized multicenter and multinational trials (ProCESS, ARISE, ProMISe) comparing protocolized versus non-protocolized care in that patient population demonstrated no benefit to the protocolized approach [41–43]. Certain key features were evident from the trials including early recognition of those with septic shock and rapid fluid resuscitation. Both of these aspects were believed to be key elements in management common to both protocolized and non-protocolized management.

Diuretics

Total body salt and water excess is one of the major complications of AKI and diuretics are often prescribed to control fluid balance. The use of loop diuretics may also aid in the management of hyperkalemia and hypercalcemia accompanying acute kidney injury. However, diuretics can cause hypovolemia exacerbating AKI, and their use has been associated with mortality and failure to recover renal function in observational studies [44]. Some small randomized trials of furosemide reported higher risks of AKI when used as a prophylactic agent at the time of imaging and surgical procedures, while a systematic review of trials that included patients with or at risk of AKI found no significant impact on

risk of death, requirement for renal replacement therapy, or number of dialysis sessions [45, 46]. Diuretics can be used effectively to improve fluid balance, thereby facilitating mechanical ventilation (or liberation from mechanical ventilation) in volume overloaded patients. Although furosemide has been shown to facilitate diuresis, this approach does not appear to improve renal recovery among patients receiving dialysis regardless of modality for AKI.

Vasodilators and Other Pharmacologic Agents

Several pharmacological agents with renal vasodilatory properties have been studied with the aim of increasing renal blood flow and ameliorating ischemic damage in acute kidney injury. However, none of these agents have been proven to improve the clinical outcomes of acute kidney injury. A systematic review of trials including patients with or at risk of AKI found that low-dose dopamine had no significant impact on survival, need for dialysis, or adverse clinical events [47]. Dopamine has been associated with arrhythmias and intestinal ischemia and is not currently recommended to prevent or treat AKI. Fenoldopam is a dopamine type-1 receptor that also increases renal blood flow, although it decreases systemic vascular resistance. A meta-analysis suggested promising results with the use of fenoldopam in critically ill patients, including a reduction in AKI, need for renal replacement therapy, and in-hospital mortality [48]. However, given its risk of hypotension along with limitations of the existing published trials, further trials remain necessary to support the use of fenoldopam for this indication. Atrial natriuretic peptide has favorable renovascular effects that have been shown to increase glomerular filtration rate in animals. Large trials of atrial natriuretic peptide (0.2 μg/kg/min) in critically ill patients with AKI showed no impact on mortality or dialysis-free survival but a higher incidence of hypotension with atrial natriuretic treatment [49, 50]. One systematic review has suggested that low-dose atrial natriuretic peptide (0.1 μg/kg/min) is not associated with hypotension and may lead to a reduction in the requirement for renal replacement therapy [51]. Yet again, further large trials of low-dose atrial natriuretic peptide will be required before this agent can be recommended for prevention or treatment of AKI.

There is inadequate efficacy and safety data to support the use of growth factors for acute kidney injury. Although insulin-like growth factor-1 showed promising results on recovery of renal function in animals, small trials have failed to demonstrate beneficial results on kidney function in humans. A small trial of erythropoietin for the prevention of AKI following cardiac surgery reported a reduction in incidence of AKI in treated patients; however, a subsequent trial in the ICU detected no impact on the incidence of AKI. N-acetylcysteine gained widespread use for prevention of radiocontrast-associated nephropathy. However, the effects of N-acetylcysteine for prevention of acute kidney injury has been heterogeneous across studies, and the results from the most rigorously performed trials demonstrate no effect on the incidence of AKI, requirement for dialysis, or mortality.

Nutritional Support

Combined protein-calorie malnutrition is common in patients with AKI and has been consistently associated with mortality. Although clinical trials assessing the impact of nutrition on clinical end points are lacking, it is broadly accepted that appropriate nutritional support should be provided to meet the metabolic requirements of patients with AKI. Total energy consumption is not increased in AKI and only mildly increased above resting energy expenditure even in patients with critical illness. A total (not only nonprotein calories) energy intake of 20–30 kcal/kg/day is recommended to provide nutritional support in patients with acute kidney injury, while avoiding hyperglycemia, hypertriglyceridemia, and the net excess fluid load that is frequently observed with higher calorie regimens [52].

The optimal protein intake in AKI is not known. Given the association between protein-calorie malnutrition and mortality in patients with AKI, dietary restriction of protein is not considered appropriate in attempts to delay or prevent the initiation of renal replacement therapy for azotemia or acidosis. Protein wasting and negative nitrogen balance may occur in patients with AKI due to the inflammatory and physiological stresses of accompanying acute illnesses, particularly those occurring in critical illness. Nutritional protein administration is therefore usually increased to meet the greater metabolic demands of hypercatabolic patients. Furthermore, additional losses of amino acids and protein occur in the filtrate on continuous renal replacement therapy and via peritoneal dialysis resulting in additional nutritional requirements for patients receiving of these forms of renal replacement therapy; similar losses occur in those managed with an open abdomen and such losses should be addressed in the nutritional prescription. It is common to aim for a protein intake of 0.8–1.0 g/kg/day in non-catabolic patients not requiring renal replacement therapy, with increases of 2.0 g/kg/day as a common protein goal for hypercatabolic patients. Higher doses may be required for those receiving renal replacement therapy especially in the setting of septic shock, major injury, traumatic brain injury, or severe burn injury. Clinical guidelines are available to aid in this process including specific applications to those with clinically severe obesity, hyperglycemia, and those with AKI or CKD [53, 54].

Consultation with a registered dietician is valuable to estimate the appropriate energy and protein requirements for an individual patient given the multiple approaches that are available to provide guidance. Since net nitrogen balance analysis often relies on determining urinary nitrogen losses (i.e.,, UUN assay), the oliguric or anuric patient represents a unique challenge in this respect. Prealbumin has a shorter half-life than albumin but varies inversely with C-reactive protein leading to the recommendation that they should be concomitantly assessed to determine the fidelity of the prealbumin concentration. Serial assessments generally have limited value when obtained more frequently than once per week. Novel assessment strategies such as ultrasound assessment of muscle thickness may ultimately prove useful, but data are limited and no recommendation regarding this parameter may be made at present.

Long-Term Follow-Up

AKI is associated with an increased risk of progressive chronic kidney disease and ESRD after hospital discharge with 2.1 % of survivors in a regional study progressing to AKI [55]. Post-discharge follow-up of renal function is recommended for survivors of AKI [12]. Subsequent long-term management of patients with CKD after AKI usually proceeds according to the principles of CKD management [12, 56].

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Renal Replacement Therapy in the Critically Ill Surgical Patient

15

Kevin K. Chung and Ian J. Stewart

Introduction

The diagnosis of clinically significant acute kidney injury (AKI) among the critically ill surgical population occurs in approximately one in four admissions [1]. About 5 % of all patients admitted to the intensive care unit (ICU), or 1 out of every 20 admissions, require some form of renal replacement therapy (RRT) [1]. Among all critically ill patients who require RRT, the mortality has consistently been around 60 % [2]. Practically speaking, RRT refers to the clearance of excessive electrolytes, toxic solutes, and volume that accumulates in the intravascular and extravascular space in the setting of AKI. Most often, this type of therapy is delivered via a venovenous extracorporeal circuit with a blood pump that drives venous blood through an artificial "kidney" membrane. Less commonly, the peritoneal cavity could be used to exchange electrolytes and solutes in the form of peritoneal dialysis. We will focus our discussion in this chapter mainly on extracorporeal RRT with only a brief section on peritoneal dialysis.

Overview of Modalities

There are a number of RRT "modes" that can be used in the ICU. The various modes are typically divided into continuous RRT (CRRT) or intermittent hemodialysis (IHD) based on how long the therapy is applied and what type of machine is used. Regardless of the length of therapy, it is important to differentiate the two different ways that solutes can be cleared through a hemofilter within the context of an extracorporeal circuit. The two modes of clearance are "diffusive clearance" (a.k.a. hemodialysis) and "convective clearance" (a.k.a. hemofiltration). Before being able to understand this difference, we must understand the anatomy of a hemofilter, which does not differ significantly regardless of "mode."

Hemofilter Anatomy

Standard hemofilters that are utilized for the purposes of RRT are comprised of thousands of parallel hollow fibers encased in a cylindrical casing through which blood can flow (Fig. 15.1). These hollow fibers are analogous to tiny garden hoses with semipermeable walls, allowing small solutes and fluid to leak through the walls while blood is contained and passes through the middle portion of the fibers. In between the individual fibers naturally exists the "interstitial space" where leaked solutes can then escape through an opening in the cylindrical casing through the generation of a steady negative pressure or hydrostatic pressure alone.

Hemodialysis (Diffusive Clearance)

As blood flows through the fibers of a standard hemofilter, a port exists on one end of the outer cylindrical casing through which an electrolyte balanced solution (dialysate) can be infused to bathe the "interstitial space" and exit through another port on the other end of the outer casing. The steady flow of dialysate through this space creates a gradient between the concentration of any given electrolyte or solute in the blood contained in the hollow fibers and the concentration of the electrolyte or solute contained in the dialysate in the interstitial space. This concentration gradient allows solutes to passively move across the semipermeable membrane, from the space of high concentration, in the blood, to the space of low concentration, in the dialysate (Fig. 15.2). To

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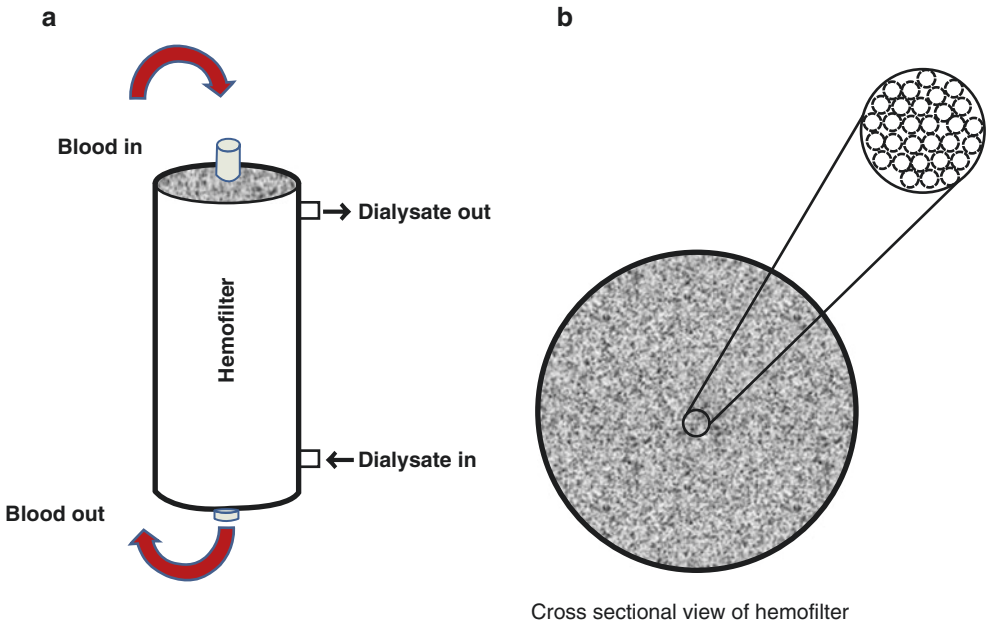

Fig. 15.1 (**a**) Schematic of a hemofilter used in this case for hemodialysis. The patient's blood enters the device at the top and is distributed into a multitude of semipermeable hollow fibers, demonstrated by the cross-sectional view (**b**). The patient's blood exists the filter at the bottom and is returned. Dialysate flows in a countercurrent fashion (i.e., the opposite direction of blood flow) to optimize the concentration gradient across the entire length of the hemofilter

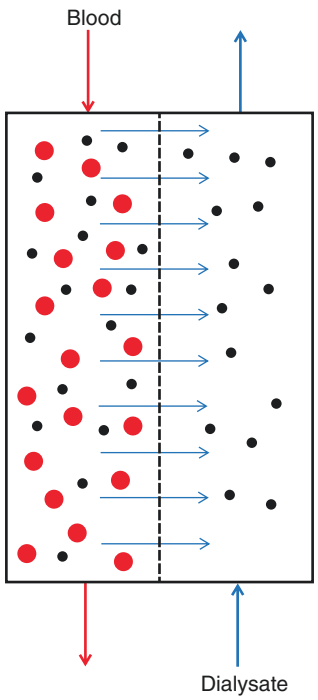

Fig. 15.2 Schematic representation of diffuse clearance in the setting of hemodialysis. Large particles (such as cells or albumin) are represented by the *red circles*. As these particles are too large to fit through the pores of the semipermeable membrane, they pass through the hemofilter and are returned to the patients. Small molecules (such as potassium and urea) are represented by the *black circles*. These molecules flow down their concentration gradient across the semipermeable membrane from the blood space to the interstitial space. To optimize the concentration gradient across the length of the hemofilter, the blood and dialysate go in opposite directions (countercurrent)

optimize the gradient between the two compartments, the dialysate is run in a countercurrent fashion (i.e., the blood and dialysate flow in opposite directions). This movement of solutes across a membrane down the concentration gradient is described as "diffusive clearance." Simply, dialysis removes various excess solutes from the bloodstream by maintaining a gradient to optimize "diffusion." Although highly efficient, this mode of clearance targets mostly solutes and molecules that are of low molecular weight in size (i.e., ≤10 kDal). Potassium and urea are examples of molecules that are in this range. Depending on the type of machine utilized, dialysate can be generated through the machine (IHD machines), come in premixed bags, or mixed by the hospital pharmacy.

Hemofiltration (Convective Clearance)

Hemofiltration, on the other hand, is a mode of solute removal that utilizes "convective clearance." In this mode, a negative pressure is generated in the interstitial space of the hemofilter, actively pulling solutes across the semipermeable membrane while an electrolyte balanced solution is introduced simultaneously either into the extracorporeal circuit or into the venous system of the body at the same rate (Fig. 15.3). This fluid is appropriately designated as "replacement fluid." Replacement fluid solutions are typically premade and commercially available in sterile packaging from various CRRT vendors. Alternatively, balanced crystalloid solutions, such as PlasmaLyte A® (Baxter Healthcare Corporation, Deerfield, IL), can be utilized as replacement solution. Of note, dialysate that is generated by IHD machines, typically through a reverse osmosis system

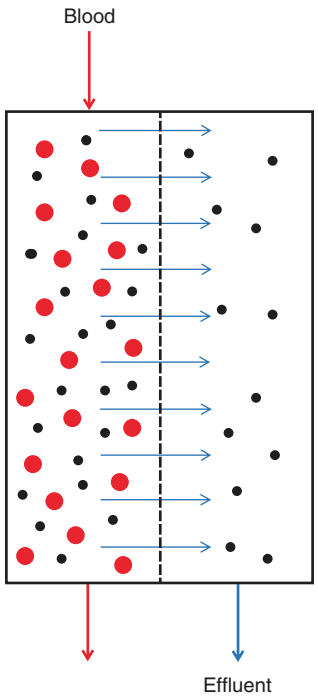

Fig. 15.3 Schematic representation of convective clearance in the setting of hemofiltration. With hemofiltration, there is no dialysate in the interstitial space. Negative pressure in the interstitial space pulls both solvent and fluid across the semipermeable membrane. Replacement fluid is infused either proximal to the hemofilter (pre-dilution) or distal to the hemofilter (post-dilution)

utilizing tap water, cannot be utilized as replacement solution as it is not considered "sterile."

Convective clearance, due to its active nature, can target solutes and molecules of higher molecular weight generally described as "middle molecules" (i.e., – 10–50 kDal). Examples of such molecules include beta2-microglobulin, most drugs such as antimicrobials, and pro- and anti-inflammatory mediators such as interleukin-1, interleukin-6, and interleukin-8. The ability of hemofiltration (convection) to remove such molecules has direct implications in the way electrolytes are managed, how drugs are dosed, and may impart extrarenal benefits.

Intermittent Hemodialysis

IHD describes a mode of extracorporeal therapy that is based on diffusive clearance and applied for a fixed period of time. Generally, IHD utilizes the same machines, personnel (dialysis technicians), and principles as chronic outpatient hemodialysis. In IHD, clearance is dependent on the blood flow rate and the dialysate rate. Treatments in the ICU, lasting 2–4 h in length, are prescribed three to five times weekly.

Compared to CRRT, IHD results in much greater clearances because of higher dialysate flow rates. This may be advantageous in patients that require high clearance (such as severe crush injury with rhabdomyolysis and resultant hyperkalemia). However, IHD may not be the preferred modality in critically ill surgical patients, because it can result in more hemodynamic instability than CRRT via two mechanisms. The first mechanism is due to the high clearance of IHD with resultant decrease in plasma osmolality [3]. When solute is removed from the intravascular space, equilibration from the extravascular space is not immediate. This establishes a gradient between these two compartments. Via oncotic pressure, water will flow out of the intravascular space leading to decreased blood volume. The second mechanism is due to the short treatment time during which volume can be removed. Similar to solute, equilibration of volume from the extravascular to the intravascular space is not immediate, and ultrafiltration can result in decreased blood volume. The rate at which volume is removed is therefore a key determinant in how a treatment is hemodynamically tolerated. For example, if 2 L of volume needs to be removed, the rate at which this occurs during a 4 h IHD treatment is 500 ml/h. This is much greater than the rate of ~83 ml/h that could be achieved using a continuous modality (2 L removed over 24 h). Therefore, IHD should only be used on hemodynamically stable patients, unless high clearances are required, for example, severe rhabdomyolysis with hyperkalemia that cannot be maintained at a safe level with a continuous modality. Decreasing the rate at which fluid is removed, by either increasing time or frequency, has been shown to decrease intradialytic hypotension in outpatient IHD [4] and can be considered in the critical care setting to minimize hemodynamic instability.

Continuous Modalities

Continuous modalities are typically delivered via machines that are specifically designed and marketed for inpatient use as CRRT machines. Unlike IHD, these machines typically do not utilize a water source (tap water) as they do not generate dialysate real time. Instead, the machines rely on premade sterile solutions that can be utilized for the purposes of both hemodialysis and hemofiltration. In fact, the exact same bag of solution can be labeled as "dialysate" or "replacement fluid" based entirely on how the solution is employed. The four modes described below are all commonly grouped under the term "CRRT." See Table 15.1 for suggested initial prescriptions.

Slow Continuous Ultrafiltration (SCUF)

In SCUF mode, a steady negative pressure is applied to the interstitial space pulling solutes and water across the semipermeable membrane and discarded through an opening in the outer filter casing through a tube that leads to an empty

Table 15.1 Typical starting prescription for the various modes of CRRT

Mode	Blood flow rate (BFR)	Replacement fluid rate	Dialysate flow rate	Ultrafiltrate rate (fluid removal)
SCUF	50–200 ml/min	None	None	50–500 ml/h
CVVH	100–400 ml/min	2–4 L/h	None	0–500 ml/h
CVVHD	100–400 ml/min	None	2–4 L/h	0–500 ml/h
CVVHDF	100–400 ml/min	1–2 L/h	1–2 L/h	0–500 ml/h

bag or directly into the sink. The fluid that is removed via this method is called "ultrafiltrate" and consists of only the fluid that is pulled across the semipermeable membrane while blood moves through the hollow fibers. This mode is typically prescribed to those who only need excess volume removed as in the case of patients with diuretic resistant fluid overload. Use of this mode is uncommon for surgical ICU patients as most have some degree of AKI and could benefit from the solute balance that is achieved through the other CRRT modes.

Continuous Venovenous Hemodialysis (CVVHD)

CVVHD is a mode of extracorporeal therapy that is based on diffusive clearance and applied continuously. CVVHD, being a mode of CRRT, is delivered by machines specifically designed for the ICU environment and utilizes premixed solutions. These solutions, typically in 5-L bags, are termed "dialysate" since it is used to provide the concentration gradient necessary for diffusive clearance.

Continuous Venovenous Hemofiltration (CVVH)

CVVH is a mode of extracorporeal therapy that is based on convective clearance and applied continuously. CVVH is also delivered by machines specifically designed for the ICU environment and utilizes premixed solutions. In contrast to CVVHD, these solutions, now termed "replacement fluid," are infused directly into the extracorporeal circuit and mixed directly with the circulating blood. Simultaneously, the negative pressure exerted in the interstitial space in between the hollow fibers of the hemofilter generates solute drag across the semipermeable membrane, removing solutes and water as the same rate that replacement fluid is being infused. The replacement fluid infusion can enter the circuit prefilter (proximal to the hemofilter), post-filter (distal to the hemofilter), or both depending on the type of machine used. The advantage of prefilter infusion of replacement fluid is a prolonged filter life that results from the dilution of blood prior to its entrance into the hemofilter. However, dilution of the blood also has the disadvantage of decreasing the efficiency of solute clearance. Post-filter infusion of replacement fluid optimizes efficiency but increases the chance of hemofilter clotting. Some CRRT machines allow the infusion of replacement fluid both pre- and post-filter. Regardless of where the replacement fluid is infused relative to the filter, an important concept to emphasize is filtration fraction. In an effort to minimize the hemoconcentration within the hollow fibers of the hemofilter, the filtration fraction must be kept below 25 %. Filtration fraction is simply calculated by adding all the effluent together and dividing it by the blood flow [5].

$$\text{Filtration Fraction} = \text{Total effluent} \left(\text{replacement fluid} + \text{ultrafiltrate}\right) / \text{blood flow}$$

The effluent consists of all the solute and water that is pulled into the interstitial space and directed out of the hemofilter casing into a waste bag or into a drain. This can be estimated by adding the replacement fluid rate and the additional ultrafiltrate set each hour. This equation is precise for post-filter infusion of replacement fluid. Prefilter infusion would further lower the filtration fraction by partially diluting the blood prior to it entering the hemofilter. Thus, this simple equation can be used as a rough estimate with the knowledge that the actual filtration fraction will always be lower if any portion of the replacement fluid is given prefilter.

Continuous Venovenous Hemodiafiltration (CVVHDF)

CVVHDF is a mode of extracorporeal therapy that utilizes both diffusive clearance (hemodialysis) and convective clearance (hemofiltration) applied continuously. Thus, a 5-L bag of premixed solution is connected to be infused as dialysate, while another bag is connected to be infused as replacement fluid. Although the same bag of solution, they are appropriately labeled differently based on the function the solution performs.

Hybrid Therapy: SLED

Slow low-efficiency dialysis (SLED) is a hybrid therapy of CRRT and IHD. In the literature, it is sometimes termed sustained low-efficiency dialysis, extended daily dialysis, or prolonged intermittent renal replacement therapy. The main advantages of SLED are that it can be performed with a conventional IHD machine, does not require specialized equipment, and requires less anticoagulation [6]. The differences between SLED and IHD are flows and time. In SLED, the

dialysate and blood flows are usually 100–200 ml/min, while in IHD the blood and dialysate flow rates are 350–400 ml/min and 700–800 ml/min, respectively. Conversely, while IHD is usually limited to 4 h, most SLED treatments last 8 h, but can be extended to 24 h which has been described as continuous SLED (C-SLED) [7]. Practically, C-SLED is no different than CVVHD; however the former usually involves higher dialysate flow rates. Otherwise, the only difference is that C-SLED is delivered using conventional outpatient machines, while CVVHD is delivered using CRRT machines that use premixed solutions. SLED allows for slower clearance of solute and volume, compared to IHD, which results in improved hemodynamic stability. The main disadvantage to SLED, particularly when treatments last more than 8 h, is uncertainty regarding appropriate dosing of essential medications (such as antibiotics) [8]. Additionally, staffing longer treatments for SLED becomes an issue if dialysis technician resources are limited.

There is a paucity of evidence comparing SLED to CRRT. A recent meta-analysis examined 17 studies (7 randomized controlled trials and 10 observational studies) that compared SLED to CRRT [9]. The investigators found a trend toward lower mortality in the observational studies but no difference in mortality in the randomized trials. This trend toward improved outcomes with SLED in the observational studies should be interpreted with caution given the inherent bias in these types of studies. The meta-analysis also reported no significant differences between CRRT and SLED in rates of renal recovery, fluid removal, length of ICU stay, clearance, or vasopressor escalation. However, SLED was less expensive in all three of the studies that reported on cost.

Overview of Controversies

Dose

Providers regularly prescribing or caring for critically ill patients on RRT must pay close attention to the dose of therapy. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommends frequent assessment of the prescription of and the delivery of actual dose [10]. At a minimum, RRT applied in the critically ill surgical patient should be able to achieve correction of any metabolic derangement or fluid imbalance for which the therapy was initiated. The nomenclature used for the dosing of RRT differs when describing IHD and CRRT. It should be noted that the highest grades (1A) were assigned for both dosing recommendations, reflecting strength and quality of the evidence that exists to result in those recommendations. For IHD, the KDIGO guidelines recommend delivering a Kt/V of at least 3.9 per week when prescribing either IHD or SLED in AKI [10]. Kt/V is a measure of the fractional clearance of urea, with K being the urea clearance (in L/h), t being time (in hours), and V being the volume of distribution of urea (in L, equal to total body water). As the units (L and hour) cancel out, Kt/V is a unit-less measure that describes the dose of IHD normalized for body size and time. Practically, this equates to a Kt/V of approximately 1.3 per IHD session for an every other day or three times a week schedule. A Kt/V of 1.3 equates to a urea reduction ratio (URR) of at least 60 % (depending on patient weight and ultrafiltration). Thus, if a patient is initiated on IHD with a blood urea nitrogen (BUN) level of approximately 100 mg/dL, the post-IHD level should be <40 mg/dL. For clinical use, however, modern dialysis machines have built-in conductivity sensors that can estimate Kt/V in real time. If this target dose is not achieved, the patient has been underdosed and could benefit from either more frequent IHD treatments or extended treatment times to achieve the minimum acceptable weekly dose recommended by KDIGO. For CRRT, KDIGO recommends delivering a total effluent volume of 20–25 ml/kg/h for AKI [10]. The total effluent volume consists of any fluid that flows through the interstitial space of the hemofilter to dump into the waste line into the effluent bag or into the sink. This can consist of ultrafiltrate only (SCUF), effluent with or without ultrafiltrate (CVVH), dialysate with or without ultrafiltrate (CVVHD), or dialysate plus effluent with or without ultrafiltrate (CVVHDF). All commercially available CRRT machines can display the total effluent volume (ml/kg/h) on the monitor.

Multiple studies have demonstrated that increasing doses beyond that recommended by KDIGO for both IHD and CRRT does not result in improved outcomes. The Veteran's Affairs and the National Institutes of Health Acute Renal Failure Trial Network study (ATN study) evaluated RRT dose in 1,124 patients [11]. The trial randomized patients needing RRT to either an intensive regimen of RRT or a less intense regimen. The intervention in the intensive group consisted of six sessions of IHD per week for hemodynamically stable patients and CVVHDF at a dose of 35 ml/kg/h or daily SLED for unstable patients. The less intensive group received three sessions of IHD per week for hemodynamically stable patients and CVVHDF at a dose of 20 ml/kg/h or every other day SLED for unstable patients. The Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group conducted their own multicenter trial, called the Randomized Evaluation of Normal versus Augmented Level RRT study (RENAL study) comparing high-dose CVVHDF (40 ml/kg/h) to lower-dose CVVHDF (25 ml/kg/h) in 1,508 patients [12]. Neither the ATN study nor the RENAL study demonstrated a survival advantage to delivering a higher dose of RRT regardless of mode.

Mode

The optimal mode of RRT in the treatment of surgical ICU patients has been the subject of much debate. As mentioned above, CRRT offers the advantage of being better tolerated

in hemodynamically unstable patients while allowing for slow and steady removal of volume over time when needed. However, a disadvantage is the need for continuous anticoagulation that increases the need for monitoring and, in turn, increases workload. IHD offers the advantage of rapid solute removal and rapid correction of electrolytes. There is also virtually no need for regional anticoagulation, and the intermittent nature of the therapy allows time for certain procedures and diagnostics without the need to interrupt therapy. Disadvantages of IHD include the potential for sudden fluid shifts which can be harmful in certain populations such as those with traumatic brain injury [13] with increased intracranial pressures and the potential for hemodynamic instability. The potential for hemodynamic instability can be mitigated by converting IHD to SLED and may be done seamlessly as long as staffing is available. CRRT is preferred in patients with brain injury because of the lower clearance offered by that mode. If CRRT is not available, SLED is an alternate mode for these patients. However, since SLED generally has larger clearances than CRRT potentially resulting in a greater osmotic shift, CRRT is the preferred modality if available.

Despite the theoretical advantages of one mode versus another, studies have demonstrated that at equivalent doses, no short-term survival advantage exists when comparing IHD to CRRT [14]. The KDIGO guidelines view IHD and CRRT as "complementary therapies" in the management of AKI in the ICU [10]. We are biased in favor of CRRT in most surgical ICU patients for the following reasons. First, KDIGO recommends choosing CRRT over IHD in hemodynamically unstable patients [10]. In many surgical ICU patient populations, such as burns [15], cardiothoracic [16, 17], or liver transplants [18], hemodynamic instability commonly accompanies acute care needs. Second, patients with intracranial hypertension from brain edema from any cause with AKI should be managed with CRRT over IHD [10, 13]. Lastly, long-term follow up studies, published after the KDIGO guidelines, suggest a possible advantage to a CRRT-based strategy in the ICU as less patients appear to be dialysis dependent when compared to an IHD-based strategy [19, 20]. It is quite compelling that among ATN trial survivors, the presence of dialysis dependence at discharge was 25 %, while among RENAL trial survivors, only 5 % of survivors were dialysis dependent [21, 22]. Thus, CRRT may be the therapy of choice in most surgical ICU patients.

Timing

The optimal time to initiate RRT in the critically ill surgical patient with AKI is also a controversial topic. Early studies showed benefit but were small in sample size [23]. Others suggest that early initiation in the critically ill is no better than waiting for clinical scenarios that would prompt the initiation of RRT in outpatients with chronic kidney disease who develop fluid overload or a metabolic disturbance of some kind (electrolyte imbalance, uremia, or acidosis) [24]. A recent systematic review suggested a possible beneficial impact on survival but concluded that the evidence was weak at best to make a strong recommendation [25]. Perhaps studies that are currently enrolling patients will help shed more clarity on this topic and help inform the nephrology and critical care community [26, 27]. Currently the KDIGO recommendation strongly encourages clinicians to consider the broader clinical context while identifying the specific conditions that can potentially be modified with RRT when considering initiation [10].

Clinical Considerations

Access

The KDIGO guidelines [10] suggest that RRT in the ICU setting be initiated with an un-cuffed, non-tunneled dialysis catheter. As has become the standard of practice, ultrasound guidance should be used for line insertion. The KDIGO guidelines recommend that access be preferentially placed in the right internal jugular vein. The second choice is a femoral vein and the third choice is the left internal jugular vein. This recommendation is based on balancing the need for adequate RRT and the infectious risk associated with central line placement. The right internal jugular vein is preferred because it is associated with the least amount of catheter dysfunction (defined as the ability to maintain adequate blood flows) [28]. However, this was only a trend ($p=0.09$) for femoral catheters compared to right internal jugular catheters. Clearance also appears to be equivalent between femoral and jugular catheters as long as a 25-cm catheter is used in the femoral vein. Conversely, the left internal jugular is associated with the most catheter dysfunction [28]. A concern with the use of femoral access is catheter-related bloodstream infection. However, in a randomized trial, femoral catheters were not associated with an increased risk of infection except in overweight patients (BMI >28.4) [29].

The use of subclavian catheters is discouraged in patients with AKI on RRT [10]. Because critically ill patients that require RRT are at an increased risk of developing end-stage renal disease [30], they may require permanent IHD access in the future. Central venous lines in the subclavian can cause central venous stenosis [31], which can complicate subsequent arteriovenous fistula placement. Therefore, the subclavian should only be used for access if no other options exist and, if needed, should be inserted on the dominant side [10].

Anticoagulation

While anticoagulation may be deferred in certain situations, such as patients with a coagulopathy or other contraindications, it is commonly used to prevent clotting of the filter. Filter clotting can decrease the amount of time on RRT, which impacts the delivered dose, and can also result in blood loss with subsequent transfusion requirement. If a patient requires systemic anticoagulation for another indication (such as a deep vein thrombosis or pulmonary embolism), it is adequate for the purposes of RRT. Otherwise, specific anticoagulation for the RRT circuit should be considered.

The most commonly used anticoagulants used to prevent clotting of RRT circuits are heparin and citrate. When heparin is used, a bolus of 2,000–5,000 units (or 30 international units/kg) can be considered, followed by a continuous infusion to maintain aPTT 1.5–2.0 times normal [32]. In patients with an elevation in aPTT at baseline (PTT > 35 s), the initial bolus can be deferred [33]. While a variety of citrate protocols have been described [34], the underlying concept is the same; citrate binds to calcium, decreasing the ionized calcium concentration. Because calcium is a key cofactor in the clotting cascade, this prevents filter clotting [35]. To avoid systemic hypocalcemia, calcium is infused in either the venous return line or centrally. When using citrate anticoagulation, the replacement fluid or dialysate should have a calcium concentration of 0 to avoid increasing the ionized calcium concentration within the circuit and reversing the anticoagulant effect. If a hypertonic solution compared to plasma is used, such as trisodium citrate (408 meq/L of sodium), the replacement fluid should be slightly hypotonic. Citrate also binds magnesium, therefore extra supplementation in the dialysate or replacement fluid should be considered. As citrate is metabolized predominantly by the liver to bicarbonate, the bicarbonate concentration should also be lowered to avoid alkalemia. If the citrate is not metabolized, such as in the setting of liver failure or profound hypoperfusion, citrate toxicity can occur. Citrate toxicity is characterized by an anion gap metabolic acidosis and a total to ionized calcium ratio of >2.5 (note that units must be equivalent). There are no citrate solutions that are approved by the Food and Drug Administration for anticoagulating an RRT circuit. In the United States, this requires the use of hypertonic citrate intended for blood banking purposes [36].

The optimal method for anticoagulation in RRT is not defined. On the basis of clinical trials demonstrating longer filter life and less bleeding complications, the KDIGO guidelines recommend citrate over heparin if the former is not contraindicated [10]. Since these guidelines were published in 2012, several other studies that compared heparin to citrate for anticoagulation have broadly confirmed these findings [37–39]. We agree that regional citrate should be considered first line for anticoagulation in CRRT. However, given the lack of standardized, approved citrate solutions and protocols, this should only be done at centers where physicians and nursing staff are comfortable with the technique.

Other anticoagulants such as argatroban can be used in the setting of heparin-induced thrombocytopenia, which requires systemic anticoagulation. One study used a loading dose of 100 μg/kg followed by a maintenance infusion of 1 μg/kg/min [40]. This maintenance dose was then titrated by 0.25 μg/kg/min to achieve a 1.5- to 3.0-fold elevation in aPTT. The authors found that measures of illness severity (APACHE II and SAPS II) could be used to predict the required maintenance dose. If argatroban is contraindicated, such as with severe liver failure, bivalirudin can also be used for anticoagulation in a CRRT circuit [41].

General Antimicrobial Dosing for RRT Recommendations (Table 15.2)

Optimal dosing varies based on agent, hemofilter, mode, dose, and patient characteristics which include protein binding, sieving coefficient, mode and dose of therapy, and volume of distribution. Please consult a critical care pharmacologist for more accurate initial dosing, maintenance, and monitoring.

Special Considerations

As already discussed, in the setting of traumatic brain injury, or other causes of increased intracranial pressure, CRRT is preferred over IHD. Greater clearance of IHD is not tolerated as well as CRRT from a hemodynamic standpoint. In the setting of increase intracranial pressure, this can result in decreased cerebral perfusion pressure and increased brain edema [13, 44, 45]. Another factor in patients with brain injury is anticoagulation. Systemic anticoagulation should be avoided in favor of no anticoagulation or regional citrate anticoagulation [44]. The final factor to consider in patients with brain injury is the serum sodium, which is usually kept artificially high to decrease edema. Commercially available solutions have fixed sodium concentrations, therefore additional hypertonic infusions of sodium should be given to maintain sodium at goal. For these reasons, CRRT is clearly the preferred modality in these patients.

Peritoneal dialysis (PD) is a form of RRT that utilizes the peritoneal membrane to achieve clearance via diffusion with fluid in the peritoneal space. The International Society for Peritoneal Dialysis (ISPD) has recently published guidelines for PD in the setting of AKI [46]. In the setting of AKI, it is

Table 15.2 General antimicrobial dosing for RRT recommendations

Antibiotic	IHD	SLED[c]	CRRT[e]
Vancomycin	15–25 mg/kg loading dose, then 500–1,000 mg after each IHD[a]	20 mg/kg loading dose[d]	15–20 mg/kg loading dose[d]
Daptomycin	4–6 mg/kg every 48–72 h, give after IHD on dialysis days	6 mg/kg every 24 h, give 2–12 h before treatment	8 mg/kg every 48 h
Piperacillin/tazobactam	2.25 g every 8–12 h, give after IHD on dialysis days	4.5 g every 8 h, infuse each dose over 4 h	3.375 g every 6 h, infuse each dose over 3 h
Cefepime	1,000 mg q 24 h, give after IHD on dialysis days	Not defined	Loading dose of 2,000 mg, then 1,000–2,000 mg every 12 h
Meropenem	500 mg every 24 h, give after IHD on dialysis days	500–1,000 mg every 8 h, time to infuse after end of treatment	1,000 mg every 8 h
Imipenem/cilastatin	250–500 mg every 12 h	Not defined	Loading dose of 1,000 mg, then 500 mg every 6–8 h
Levofloxacin	250–500 mg every 48 h	250–500 mg every 24 h	Loading dose of 500–750 mg, then 250 mg every 24 h
Amikacin	5–7.5 mg/kg every 48–72 h[b]	Not defined, dose based on drug level	Loading dose of 10 mg/kg, then 7.5 mg/kg every 24–48 h[f]

Modified from Scoville et al. [8] Additional references: Heintz et al. [42] and Jamal et al. [43]
[a]Redosing based on pre-IHD drug levels: <10 mg/L give 1,000 mg after IHD; 10–25 mg/L give 500–750 mg after IHD; >25 mg hold
[b]Redose when based on levels: Pre-IHD <10 mg/L; post-IHD <6–8 mg/L
[c]Assumes treatment for 8 h per day with blood and dialysate flow rates of 160 ml/min
[d]Give supplemental doses for goal trough of 15–20 mg/L
[e]Assumes effluent rate (sum of dialysate flow rate, replacement fluid and ultrafiltrate) of 25 ml/kg/h or 2 L per hour
[f]For severe infection, monitor level with goal peak concentration of 15–30 mg/L, redose when <10 mg/L

more commonly used in the developing world owing to its low cost compared to CRRT [46]. While there is limited evidence examining outcomes between PD and extracorporeal RRT methods, there is no evidence that one is superior to the other in terms of mortality [47]. When compared to CVVHDF, PD was not as effective in terms of creatinine and urea clearance or volume control [48]. However, the therapies were similar in terms of control of hyperkalemia and impact upon hemodynamics. Therefore, in an environment where IHD and CRRT are not available, PD should be considered for the primary management of severe AKI requiring RRT. In patients with impaired ability to convert lactate, such as liver failure or shock, bicarbonate-containing solutions are preferred over lactate-containing solutions as the former more rapidly corrects acidemia [49].

PD is also a method of home hemodialysis used for the chronic management of end-stage renal disease. Given changes to the way in which Medicare reimburses nephrologists, it is likely that this form of chronic RRT will become more prominent in the United States and thus may be encountered in the surgical ICU more frequently. We suggest that, if possible, PD be continued in such patients if they are admitted to the surgical ICU. However, if patients are catabolic, requiring more clearance, or volume overloaded, they may need to be transitioned to another form of RRT.

Novel anticoagulants used in the outpatient setting for atrial fibrillation, deep vein thrombosis, and pulmonary embolism may be encountered in the surgical ICU. One such is the direct thrombin inhibitor dabigatran. As there is no approved reversal agent for dabigatran, and the drug is cleared renally [50], these patients can present a therapeutic dilemma when they present with AKI. Dabigatran can be cleared by hemodialysis [50, 51] and hemodialysis has been shown to decrease the anticoagulant effect [51, 52]. As would be expected given the higher clearances inherent in IHD compared to CRRT, agent removal is higher with IHD [53]. Therefore, we suggest rapid initiation of IHD in patients with life-threatening bleeding in the setting of impaired renal function. Treatments longer than 4 h may be required to sufficiently clear the agent to have a clinically relevant effect [52, 53].

Discontinuation of Therapy

No specific guidelines exist for when to stop CRRT in the setting of AKI. The KDIGO Guidelines recommend stopping RRT when "it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs or because RRT is no longer consistent with the goals of care" [10]. In our practice, we

transition patients from CRRT to thrice weekly IHD when they are hemodynamically stable. An increase in urine output coupled with stability or improvement in serum creatinine between IHD sessions is our criteria for cessation of RRT in patients with AKI.

Emerging Concepts

While CRRT is the most widely utilized form of extracorporeal therapies available to clinicians, other emerging therapies exist that providers caring for critically ill surgical patients should be aware of [54]. All of these therapies come under the umbrella of extracorporeal life support (ECLS) and have been adopted at varying degrees. Extracorporeal membrane oxygenation (ECMO) has been utilized in the treatment of severe cardiopulmonary dysfunction for over 40 years. However, for years its use has been limited to just a few specialized centers around the world. Wider adoption of this ECLS technique has been spurred by one large randomized controlled trial demonstrating possible benefit [55] and the reports of its wide application during the 2009 H1N1 influenza outbreak [56]. Partial lung support, an extracorporeal therapy focused on CO2 removal, is an ECLS technique that most closely resembles CRRT in terms of the level of vascular access and blood flows [54]. In fact, some ECLS platforms have combined the ability to provide renal support and partial lung support to treat those patients who have concomitant pulmonary-renal dysfunction [57, 58]. Other ECLS applications include blood purification in septic shock and liver support in the form of molecular adsorbent recirculating system (MARS) or extracorporeal liver assist device (ELAD) [59]. Rapid advances in ECLS technologies have resulted in the emergence of the concept of multiple organ support therapy (MOST) which combines the various capabilities that are available in support of the critically ill surgical patient with multiple failing organ systems [59]. Clinician caring for the most critically ill surgical patients should become knowledgeable about these various emerging ELCS capabilities that go far beyond just renal support.

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Gastrointestinal Hemorrhage

16

Michael A. Samotowka

Introduction

There are over half a million patients hospitalized annually for gastrointestinal hemorrhage (GIH) in the USA [1]. The overall inpatient mortality rate in the USA is approximately 3 %. The majority of bleeds (~75 %) arise from the upper gastrointestinal tract, defined as proximal to the ligament of Treitz. GIH is most common in the elderly, and this population is prone to having a higher incidence of associated medical comorbidities. In the GIH patient population, 80 % of the mortality is attributable to their associated comorbidities rather than as a direct consequence of their GI hemorrhage. As the elderly population of America continues to expand, it can be expected that the incidence of GI hemorrhage patients will also increase in a proportionate fashion.

The presentation of acute upper GIH usually relates most commonly to the route of exodus of blood from the GI tract rather than hemodynamic abnormalities. In contrast, chronic UGIH may present with anemia, weakness, or dyspnea [2]. Active hematemesis is generally indicative of an upper and not lower GI tract source. Melena suggests a minimum blood loss of at least 200 ml and its presence is indicative of blood being present in the digestive tract for at least 12 h to allow RBC lysis and hemoglobin metabolism. Hematochezia may arise from either an upper or lower GI tract source and implies that blood has been present in the GI tract for less than 12 h.

Historically, bleeding that originates from the small bowel was included in the category of lower GIH, but today it is viewed as a separate entity and will be treated as such in this chapter. Bleeding from the small bowel may be occult or sporadic and thus very challenging to diagnose. It most often presents with chronic anemia or melena. Obscure GI hemorrhage refers to the patient population with persistent or recurrent GIH where the initial endoscopic evaluation did not identify the etiology of the bleed. This is estimated to be the case in about 5 % of patients with GIH [3]. Small bowel pathology accounts for up to 75 % of these patients. With the advent of capsule endoscopy and push enteroscopy as well as double-balloon endoscopy, many previously unidentifiable lesions are now readily localizable.

Lower GI (LGI) tract hemorrhage includes hemorrhage from the colon and rectum and typically presents with melena or hematochezia. Diverticular disease is the most common cause of lower gastrointestinal hemorrhage (LGIH); the incidence of this entity increases with advancing age. While severe hemorrhage progressing to shock does occur in UGIH, it is much less common in those with LGIH.

Upper Gastrointestinal Hemorrhage

Upper GI tract hemorrhage (UGIH) occurs at least fivefold more commonly than LGIH. Bleeding in the upper GI tract is separated into two distinct categories, those bleeds that are associated with varices (variceal) and those that are not associated with varices (non-variceal). Common causes of non-variceal UGIH are:

1. Peptic ulcer disease (PUD)
2. Esophagitis
3. Stress-related mucosal disease (SRMD)
4. Zollinger-Ellison syndrome
5. Vascular lesions
6. Mallory-Weiss tear
7. Tumors
8. Injury
9. Postsurgical
10. Other

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Peptic Ulcer Disease (PUD)

This is the most common cause of UGIH in both non-variceal and variceal hemorrhage patients. It accounts for an estimated 40–75 % of all episodes of upper tract hemorrhage [4]. The most common symptom is epigastric pain. Duodenal ulcers typically are characterized as a burning type of pain that is relieved by food or antacids. Gastric ulcers usually do not respond to food intake. In 1983 Warren and Marshall published a landmark paper demonstrating the association of the bacteria *Helicobacter pylori* and certain peptic ulcers [5]. *H. pylori* produces an intense local inflammatory response despite not invading the gastric mucosa. It also disrupts the normal gastric secretory physiology, which leads to high acid secretion in some areas and low acid secretion in others. The actual incidence of *H. pylori* involvement in PUD is not clear but studies have shown it to be in the range of 73–90 % [6].

Upper esophagoduodenal gastrointestinal endoscopy (EGD) remains the first-line mode for both diagnosis and therapy of bleeding ulcers. Severe hemorrhage is usually defined as greater than 1,000 ml of blood loss. It is important to remember that even in patients with a history of alcohol abuse and cirrhosis, the most likely etiology of acute UGIH is still peptic ulcer disease. Biopsies of an identified ulcer bed should be taken at the time of endoscopy to check for the presence of *H. pylori* as well as to rule out an underlying malignancy. If no endoscopy is performed, then serological or urea breath test or stool testing are also options to assess for the presence of *H. pylori*. The urea breath test can be adversely affected by the use of proton pump inhibitor medications. Serological tests are not useful to determine the efficacy of therapy as *H. pylori* antibodies remain detectable even after active infection has resolved.

Initial care of the patient with a significant UGIH begins with the basic principles of resuscitation. Securing the airway in those patients at risk for aspiration can be life saving. Establishment of large-bore and high-flow vascular access for volume resuscitation and discontinuation of any anticoagulants the patient may be taking should be done promptly. As the number of patients on various anticoagulants continues to increase, it is imperative to have the proper reversal agents available. For example, patients on aspirin will benefit from transfusion of platelets, while those on warfarin may require fresh frozen plasma, vitamin K, or a four-factor concentrate (PPC (plasma protein concentrate)). Chronic kidney disease (CKD) patients may require DDAVP to improve platelet function. Table 16.1 summarizes some of the currently available agents.

In patients who are *H. pylori* negative, the most common cause of PUD is chronic ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen. These drugs inhibit the formation of prostaglandins, which are essential in preserving gastric mucosal blood flow, the maintenance of the protective layer of mucus, as well as mucosal integrity. NSAIDs can also cause submucosal erosions by a direct cellular injury mechanism leading to destruction of gastric mucosa [7].

Aspirin is one of the most commonly used medications by prescription as well as over-the-counter use. The peak anti-platelet affect of aspirin is reached at a dose of just 31 mg in most patients; some patients require much higher doses for complete platelet inhibition. The anti-inflammatory affect increases with higher doses and most patients on aspirin are taking low-dose aspirin (81 mg/day). The use of aspirin and other nonsteroidal anti-inflammatory medications remains a major contributing factor to a peptic ulceration. Other risk factors for PUD include use of corticosteroids, tobacco abuse [8], chronic or binge alcohol abuse, as well as ulceration in association with cocaine intoxication [9]. In particular, alcohol and tobacco use increase gastric acid secretion and gastroesophageal reflux. Similar to NSAIDs, tobacco also inhibits prostaglandin production leading to defective gastric mucosal protection and an increased risk for mucosal erosion to expose the vulnerable submucosal vascular network. Cocaine use may induce local ischemia from intense vasoconstriction with resultant mucosal injury.

Table 16.1 Anticoagulant agents

	Mechanism of action	Duration of effect	Emergent reversal strategies
Warfarin	Inhibition of vitamin K-dependent clotting factors	Half-life ~40 h (highly variable)	Vitamin K
		Duration 2–5 days	KCENTRA (PCC)
			FFP
Dabigatran (Pradaxa)	Inhibitor of free and clot-bound thrombin	Half-life: 12–17 h (longer in acute kidney injury or CKD)	FEIBA-NF (PCC)
			~60 % dialyzable
			Praxbind recently FDA approved[a]
Rivaroxaban (Xarelto)	Factor Xa Inhibitor	Half-life: ~5–9 h	FEIBA-NF (PCC) may be considered
Apixaban (Eliquis)	Factor Xa Inhibitor	Half-life: ~12 h	FEIBA-NF (PCC) may be considered

[a]Idarucizumab (Praxbind) is a monoclonal antibody possessing an affinity for dabigatran 350×'s greater than that of thrombin

Esophagitis

Esophageal injury leading to hemorrhage accounts for about 2 % of UGIH [10]. Most causes of esophagitis develop from chronic reflux of gastric acid and irritation of the esophageal mucosa. Chemical (inadvertent or intentional) or therapeutic agent ingestion are other potential causes of esophageal injury and hemorrhage. Potassium supplement tablets are among the most common medication causing esophagitis. Serious bleeding that requires invasive intervention or transfer to the ICU is rare. Mechanical injury from indwelling drainage or enteral access catheters (or both) as well as post-instrumentation is more commonly implicated in hospitalized patients, especially those with critical illness. Non-massive hemorrhage from esophagitis is more common in the elderly and is generally repaired by cessation of the offending agent or treating previously undiagnosed or inadequately treated gastroesophageal reflux disease with acid suppression [11].

Stress-Related Mucosal Disease (SRMD)

Despite increased focus on stress ulcer prophylaxis in the ICU, this remains an important clinical problem in critically ill patients, having been initially described in 1969. A meta-analysis by Lin and colleagues found that 75–100 % of critically ill patients exhibit some degree of gross gastric lesions on upper endoscopy performed within 72 h of the onset of critical illness [12]. Most lesions were minor diffuse subepithelial hemorrhages or erosions and rarely progressed to massive bleeding [13]. Substantial GI hemorrhage (transfusion and intervention requiring) complicates approximately 1 % of all ICU admissions. The most important clinical factors that presage an increased risk of bleeding are acute respiratory failure defined as a need for mechanical ventilation for more than 48 h and the presence of coagulopathy. In this context, coagulopathy is defined as a platelet count <50,000 or an international normalized ratio (INR) >1.5 or an activated partial thromboplastin time of more than two times the control value. This data stems from a 1994 landmark study by Cook and colleagues that included over 2,000 ICU patients [14].

Subsequent inquiries identified acute kidney injury, age >50 years, hepatic injury, sepsis, shock, and male gender as less important risk factors [15]. The use of histamine-2 receptor antagonists (H2RA) or proton pump inhibitors (PPI) for stress ulcer prevention in high-risk critically ill patients is standard practice in most intensive care units, but the literature is not clear about their comparative efficacies or cost-effectiveness allowing clinical equipoise with regard to a preferred agent for prevention. Furthermore, acid suppression has in some studies been linked with an increased risk of ventilator-associated pneumonia [16].

Pooled results from ten randomized trials of prophylactic therapy spanning from 1980 to 1998 found an incidence of 17 % in the critically ill [17]. Analysis of trials published between 1993 and 2010 suggested a much reduced incidence of only 1 % [18]. This decrease in incidence is liberally attributed to improved critical care of, increased use of enteral nutritional support, and appropriate prophylactic therapy related in part to an increase in regulatory benchmarks driving prophylaxis. The pathophysiology of SRMD is not fully understood but is most likely multifactorial in etiology. Splanchnic hypoperfusion, as occurs during shock regardless of cause, is believed to be a major underlying cause contributing to the development of SRMD even with appropriate prophylaxis [19].

Zollinger-Ellison Syndrome (ZES)

This syndrome describes a specific hypersecretory state with antral G-cell hyperplasia and systemic mastocytosis that is associated with PUD [20]. It is a very rare cause of PUD accounting for less than 0.1 % of all duodenal ulcers. Typically it is associated with multiple duodenal ulcers or ulcers that fail to respond to conventional therapy. The ulcers can be found in unusual locations such as beyond the first portion of the duodenum. Most behave like typical ulcers that are associated with *H. pylori* although ZES patients may present with additional symptoms of cutaneous flushing, diarrhea, or heartburn. Treatment usually involves resection of the affected areas as ZES is not definitively treated using only medical therapy [21]. Hemorrhage in association with ZES-induced ulceration is generally not associated with perforation.

Vascular Lesions

Dieulafoy lesions lead to approximately 2 % of UGIH and are due to a large anomalous artery located in the digestive tract [22]. They are more common in the elderly and can be located anywhere in the GI tract but usually are located along the lesser curvature of the stomach. Most lesions can be diagnosed and then treated endoscopically with thermal coagulation, clips, as well as epinephrine injection. There are other vascular lesions of the UGI tract but they are much less common. Similar to hemorrhage in patients with ZES, resolution requires intervention as medical therapy alone is insufficient.

Mallory-Weiss Tear

A Mallory-Weiss tear refers to a longitudinal laceration of the mucosa that involves the distal esophagus or proximal

stomach or a combination of both with hemorrhage arising from the injured and exposed submucosal vessels [23]. In the vast majority of cases (90%), bleeding is self-limited. If bleeding persists the source area can usually be controlled with band ligation or clips. The etiology of the tear is thought to be related to changes in intraluminal pressure associated with violent retching and vomiting. Previously, therapy required operative management with an attendant increase in morbidity and mortality. One must remain cognizant that hemorrhage from a Mallory-Weiss tear may coexist with a full-thickness laceration, in particular of the esophagus, which when present drives a different therapeutic approach. Uncommonly, Mallory-Weiss tears may be associated with diagnostic intervention such as transesophageal echocardiography; such injuries may be considered as a separate entity due to the significantly higher mortality compared to patients with Mallory-Weiss tears that were not related to recent instrumentation [24].

Tumors

Tumors of the UGI tract do not characteristically present with acute massive hemorrhage but instead tend to a more insidious presentation. Indolent GIH is associated with both malignant and benign tumors. This group as a whole represents only a small percentage of UGI tract hemorrhage, but early diagnosis is essential especially for those with malignancy leading to the practice of routine biopsy of endoscopically identified ulceration or mass for diagnostic purposes. Examples of tumors associated with GIH include but are not limited to adenocarcinoma, gastrointestinal stromal tumors (GIST), lymphoma, leiomyoma, leiomyosarcoma, and lymphoma. Surgical resection, if not contraindicated by other patient comorbidities, is usually indicated although some cases of lymphoma may be treated with chemotherapy. Similarly, many cases of leiomyoma may be endoscopically resected as well.

Injury

Penetrating trauma (as opposed to blunt injury) to the upper GI tract can cause substantial bleeding. Gastric injury in particular may lead to substantial hemorrhage due to the multiple sources of blood supply to the stomach as well as the well-connected submucosal plexus. In this setting, endoscopic therapy is contraindicated and operative management is indicated. The clinician should remain aware that duodenal injury may not present with hemorrhage in an OGT in the presence of an intact pyloric sphincter mechanism, and the absence of blood should not be construed as evidence of the lack of injury. Injury from caustic ingestions cause widespread esophageal and gastric damage but uncommonly leads to major diffuse bleeding immediately after ingestion; hemorrhage hours to days after is instead more common. The surgical management of penetrating, blunt, and caustic ingestion injuries is beyond the scope of this text. However, the critical care aspects of management include distal enteral access for luminal nutritional support, acid suppression, and resuscitation to support mucosal blood flow.

Post-intervention and Postsurgical

Patients who undergo endoscopic intervention such as biopsy or polypectomy at the time of EGD are at risk for bleeding at the site of intervention, but these are almost always self-limiting and stop without intervention; similar bleeding risks are noted for those who undergo endoscopic sphincterotomy during endoscopic retrograde cholangiopancreatography. On occasion, angioembolization is required to control bleeding, but this is much less common than spontaneous cessation with supportive measures including ensuring an intact coagulation cascade.

In contradistinction, patients who have previously undergone aortic reconstruction with a synthetic graft are at risk for developing an aortoenteric fistula by erosion of the graft or stent directly into the lumen of the GI tract. If this occurs it is usually at the level of the third portion of the duodenum but can occur at any level of the GI tract. Massive hemorrhage can occur suddenly and is usually fatal. Many patients will have a history of a self-limited sentinel (or herald) bleed that occurred days or even weeks prior to the onset of life-threatening hemorrhage. The diagnosis is best made by CT scan or CT angiogram as endoscopy is frequently nondiagnostic. Definitive treatment involves emergent laparotomy with removal of the graft and creation of an extra-anatomic bypass such as an axillobifemoral bypass coupled with repair of the duodenal erosion; the options for surgical repair of the GI tract are multiple and are beyond the scope of this chapter. However, distal enteral access is rather useful to help avoid the need for TPN in the perioperative period and to help promote GI luminal health by providing essential glutamine. There are recent reports of repairing aortoenteric fistulas using covered endovascular stents [25], but this should only be a temporary step in stable patients until future definitive repair. Only in those patients with limited life expectancy or poor candidates for surgery should this be the sole treatment of the fistula.

Any operative intervention that involves intestinal resection and anastomosis embraces a risk for bleeding at the site of the anastomosis. This holds true whether the anastomosis was created using stapling or suture techniques or a combination of both. Bleeding at the anastomotic line is usually self-limited and may only require correction of coagulopathy

or discontinuing perioperative anticoagulants. Options for therapy depend on the timing of the bleed with regard to the operation as well as the hemodynamic impact of the bleeding. In general hemodynamic instability is best managed in the OR, especially when the event is in the immediate perioperative period; anastomosis revision or opening with suture control and reclosure are most commonly applied techniques. When more remote, endoscopic therapy is a viable option but often requires pre-intervention airway control. Such control also allows the procedure to be done at the bedside instead of moving the patient to the GI suite or OR. Endoscopic techniques including cautery and clip application with or without vasoconstrictor injection may afford control when the bleeding site is visualized. Similarly, angioembolization has been used for acute control as well but carries with it a risk of anastomotic ischemia (colon and small bowel > stomach). It should be noted that more often than not, anastomotic hemorrhage is arrested with correction of coagulopathy and control of elevated blood pressure when present.

As the number of patients in the USA who undergo operative intervention to control clinically severe obesity continues to rise, it is likely that the incidence of postoperative hemorrhage will rise in parallel. Those patients who have undergone gastric banding are at risk for erosion of the band through the gastric wall with subsequent hemorrhage and require prompt operative intervention; endoscopic or angioembolization techniques are not appropriate due to the combined hemorrhage and perforation; while uncommon, it is an important complication to recognize. In contrast, the most common operation for clinically severe obesity at present is gastric bypass with Roux-en-Y reconstruction. In this focused patient population, the incidence of postoperative GI tract bleeding complicates up to 4.4 % of patients [26]. The incidence is reported as threefold higher in those who were cared for using a laparoscopic approach versus in an open technique; the genesis of this difference remains unclear.

Early postoperative (>48 h) bleeding after gastric bypass is typically manifested by hematemesis or bright red blood per rectum in the presence of clinical signs of shock and is an indication for urgent surgical re-exploration. Hematemesis suggests that the gastrojejunal anastomosis is the origin of the bleed. Bright red blood per rectum could stem from the gastric remnant or the jejunojejunostomy anastomosis. In cases of late (<48 h postoperative) hemorrhage and hemodynamic stability, the patients can typically be treated nonoperatively with avoidance of anticoagulants and routine supportive critical care interventions. When the site is unclear and hemorrhage continues but is unaccompanied by hemodynamic compromise, some advocate using a tagged red blood cell nuclear scan to help identify the source, while others pursue a CTA as the initial step in site identification. It is likely that the selected diagnostic test is more related to availability and may vary from institution as a reflection of local resources. In gastric bypass patients who present with GI tract hemorrhage several months or even years after surgery, the most likely etiology is a marginal ulcer. Timely endoscopy (EGD) with therapeutic intervention is indicated in this situation and is generally coupled with acid suppression.

Other

There are several other potential causes of UGIH. Patients with a Crohn's exacerbation may present with GI tract hemorrhage and are generally self-limited. The pancreatic and hepatobiliary tract may rarely be the source of UGIH with patients presenting with hemobilia (post-injury or post-intervention) or hemosuccus pancreaticus, respectively. Additionally, Cameron lesions (linear erosions in the gastric portion of a hiatus hernia that is above the diaphragmatic orifice of the hernia) complicate approximately 3–5 % of such hernias and rise in proportion to the size of the hernia. Cameron lesions are very rare causes of over hemorrhage but may account for up to approximately 4 % of causes of occult GI bleeding [27].

Guideline-Derived Recommendations

To assist clinicians in the management of patients with nonvariceal upper gastrointestinal hemorrhage, a multidisciplinary consensus group was formed that reviewed relevant literature and constructed several evidence-based management recommendations [28]. Below is a brief synopsis of the group's findings:

Recommendation 1: Hospitals should develop institution-specific protocols for multidisciplinary management that should include access to an endoscopist with training in endoscopic hemostasis.

Recommendation 2: Support staff trained to assist in endoscopy should be available for urgent endoscopy. Patients identified as high risk for re-bleeding should be admitted to a monitored setting for at least the first 24 h.

Recommendation 3: Immediate evaluation and appropriate resuscitation are critical to proper management.

Recommendation 4: In selected patients, the placement of a nasogastric tube can be considered because the findings may have prognostic value.

Recommendation 5.1: Clinical (non-endoscopic) stratification of patients into low-risk and high-risk categories for re-bleeding and mortality is important for proper management. Available prognostic scales may be used to assist in decision-making.

Recommendation 5.2: Early stratification of patients into low-risk and high-risk categories for re-bleeding and mortality based on clinical *and* endoscopic criteria is important for proper management.

Recommendation 6: Early endoscopy (within the first 24 h) with risk classification by clinical and endoscopic criteria allows for safe and prompt discharge of patients classified as low risk.

Recommendation 7: A finding of low-risk endoscopic stigmata (a clear-based ulcer or a non-protuberant pigmented dot in an ulcer bed) is not an indication for endoscopic hemostatic therapy. A finding of a clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgment, with appropriate treatment of the underlying lesion. A finding of high-risk endoscopic stigmata (active bleeding or a visible vessel in an ulcer bed) is an indication for immediate endoscopic hemostatic therapy.

Recommendation 8: No single solution for endoscopic injection therapy is superior to another for hemostasis.

Recommendation 9: No single method of endoscopic thermal coaptive therapy is superior to another.

Recommendation 10: Monotherapy, with injection or thermal coagulation, is an effective endoscopic hemostatic technique for high-risk stigmata; however, the combination is superior to either treatment alone.

Recommendation 11: The placement of clips is a promising endoscopic hemostatic therapy for high-risk stigmata.

Recommendation 12: Routine second-look endoscopy is not recommended.

Recommendation 13: In cases of re-bleeding, a second attempt at endoscopic therapy is generally recommended.

Recommendation 14: Surgical consultation should be sought for patients who have failed endoscopic therapy.

Recommendation 15: H-2 receptor antagonists are not recommended in the management of patients with acute upper GI bleeding.

Recommendation 16: Somatostatin and octreotide are not recommended in the routine management of patients with acute non-variceal UGIH.

Recommendation 17: An intravenous bolus followed by continuous infusion proton pump inhibitor is effective in decreasing re-bleeding.

Recommendation 18: In patients awaiting endoscopy, empirical therapy with a high-dose proton pump inhibitor should be considered.

Recommendation 19: Patients considered at low risk for re-bleeding after endoscopy can be fed within 24 h.

Recommendation 20: Patients with upper GI bleeding should be tested for *Helicobacter pylori* and receive eradication therapy if infection is present.

These recommendations were updated in 2010 [29]. There were only a few minor additions. More emphasis was placed on early risk stratification of patients for re-bleeding. Epinephrine injection alone is not advised. High-risk patients for re-bleeding should be hospitalized for at least 72 h. Blood transfusion for patients with a hemoglobin level <7 mg/dl is advised. A negative *H. pylori* test in the acute setting should be repeated. The most important addition addresses patients who need cardiovascular prophylaxis. Patients with an UGIH who require secondary cardiovascular prophylaxis should start receiving aspirin again as soon as cardiovascular risks outweigh gastrointestinal risks. This threshold is generally crossed within 7 days of cessation of hemorrhage. Aspirin plus a proton pump inhibitor therapy is preferred over clopidogrel alone to reduce re-bleeding.

Variceal Hemorrhage

Varices are thin-walled and dilated veins located in the distal esophagus that are characterized by a higher venous pressure than normal as well as a higher venous flow than normal; varices are not normally present and indicate the presence of a concomitant disease process. They are typically associated with a cirrhotic liver but the converse is not true as only about half of all cirrhotics have varices. The main factor that determines variceal rupture risk is the hepatic vein pressure gradient. Most variceal bleeds are esophageal with only 3 % having a gastric origin. Early (<12 h) esophagogastroduodenoscopy (EGD) is essential in the management of patients with known varices and active UGI hemorrhage. Early endoscopy accomplishes two key goals: (1) excludes a non-variceal source of hemorrhage and (2) provides endoscopic control for identified variceal hemorrhage (the mainstay of therapy for such bleeding).

Mortality after acute variceal hemorrhage remains high (15–20 %) despite advances in medical management. It is important to note that historical mortality rates were as high as 40 % in the 1980s. Historically, the Child-Pugh score and other subjective clinical data was used to estimate patient mortality. Reverter et al. showed that the MELD (model for end-stage liver disease) score demonstrated superior performance and a more strong correlation with 3-month mortality and is now the most commonly used and durable predictor of patient mortality associated with hepatic disease and decompensation [30]. Mortality is negatively influenced by recurrent hemorrhage.

Re-bleeding rates may reach 60 %, and the mortality associated with re-bleeding has been reported as high as 33 % [31].

Optimal care of the patient with acute variceal hemorrhage benefits from a multiprofessional approach including an intensivist. One should remain aware that those with variceal hemorrhage may require massive transfusion and a close relationship with the blood bank is essential; transfusion on a protocol with the involvement of a clot-focused hematologist in helpful in

guiding management and for participation in a quality improvement program for the massive transfusion protocol as well [32]. Early airway control may reduce pulmonary soilage and facilitate rapid diagnostic and therapeutic intervention using EGD. Administration of prophylactic antibiotics has been shown to be of some incremental benefit [33]. Early antibiotic administration has been shown to decrease the incidence of early re-bleeding and improve overall survival [34].

Endoscopic therapy offers several techniques to control hemorrhage and have in general replaced the Sengstaken-Blakemore or Linton tube for initial hemorrhage control in all but those with presentation hemodynamic instability. Esophageal varices may be treated using rubber banding or intra-variceal sclerotherapy with a sclerosing agent. There are several types of sclerosing agents that are FDA approved including 1.5 % sodium tetradecyl sulfate, absolute alcohol, ethanolamine, or sodium morrhuate. No single agent has been shown to be superior to others.

Concomitant medical management is essential to help reduce the likelihood of recurrent hemorrhage by reducing flow through the existing varices. A mainstay of such therapy is intravenous somatostatin. It was shown to be superior to placebo in controlling variceal hemorrhage when used in conjunction with endoscopic sclerotherapy [35]. Combined therapy using endoscopic intervention and vasoactive agents has been shown in several randomized controlled trials to be superior to either treatment alone [36]. If initial therapy fails, then consideration of an interventional radiologist placing a covered transjugular intrahepatic portosystemic shunt (TIPS) is indicated rather than any of the surgical procedures that are primarily of historic interest including a variety of systemic or selective shunts or esophageal devascularization procedures. The additional use of vasopressin as a vasoactive constrictive agent can be considered but it is associated with more side effects [37]. Adjunctive agents such as estrogen, long-acting nitrates, and bet-blockers may be considered as well with combination therapy outperforming monotherapy in preventing recurrent hemorrhage.

In the case of esophageal varices that are able to be initially endoscopically controlled, repeat therapeutic endoscopy is indicated if the patient is stable and has recurrent bleeding. For gastric varices repeat endoscopic treatment is not indicated. In this case a TIPS or other intervention should be considered. Garcia-Pagan et al. showed that in certain high-risk patients that included patients with Child B cirrhosis and active bleeding at endoscopy and Child C cirrhotics with less than 14 points after medical and endoscopic treatment was performed, the early placement of a covered TIPS (<72 h from admission) was associated with a better prognosis [38].

Additionally, when only gastric varices are noted, an evaluation for splenic vein thrombosis should be undertaken as appropriate therapy is splenectomy for gastric variceal hemorrhage due to unimpeded arterial inflow but blocked venous outflow. This condition has also been known as left-sided portal hypertension or sinistral hypertension. In a hybrid room or OR suite, initial control may be achieved with splenic artery embolization or balloon occlusion to allow resuscitation and achieve temporary hemorrhage control in those with prior abdominal surgery with the potential for the need for an extensive adhesiolysis to reach the spleen.

Hepatic Transplantation

Patients with variceal hemorrhage that requires intervention should be evaluated for transplant candidacy early in the course of their evaluation and therapy [39]. In particular, those with inadequate response to therapy may have few options other than hepatic transplantation to decrease variceal pressures and control bleeding. While the indications for acute transplantation are fairly consistent between centers in the USA, the use of supportive technologies such as CRRT for concomitant AKI or CKD, as well as bioartificial liver techniques, vary by center and are beyond the scope of this chapter.

Small Bowel Hemorrhage

The reported incidence of the small bowel as the source of hemorrhage is between 1 % and 7 % of patients who present with blood per rectum [40]. The most common cause is angiodysplasia. Other causes are:

1. Tumors (benign and malignant)
2. Crohn's disease
3. Meckel's diverticulum
4. Toxicity related to therapeutic agents
5. Toxicity related to illicit agents
6. Varices
7. Injury (blunt, penetrating, post-intervention)
8. Dieulafoy lesion

The most commonly used test to diagnose (presence and location) small intestinal hemorrhage is the ^{99m}Tc-tagged red blood cell scan. Unfortunately, the test is not very accurate due to the inability to spatially resolve location despite the test's excellent sensitivity to the presence of very small volume bleeding. Instead, there are now three relatively new modalities that improve localization quite substantially including:

1. Capsule endoscopy
2. Push enteroscopy
3. Double-balloon enteroscopy

Capsule endoscopy involves the patient swallowing a small pill with an embedded camera that takes images of the

bowel lumen during its aboral passage. The images are wirelessly sent to a monitor the patient wears allowing delayed image retrieval and analysis. The test is very sensitive and minimally invasive but cannot be used if there is any concern about the presence of a bowel obstruction that could preclude the patient passing the camera out the rectum; while the camera does not need to be recovered, intestinal obstruction will lead to an incomplete evaluation of luminal surfaces past the site of obstruction.

Double-balloon enteroscopy (DBE) uses a dedicated 200 cm enteroscope with two balloons. One of the balloons is attached to the tip of the endoscope and the other to the tip of a flexible overtube. By sequentially inflating and deflating the balloons, the scope can be advanced progressively more distally in the small bowel. The scope can be passed orally as well as transanally thus allowing for visualization of the entire length of small bowel. An advantage of DBE over capsule endoscopy is that it permits biopsies to be obtained of suspicious lesions and allows interventions to be deployed to control hemorrhage when discovered. In a meta-analysis comparing DBE to capsule endoscopy, Chen et al. found the yield of localizing the bleeding lesion was comparable for the two modalities [41], but there is clear asymmetry in terms of intervention.

Push enteroscopy uses an enteroscope that allows for visualization of the proximal 100 cm of small bowel. Push enteroscopy may be used in or out of the OR. Intraoperatively, push enteroscopy may be aided by manual of laparoscopic manipulation of small bowel, allowing telescoping for more than 100 cm of small intestine onto the enteroscope. In the ICU, similar manipulations may be made in those managed with an open abdomen, although the need for this is uncommon. In the GI suite, push enteroscopy may be aided by gravity and positional changes of the patient to facilitate passage of the enteroscope; airway control is essential in facilitating push enteroscopy. Like double-balloon enteroscopy, push enteroscopy also allows the operator to perform diagnostic and therapeutic interventions. Triester et al. in a meta-analysis comparing the yield of finding the source of small bowel hemorrhage with capsule endoscopy versus all other modalities found that capsule endoscopy was significantly superior with regard to diagnostic capacity to all other modalities [42].

Angiodysplasias are a common cause of small bowel hemorrhage and are small ectatic blood vessels that are found in the mucosa or submucosa of the GI tract. They are also called vascular ectasias or arteriovenous malformations (AVM). They are more common in the elderly and in patients with chronic kidney disease. Typically, they are multiple in number which can make it difficult to determine exactly which one is the source of hemorrhage. If the bleeding angiodysplasia is identified on endoscopy, it can be most effectively treated with clipping or thermal probe coagulation and injection of epinephrine. Argon plasma coagulation [43], as well as photodynamic therapies, has also been explored for these lesions.

If the exact one responsible cannot be identified, then surgical resection of the segment of involved small bowel can be considered, but patients with angiodysplasia are prone to develop new lesions and recurrence of bleeding in the remaining small bowel.

If a tumor is the etiology of small bowel hemorrhage, then resection is warranted if there are no other contraindications to surgery. Crohn's disease-associated bleeding is treated with immune suppression initially and only patients who fail conservative therapy go on to resection. Meckel's diverticulum-induced hemorrhage is best diagnosed with a Meckel's scan (99mTc-pertechnetate scintigraphy), and surgical resection is the treatment of choice. Varices and Dieulafoy lesions would be treated as discussed earlier.

Lower GI Hemorrhage (LGIH)

Patients with LGIH typically present with hematochezia or blood per rectum. Lower GI hemorrhage is one fifth as common as upper GI hemorrhage. The annual incidence in the USA is reported to be 20.5–27 cases per 100,000 adult population at risk. The majority of LGIH requires no intervention to stop [44]. The mean age of patients with LGIH ranges from 63 to 77 years of age. Mortality spans 2–4 %, and LGIH is more common in men than in women.

The basic principles of management are: (1) evaluation and resuscitation or hemodynamic stabilization of the patient (unlike UGIH cases the LGIH patients do not commonly present with massive hemorrhage), (2) localization of the bleeding site, and (3) site-specific therapeutic intervention. Patients with presentation hypotension, transfusion-requiring hemorrhage, all benefit from ICU admission and monitoring. Telemetry monitoring of preexisting arrhythmias, as well as known but not active coronary disease, does not require ICU admission. Patients with drug-eluting stents who have their antiplatelet therapy held may benefit from ICU admission for monitoring and potentially more rapid intervention as needed for myocardial ischemia.

Localization is the challenging step in this algorithm. Several large series have shown that colonoscopy has an overall diagnostic yield ranging from 53 to 97 % reflecting operator skill, intestinal preparation, and the intermittent nature of many etiologies of LGIH [45]. Early colonoscopy is considered the procedure of choice; however, its utility can be limited by massive ongoing bleeding. Arteriography is typically reserved for those patients. Jacovides et al. assessed the value of performing a computed tomographic angiogram (CTA) prior to visceral angiogram (VA) to improve the yield and found that it did in fact improve the efficacy of finding

the bleeding lesion [46]. To improve the yield of VA, some clinicians will use provocative angiography that entails systemic heparinization plus selective transcatheter injection of a vasodilator *and* tissue plasminogen activator into the suspected vessels. Push enteroscopy using a pediatric scope may be of benefit in certain stable patients [47].

Farrell et al. reviewed the utility of radionuclide imaging and found that although it was well tolerated by patients, it is an inconsistent technique for identifying the source of bleeding with a widely ranging accuracy of 24–91 % [48]. While demonstrating great sensitivity to the presence of small amounts of hemorrhage (0.1–0.2 ml blood loss per minute are identifiable), the patient must be bleeding at the time of the scan for it to be positive. Abnormal vasculature devoid of bleeding is not demonstrated by nuclear medicine studies and is better demonstrated on CTA or VA. The study should only be done in hemodynamically stable patients and when positive still requires a therapeutic intervention as this technique offers only diagnosis. The most common causes of LGIH are:

1. Diverticular disease
2. Angiodysplasia
3. Inflammatory bowel disease
4. Neoplasm
5. Hemorrhoids
6. Proctitis

Diverticulosis is common in the Western Hemisphere but rare in Asia and Africa. This difference has been attributed to a higher fat and processed substrate content in the US diet. The increased pressure required by the colon to aborally propel less well-hydrated stool results in pressure gradient-driven mucosal herniation through the muscular layer of the colon along the course of penetrating vessels. Expansion of the diverticulum during mass movement leads to vascular injury from stretch and tearing resulting in hemorrhage. Treatment of diverticular hemorrhage includes application of hemoclips, thermocoagulation, or epinephrine injection at the time of diagnostic and then therapeutic endoscopy. In the majority of cases, hemorrhage may be arrested endoscopically. In those who fail endoscopic management, options include angioembolization as well as resectional therapy. While previously believed to create very high risk for intestinal ischemia and perforation, angioembolization techniques infrequently require subsequent operative therapy for perforation [49]. Angiodysplasia-associated hemorrhage maybe treated in a similar fashion.

There are a host of less common causes of LGIH of which the clinician should be aware but which generally do not require ICU care; the majority of ICU care in these patients occurs after therapeutic intervention in the OR with less common care occurring during resuscitation. In patients with inflammatory bowel disease, severe life-threatening hemorrhage is uncommon, but it is the primary indication for 10 % of emergency colectomies in this patient population. Bleeding from a neoplasm is common but rarely massive. The vast majority of these bleeds can be treated endoscopically. Thus, if the patient has a malignant lesion, resection can be performed after the patient has been properly resuscitated and stabilized. Colonic polyps may bleed spontaneously (generally leading to fecal occult blood) or more commonly after biopsy.

Radiation proctitis may develop in patients who have previously undergone either external beam radiation therapy or the implantation of radioactive seeds for an unrelated system such as the prostate. Bleeding can occur at any time after radiation therapy, even years after treatment had been completed. Since radiation-induced changes in the microvasculature lead to friability, even minor mucosal challenges may lead to bleeding. In the elderly who have diminished thirst sensation and are more prone to stool dehydration, stercoral injury will more commonly occur in those with prior irradiation. Treatment of radiation proctitis is as outlined above for the other causes of LGIH. Proctitis that is due to inflammatory bowel disease may benefit from steroid enemas to reduce local inflammation. Proctitis that has an infectious underpinning generally responds to targeted anti-infective therapy. Periprocedural or autoerotic lacerations that are not full thickness but that are complicated by bleeding often respond to topical hemostatic agents. It is uncommon for any of the above to require ICU care.

Hemorrhoids are the most common cause of rectal bleeding. If unresponsive to topical agents, they are optimally band ligated, stapled using a circular stapler, or simply sutured. One must be aware of the relationship of hemorrhoidal hemorrhage to portal hypertension as mechanical hemorrhage control strategies alone may fail in that unique patient population. That group of patients often requires ICU admission for care of the portal hypertension.

Acute arterial or mesenteric venous occlusion may be complicated by LGIH, although this is quite rare. Hemorrhage in this setting occurs when there is enough ischemia to lead to mucosal death and slough. Bleeding from the junction of mucosa and submucosa may occur. Acute mesenteric ischemia is defined as a sudden decrease in blood flow to a level that is inadequate to meet the metabolic demands of the viscera [50]. The most common etiologies of acute mesenteric ischemia and their relative frequency are:

1. Arterial embolus (50 %)
2. Arterial thrombosis (20 %)
3. Low-flow state (20 %)
4. Mesenteric venous thrombosis (5 %)
5. Other (5 %)

There are many algorithms and approaches to identifying the presence of and impact of intestinal ischemia with regard

to intestinal viability and wall integrity. Techniques include CT, CTA, endoscopy, proctoscopy, and VA, with selection depending on the presence of pneumoperitoneum, peritonitis, hemodynamic instability, or hemorrhage, as well as local resources. Similarly there are a host of treatment options depending on the extent and impact of ischemia spanning therapeutic anticoagulation to resection with or without revascularization as well as lysis with or without stenting.

The intensivist should be cognizant of the association between several relationships including but not limited to:

1. New-onset atrial dysrhythmia and arterial embolization
2. Mesenteric venous thrombosis and hypercoagulability
3. Intestinal ischemia, resuscitation, and reperfusion injury to other viscera including the liver and kidneys
4. Intestinal ischemia operative therapy and a planned second-look procedure leading to open abdomen management for the initial 24–48 h after the index procedure
5. Risk for fistula formation with intestinal resection if the abdomen is unable to be closed primarily

Recognizing these relationships will help inform the intensivist with regard to diagnostic undertakings, likely procedural planning, risk, and outcome-based family discussions including the potential for hospital and ICU readmission, organ failure potential, and care coordination with the primary team.

Conclusion

GI hemorrhage spans a vast number of potential etiologies and overlaps with multiple organ systems. Key aspects in terms of diagnosis and temporary or definitive therapy including multiple hospital areas such as the GI suite, ICU, interventional radiology, and the operating room underscore the need for a team-based approach to the care of patients with GI tract hemorrhage.

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Critical Care Management of Severe Acute Pancreatitis

17

Ronald Tesoriero and Jose J. Diaz

> It is the most terrible of calamities that occurs in connection with the abdominal viscera.
>
> The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it renders it the most formidable of catastrophes [1].
>
> Sir Berkeley Moynihan Annals of Surgery, 1925

Introduction

Acute pancreatitis is a common gastrointestinal disease that results in a significant physical, psychosocial, and financial toll [2, 3]. It has become the leading gastroenterology discharge diagnosis in the United States and its incidence appears to be increasing [2, 4, 5]. The cost of caring for these patients is greater than 2 billion dollars annually, and the cost of a single survivor of severe acute pancreatitis has been estimated at $129,000 [3, 6]. There is a spectrum of disease from the mild edematous form to severe acute necrotizing pancreatitis with associated multiple organ system dysfunction. The most common form of the disease is mild with a 3–4-day self-limited course and a low mortality and occurs in nearly 80 % of patients [7, 8]. Unfortunately, 20 % of patients will develop severe acute pancreatitis with a fulminant clinical course. Those with the severe form of the disease often require prolonged intensive care unit (ICU) and hospital lengths of stay, invasive support and procedures for organ failure and management of pancreatic necrosis, and mortality rates that approach 30 % [8–11].

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The Atlanta classification, first reported in 1992 [12] and revised in 2012 [13], divides pancreatitis into three groups: mild, moderate, and severe, based on degree of organ failure and presence of local or systemic complications. It is now widely recognized that there are two phases of severe acute pancreatitis, early and late, each with its own peak of mortality [13–17]. The early phase occurs in the first week and the systemic inflammatory response syndrome (SIRS) and potential for development of organ failure are its hallmark [13, 18–20]. The late phase occurs after the first week and is characterized by the development of local complications, hospital acquired and pancreatic infections, and secondary deterioration in organ failure [8, 10, 13, 20].

This chapter will first review epidemiology, etiology, diagnosis, and classification of pancreatitis. It will follow with the early ICU management of moderately severe and severe acute pancreatitis (SAP) including the issues of IVF resuscitation, prophylactic antibiotics, nutrition, invasive ICU therapies, and invasive procedures for local complications.

Epidemiology

The incidence of acute pancreatitis had been increasing over the past several decades and is as high as 73.4 cases per 100,000 population worldwide [5, 21–23]. There are over 290,000 admissions yearly for acute pancreatitis in the United States, and 75 % of patients who present to the ED will require admission [2, 24]. The annual cost of caring for acute pancreatitis is in excess of 2 billion US dollars per year [3]. Women are two times more commonly affected, likely related to the increased prevalence of cholelithiasis in females [25–27]. The peak incidence occurs between the ages of 55 and 65 years in women and 45 and 55 years in men. Unfortunately this allows ample time for the development of secondary complications of chronic medical conditions and may greatly impact the management of patients who have the severe form of the disease [22, 23, 25–27]. Most cases of acute pancreatitis

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have a benign course of disease. Although the overall mortality in acute pancreatitis is only 5 %, most of this is attributable to the 20–25 % mortality associated with severe forms of the disease [8, 9, 14, 23].

Etiology

The two most common causes of pancreatitis are gallstones (40–70 %) and alcohol (25–50 %) which account for the vast majority of disease [18, 28–30]. Gallstone pancreatitis presents acutely and generally resolves with passage or removal of the common duct stone. Alcohol-induced pancreatitis presents as a range of disease from limited episodes of acute pancreatitis to chronic irreversible disease. Patients generally have a history of over 5 years of heavy consumption, although acute pancreatitis affects less than 5 % of heavy drinkers [18, 30]. Only rarely is a large alcohol binge the inciting event for an episode of acute pancreatitis [27].

Idiopathic pancreatitis (IP) is the third most common cause occurring in approximately 25 % of cases and contributing up to 40 % of the mortality [27, 31]. Acute pancreatitis is labeled idiopathic when a specific etiology is not immediately apparent by history, physical examination, and laboratory and noninvasive imaging studies [31]. There are several large series that indicate the prevalence of biliary microlithiasis to be as high as 75 % in cases of acute IP [31, 32]. This coupled with studies showing that cholecystectomy, endoscopic sphincterotomy, and ursodiol significantly reduce recurrent attacks of IP suggests that biliary microlithiasis is a major contributor [31–33]. Other potential etiologies of "IP" include sphincter of Oddi dysfunction, anatomic pancreatic ductal abnormalities (divisum and anomalous union), choledochocele, annular pancreas, pancreaticobiliary tumors, genetic mutations, and autoimmune disorders [31]. The majority of these can be diagnosed with high-resolution computed tomography (CT) scan, magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP), endoscopic ultrasound (EUS), or endoscopic retrograde cholangiopancreatography (ERCP), thus leading to decreasing characterization of IP in affected patients.

Hypertriglyceridemia is a well-known cause of acute pancreatitis and accounts for 1–10 % of all cases [34–37]. Considering that some series suggest it as the underlying cause in more than half of acute pancreatitis cases in pregnancy and its potential contributing pathogenesis to alcohol-induced pancreatitis, it likely plays a larger role than is currently estimated [27, 38, 39]. Serum triglyceride levels greater than 1000 mg/dl are considered necessary to independently cause acute pancreatitis [18, 21, 27]. Acute pancreatitis requires high chylomicron concentrations, as seen in type I and V hyperlipoproteinemia; however it may be seen in other genetic phenotypes [35]. Hypertriglyceridemia-induced pancreatitis typically occurs in a patient with a preexisting lipid abnormality in which a secondary precipitating factor, such as poorly controlled diabetes, hypothyroidism, pregnancy, alcohol, or medication (diuretics, beta-blockers, and estrogens), occurs [27, 35]. Triglyceride levels may decrease rapidly (within 48 h) after the onset of HTG-induced acute pancreatitis and so serum levels should be checked early in the course of the disease [35, 40].

There is a long list of medications that may cause pancreatitis, but the data supporting most as causative agents is limited [18, 41, 42]. Overall, medication, infectious, and non-lipemic metabolic (hypercalcemia, hyperparathyroidism) causes are rare, more often falsely implicated than actually causing acute pancreatitis [18, 34, 41–43].

Blunt and penetrating injury may cause pancreatitis, but is relatively uncommon occurring in less than 2 % of blunt injury cases [44]. Pancreatitis after ERCP with sphincterotomy occurs 2.4–15.9 % of the time, but is generally mild and self-limited [45]. Pancreatitis may also occur secondary to ischemia related to vascular disease (atheromatous and vasculitis), embolic phenomenon, hypotension, and shock and after some common surgical procedures (cardiac surgery and cardiopulmonary bypass) [27, 31].

Genetic defects, such as cystic fibrosis transmembrane conductance regulator (CFTR), serine protease inhibitor Kazal type 1 (SPINK1), cationic trypsinogen gene (PRSS1 and N291), and celiac disease, are increasingly recognized as potentially causative of recurrent acute pancreatitis [18, 31]. Though the role for genetic testing is still unclear, it may be reasonable in patients who have more than one family member with pancreatic disease [18] or in cases of recurrent pancreatitis where no other cause is found.

Diagnosis

Clinical Presentation

Abdominal pain is the main symptom of acute pancreatitis and is present in nearly 95 % of patients [27]. Vagal stimulation secondary to pain and paralytic ileus often lead to nausea and vomiting. Pain may not be assessable in SAP when patients present in a decompensated state with severe systemic inflammatory response syndrome (SIRS), multiple organ failure, delirium, and coma.

Fever and other signs of SIRS are common in the first 24 h, although they are generally transient. Though SIRS is sensitive for the subsequent development of organ failure and mortality, it has poor specificity (41 %) for the development of severe disease. However, persistent SIRS despite early aggressive intravenous resuscitation should alert the practitioner to the need for intensive care unit-level admission for close monitoring, as should the presence of hypotension, dyspnea, and shock [18, 27].

Jaundice is generally absent at the onset of disease, although it occasionally accompanies patients presenting with gallstone pancreatitis with continued choledocholithiasis and in cases where pancreatic edema compresses the distal common bile duct. The abdominal exam is significant for epigastric or diffuse upper pain, and peritoneal findings may be present in cases of severe pancreatitis. The abdomen is often distended and tympanitic, related to gastric and focal ileus, and bowel sounds may be absent. Ecchymosis in the flanks (Grey Turner's sign), periumbilical area (Cullen's sign), and groin (Fox's sign) come from significant retroperitoneal hemorrhage that has dissected through tissue planes and reached the surface. Their presence is rare at presentation, but denotes cases of severe pancreatitis and should be investigated with diagnostic imaging [27, 46, 47].

Laboratory Tests

Although 75–80 % of patients with acute pancreatitis will have an elevated amylase level, it cannot be used in isolation to make the diagnosis due to limitations in its sensitivity and specificity [18, 27, 48]. The serum level of amylase becomes elevated within a few hours of the onset of acute pancreatitis symptoms and reaches its peak between 36 and 72 h. It remains elevated for 3–5 days in uncomplicated cases, but may normalize within 24 h due to the enzymes short half-life [27, 49]. Serum levels three times higher than normal suggest a diagnosis of acute pancreatitis [27, 50]. However, levels may be normal in up to 32 % of patients presenting with acute pancreatitis [18, 27, 51, 52]. This may be secondary to acute massive gland destruction, preexisting chronic alcoholic pancreatitis (where low levels of amylase exist in the pancreas), and hyperlipidemic pancreatitis (due to amylase inactivation) [27, 51]. Additionally, there are a number of conditions that may result in elevated amylase levels in the absence of pancreatitis. These include macroamylasemia, chronic kidney disease, diseases of or injury to the salivary glands, extrapancreatic abdominal disease processes (acute appendicitis, cholecystitis, intestinal obstruction or ischemia, ectopic pregnancy, and peptic ulcer disease) and tumors (ovarian cysts and malignancies and lung cancer), and conditions such as diabetic ketoacidosis, anorexia nervosa, and acquired immune deficiency syndrome (AIDS) [18, 27]. The level of elevation of amylase does not equate with the severity of pancreatitis, and higher levels are more commonly noted with gallstone pancreatitis than with alcoholic pancreatitis [27, 52].

As compared to amylase, lipases are mainly produced by the pancreas and appear to be more specific for the diagnosis of acute pancreatitis [18, 27, 48]. Due to the longer half-life, they remain elevated until 5–10 days, often after amylase levels have returned to normal [27, 53]. Although elevated lipase levels are seen in a number of non-pancreatic diseases, including renal disease, diabetes, appendicitis, and cholecystitis, levels greater than three times normal are very suggestive of pancreatitis [50]. In the case of diabetes and renal disease, using levels five times higher than normal to make the diagnosis is prudent [18, 53].

Given their limitations, elevated amylase and lipase cannot be used to make the diagnosis of acute pancreatitis in isolation and require corroboration with either clinical examination or imaging studies.

Imaging Studies

Plain abdominal radiographs, transcutaneous ultrasonography, and computed tomography are the most commonly utilized imaging studies obtained when acute pancreatitis is suspected. Transabdominal ultrasound should be performed in all patients that present with acute pancreatitis to evaluate for biliary stone disease.

Though contrast-enhanced CT is over 90 % sensitive and specific for the diagnosis of pancreatitis, its routine use in mild pancreatitis is unnecessary as most can be diagnosed with clinical presentation and laboratory parameters and rarely develop secondary complications [18, 54, 55]. However, its use in a patient failing to improve after 48–72 h is warranted, as it can assess for pancreatic necrosis and local extra-pancreatic complications [18, 56–58]. Additionally, as clinical scoring systems are as effective as CT scan for predicting severe acute pancreatitis and the development of necrosis is generally delayed for several days, routine admission CT evaluation is unwarranted [59]. Overall, its ubiquitous availability, sensitivity, specificity, and ability to assist with the staging of pancreatitis and diagnosis of extrapancreatic complications make it the most useful imaging study in patients with the severe form of the disease.

MRI compares well with CT in the early assessment of acute pancreatitis [60]. It has advantages over CT scan in that it can detect choledocholithiasis, pancreatic ductal abnormalities, and pancreatic duct disruption. Additionally, it can diagnose pancreatic necrosis without the administration of intravenous contrast, which can be useful in patients with multi-organ failure and acute kidney injury [60]. However, its expense, the duration of the procedure (especially in critically ill marginally stable patients), its limited availability, and the inability of most non-radiologist practitioners to accurately interpret its images still limit the use of MRI.

Overall Diagnosis

The diagnosis of acute pancreatitis requires two of the following three characteristics to be present: (1) development of acute abdominal pain consistent with the disease,

(2) serum amylase and/or lipase concentrations more than three times greater than the upper limit of normal (higher in patients with diabetes and renal dysfunction), and (3) imaging studies with typical abnormal pancreatic findings [13]. These criteria allow the diagnosis to be made without imaging in those that present with typical mild disease, in those who are incapable of elevating enzymes, and in those who are unable to report typical symptoms related to obtundation due to critical illness. The etiologic cause of pancreatitis should be sought at presentation. A history, transabdominal ultrasound, triglyceride level, and calcium level should be obtained and will establish the cause in most patients.

Severity Scoring and Risk Stratification

It is important to identify patients that would benefit from early aggressive treatment or transfer to specialized care centers, as this has been shown to improve outcomes in SAP. Unfortunately, clinicians continue to struggle with predicting the development of severe forms of the disease. There are a number of clinical and radiologic systems that have been developed to assist in identifying those at risk for developing severe disease, multiple organ dysfunction syndrome, or local and systemic complications due to pancreatitis. Unfortunately, each has limitations and none have proven to be definitive.

Clinical Scoring Systems

Ranson's Criteria

Ranson described one of the first clinically useful scoring criteria for acute pancreatitis in 1974 and it has been in use for more than four decades [61]. It utilizes patient age and basic laboratory (WBC, AST, LDH, glucose, base deficit, BUN, calcium, HCT, and PaO2) and clinical data (amount of fluid required by 48 h) to calculate a score up to 11. One of its disadvantages is the need to wait until 48 h to calculate a complete score. A score ≥3 appears to be as sensitive as more recent clinical and CT scoring systems at predicting the development of severe pancreatitis. Unfortunately the criteria lack specificity as more than 80 % of patients with a score ≥3 will not go on to have severe disease [62, 63].

APACHE II

The acute physiology, age, and chronic health evaluation II (APACHE II) scoring system was initially described and its use to predict severity of acute pancreatitis was first reported in the 1980s [64, 65]. The scoring system utilizes age, the presence or absence of chronic immunosuppression or organ failure, reason for admission (elective postoperative vs. emergent postoperative/emergent non-postoperative), and 12 laboratory values (sodium, potassium, creatinine, HCT, WBC count, pH, and PaO2) and physiologic variables (GCS, temperature, MAP, heart rate, and respiratory rate) present on admission to calculate a score up to 71. A score of ≥8 is sensitive for the development of severe acute pancreatitis, though scores ≥10 are more specific and ≥17 are better able to predict mortality [59, 65, 66]. Though APACHE II has the advantage of being able to be calculated on admission, it is more accurate at 48 h [65]. Additionally, its complexity makes its use by the bedside clinician difficult.

BISAPS

The Bedside Index of Severity in Acute Pancreatitis (BISAPS) score for prediction of mortality in acute pancreatitis was initially described in 2008 [67]. It assigns one point for BUN >25mg/dL, impaired mental status, >=2 SIRS criteria, age >60, and the presence of pleural effusion to calculate a score of up to 5 points. A BISAP score of ≥3 has been associated with a sharp increase in mortality. Although it has not been shown to be more accurate than other clinical scoring systems, it can be easily calculated on presentation with simple clinical examination, laboratory, and radiographic studies [59, 62, 66].

Clinical scoring systems, such as Panc 3, the harmless acute pancreatitis score (HAPS), and the Japanese severity score (JSS) are infrequently utilized and do not appear to show a benefit over the more common clinical scoring systems [68–71].

Computed Tomography Scoring Systems

CT Severity Index and Modified CT Severity Index

Balthazar and Ranson first proposed a CT grading scale (Balthazar grade) of intrinsic and extrinsic pancreatic changes to predict morbidity and mortality in 1985 [72, 73]. Balthazar further refined this work to include degree of pancreatic necrosis and proposed a CT severity index (CTSI) to delineate patients that would go on to have severe disease [74]. It has since become one of the most widely utilized scoring systems in both clinical settings and research [58]. The CTSI assigns a point score from 0 to 4 based on degree of pancreatic inflammation and from 0 to 6 based on amount of pancreatic parenchymal necrosis. A maximum point score of 10 may be achieved, and scores of 0–3, 4–6, and 7–10 are associated with mild, moderate, and severe disease [54, 74]. Several studies have shown a strong correlation between CTSI and the clinical severity of pancreatitis, though there are others that have not supported these findings [58, 75–81]. The development of systemic

complications and organ failure has been shown to have a significant relationship with CTSI [75, 78]; however this is not observed in all studies [80, 82] and does not seem to be as effective a predictor as APACHE II scores [58, 83]. Most studies show a strong correlation between the development of local complications, including infection, and CTSI [58, 75–78, 80, 83, 84]. Additionally, high CTSI scores have been associated with mortality in several [75, 77, 84], but not all studies [85].

The modified CT severity index (MCTSI) was first described in 2004 and seemed to better correlate with development of organ failure and length of hospital stay than the CTSI in an initial study [86]. It simplified the scoring of both pancreatic inflammation and necrosis and took into account extrapancreatic manifestations of disease, such as ascites, pleural effusion, vascular and parenchymal complications, and GI tract involvement. Scores of 0–2, 4–6, and 8–10 are considered to be consistent with mild, moderate, and severe disease respectively. Differences between the two systems can be seen in Table 17.1. Further study has shown no significant difference between the MCTSI and CTSI in predicting severity, local complications, or mortality [58, 59].

Other CT scoring systems such as Balthazar grade, pancreatic size index (PSI), mesenteric edema and peritoneal fluid (MOP) score, extrapancreatic (EP) score, and extrapancreatic inflammation on CT (EPIC) score are slightly less accurate than CTSI/MCTSI but do offer the benefit of not requiring intravenous contrast enhancement [59].

Table 17.1 CT severity index (CTSI) vs. modified CTSI (MCTSI)

Characteristics	CTSI	MCTSI
Pancreatic inflammation		
Normal gland	0	0
Focal or diffuse enlargement of pancreas	1	2
Peripancreatic inflammation	2	2
Single acute fluid collection	3	4
Two or more acute fluid collections	4	4
Pancreatic necrosis		
None	0	0
<30 %	2	2
30–50 %	4	4
≥50 %	6	4
Extrapancreatic complications[a]	NA	2
Severity		
Mild	0–3	0–2
Moderate	4–6	4–6
Severe	7–10	8–10

[a]One or more of the following: pleural effusion, ascites, vascular complications, pancreatic parenchymal complications, and gastrointestinal complications

Atlanta Classification System

The Atlanta symposium developed a universal classification system in 1992 that became known as the Atlanta classification [12]. Though it was used extensively, some of its definitions were confusing [87], and it was revised in 2012 to create more uniformity [13]. It recognizes that acute pancreatitis is a highly dynamic disease with two overlying phases and two peaks of mortality, early and late [13–17].

Phases of Acute Pancreatitis

The early phase of the disease is present during the first week and may extend into the second. Its hallmark is the systemic effects of the host response to the local pancreatic injury. This direct injury of the pancreas results in the production of cytokines and inflammatory mediators that may result in SIRS and direct injury to distant organ systems. The degree and persistence of SIRS correlate with the risk of developing organ failure [13, 19, 20, 88, 89]. Organ failure may be transient (resolving within 48 h) or persistent (continuing for >48 h) [20, 90]. As necrosis is often unreliably characterized early in the disease process, and the extent of pancreatic and peripancreatic changes are not directly correlatory with the development or severity of organ failure, local complications are generally not the main indicators of severity in this early phase [13]. Infected necrosis rarely develops during this phase of the disease and most fever and leukocytosis are related to a sterile SIRS or the development of non-pancreatic infections [91, 92].

The late phase of pancreatitis only occurs in patients with moderate and severe disease and is characterized by the development of local complications or the persistence of systemic inflammatory signs or organ failure. Ongoing organ failure continues to be the main indicator of severity of the disease during the late phase. It is important to characterize the location and features of local complications, as they will have direct effects on management and may contribute to the deterioration of organ function (e.g., development of infected necrosis, retroperitoneal hemorrhage from vascular complication).

With these phases in mind, the Atlanta classification revision of 2012 set about defining organ failure, types of pancreatitis, and systemic and local complications to better standardize the classification of pancreatitis.

Organ Failure

The assessment of organ failure was simplified by utilizing the modified Marshall scoring system, which assesses the respiratory, cardiovascular, and renal systems and assigns a

Table 17.2 Modified Marshall scoring system for organ dysfunction

	Score[a]				
Organ system	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal[b] (serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular[c] (systolic blood pressure, mmHg)	>90	<90, fluid responsive	<90, not fluid responsive	<90 pH, <7.3	<90, pH <7.2

[a]A score of ≥2 in any organ system defines the presence of failure
[b]Scoring for patients with preexisting renal dysfunction is dependent on deterioration in function
[c]Without inotropic support

score based on degree of dysfunction (Table 17.2) [93]. A score of 2 or greater is used to define failure in any one organ system. The Marshall score can be assessed at both the time of presentation and repeated at any point during hospitalization.

Types of Acute Pancreatitis

Most patients will present with *interstitial edematous acute pancreatitis*. This is characterized by diffuse enlargement of the entire gland, although occasionally there may be localized inflammation. There will often be inflammatory changes in the peripancreatic fat, acute peripancreatic fluid collections may sometimes be present, and the pancreas enhances completely on contrast-enhanced CT. Most patients with this form of acute pancreatitis will have resolution of their symptoms within the first 7 days [13, 94].

Less than 10 % of patients will develop *necrotizing pancreatitis*. Most patients with this form of the disease will have necrosis both of the pancreas and peripancreatic tissue, although it can affect either in isolation. The extent of necrosis is associated with both development of organ failure and mortality [95]. However, necrosis is rarely present at the onset of disease and instead develops over the first several days [13, 58, 59, 74, 96]. For this reason early contrast-enhanced CT often underestimates the extent and severity of disease and is not routinely recommended for early assessment. Peripancreatic and pancreatic necrosis has a highly variable course. It may liquefy or stay solid and persist or disappear over time [13].

Infected pancreatic necrosis is uncommon during the first phase of pancreatitis and rare in the first 7 days. Pancreatic and peripancreatic necrosis may remain sterile or become infected over time. Though there does not appear to be a clear correlation between the amount and degree of necrosis and the duration of symptoms and risk of infection [13], the development of infection within pancreatic or peripancreatic necrosis is associated with worsened morbidity, a secondary decline in organ function, and increased mortality [95, 97].

Systemic and Local Complications

Systemic complications occur when a preexisting comorbidity is worsened by an episode of acute pancreatitis. This may include exacerbations of chronic lung, kidney, or ischemic heart disease. It is independent of, although may contribute to, the development of organ failure. These types of complications help to define moderate pancreatitis [13].

Local complications occur as either a direct result of pancreatic injury and necrosis or due to the secondary effects of pancreatic inflammation on surrounding tissues. They include peripancreatic fluid collections, acute necrotic collections, walled-off necrosis, pseudocyst, gastric outlet obstruction, portal and splenic vein thrombosis, and colonic necrosis [13]. The timing of their development is variable but should be suspected when there is persistence of, or a secondary decline in, organ dysfunction, an acute decompensation in a previously improving patient, ongoing or recurrent abdominal pain, or new signs of infection or sepsis. A description of the various pancreatic and peripancreatic local complications can be seen in Table 17.3.

Atlanta 2012 Definitions of Severity of Pancreatitis

Mild acute pancreatitis is the most common form and develops in upwards of 80 % of patients. It is defined by the absence of organ failure and systemic or local complications. As necrosis and local complications are rare, these patients do not require routine pancreatic imaging. Mortality is extremely rare and most admitted patients will be discharged during the early phase, generally within the first 3–7 days [13, 94].

Moderately severe acute pancreatitis is defined by transient organ failure (<48 h) or local or systemic complications, and its mortality is significantly less than that of severe acute pancreatitis [13, 98]. Moderately severe disease may resolve with supportive care and without specific interventions. However, it may be necessary to provide prolonged care and can potentially require multiple interventions to manage disease-specific local complications.

Severe acute pancreatitis is defined by the presence of persistent (>48 h) organ failure during the early phase of the disease. Patients who present with either persistent or severe SIRS or early organ failure should be treated as severe acute pancreatitis. Some of these patients may resolve their organ failure and fall into the moderately severe acute pancreatitis group, though the improvement is likely due to early aggressive therapy in many of them. Persistent organ failure can be due to a single organ system, but these patients frequently have multiple organ systems affected. Patients who develop persistent organ failure often have local complications that may require specific interventions, and they should be aggressively investigated with pancreatic imaging if organ dysfunction continues after the early phase is complete. The presence of persistent organ failure has a reported mortality of 20–50% [13, 19, 20, 89], and further development of infected necrosis in these patients significantly increases the chances of death [97].

Table 17.3 Local complications of acute pancreatitis

Acute peripancreatic fluid collection[a]
Pancreatic pseudocyst[b]
Acute necrotic collection[c]
Walled-off necrosis (WON)[d]
Gastric outlet obstruction/dysfunction
Portosplenomesenteric venous thrombosis (PSMVT)
Sinistral (left-sided portal) hypertension
Gastric varices
Pancreatic/retroperitoneal hemorrhage
Arterial pseudoaneurysm
Colonic necrosis, perforation, or stricture
Gastrointestinal hemorrhage

[a]Fluid collection adjacent to the pancreas occurring within the first 4 weeks after onset of acute pancreatitis without an organized wall or associated peripancreatic necrosis
[b]Fluid collection with an organizing wall, usually outside the pancreas, occurring more than 4 weeks after the onset of acute pancreatitis
[c]A collection of fluid and necrosis, without an organizing wall, within or adjacent to the pancreas
[d]A collection of fluid and necrosis, with an organizing wall, within or adjacent to the pancreas. Usually occurs more than 4 weeks after the onset of necrotizing pancreatitis

Determinant-Based Classification System

Some have proposed using a determinant-based classification system (DBC) to identify severe pancreatitis in those with infected necrosis without persistent organ failure and critical pancreatitis in those with infected necrosis and persistent organ failure [99, 100]. This system does not consider other local or systemic complications. Both the Atlanta 2012 classification and the DBC system appear to accurately predict mortality, length of stay, and need for intervention. The Atlanta 2012 seems to better predict length of stay, likely related to the inclusion of systemic complications, and the DBC appears better able to predict need for intervention, related to its specific stratification of infected necrosis [101]. A summary of the Atlanta 2012 classification and DBC system and grades of severity can be seen in Table 17.4.

Predicting Severe Acute Pancreatitis

Acute pancreatitis is a variable and dynamic disease process. It is rare for mild disease to progress to moderately severe or severe disease. However, patients misclassified as mild at presentation and those with higher severity levels may evolve in response to, or the lack of, early aggressive care and specific therapeutic interventions. Though the Atlanta classification appears to accurately reflect clinical outcomes [101], many of its disease-specific stratification features (e.g., necrosis, local

Table 17.4 Acute pancreatitis severity classification systems

	Mild	Moderate	Severe	Critical
Atlanta 2012	No organ failure[b]	Transient[f] organ failure	Persistent[g] organ failure	NA
		And/or		
	No local[c] or systemic[d] complications	Local or systemic complications		
DBC[a]	No organ failure[e]	Transient organ failure	Persistent organ failure	Persistent organ failure
		And/or	Or	And
	No pancreatic necrosis	Sterile necrosis	Infected necrosis	Infected necrosis

[a]*DBC* determinant-based classification
[b]Organ failure (Atlanta 2012): score ≥2 in any one organ system utilizing the modified Marshall scoring system
[c]Local complications: peripancreatic fluid collections, acute necrotic collections, walled-off necrosis, pseudocyst, gastric outlet obstruction, portal and splenic vein thrombosis, and colonic necrosis
[d]Systemic complications: worsening of a preexisting comorbid disease
[e]Organ failure (DBC): score ≥2 in any one organ system using the sepsis-related organ failure (SOFA) score, or the need for cardiovascular inotropic support, PaO_2/FiO_2 ≤300, or creatinine ≥2mg/dl
[f]Transient: <48
[g]Persistent: ≥48

Table 17.5 Clinical factors associated with severe acute pancreatitis

Persistent SIRS despite adequate resuscitation and analgesia
Age >55
Obesity (BMI >30 kg/m^2)
Altered mental status
Presence of comorbid disease
Hypovolemia
BUN >20 or increasing
Elevated creatinine
HCT >44 % or increasing
Decreased urine output
Pleural effusions or pulmonary infiltrates on CXR

Most factors are present on patient presentation or can be reevaluated after a short interval of evaluation and resuscitation

complications, persistent organ failure) and those of the other scoring systems discussed above are not present on admission. Often by the time they can be accurately characterized, the patient's status is apparent [18, 102].

Fortunately, most patients who will develop persistent organ failure in the early phase of acute pancreatitis will have organ dysfunction at presentation. A careful assessment of volume status, degree of hypovolemic shock, and presence of organ dysfunction is paramount. Though SIRS lacks specificity for predicting organ failure, it is extremely sensitive, and its persistence is an excellent marker for patients at risk of severe disease. Practitioners would do well to beware the patient with persistent tachypnea and tachycardia, after appropriate analgesia, and plan admission to an intensive care unit.

Other factors that are evaluable at presentation and have been shown to be associated with the development of severe disease include age >55, obesity (BMI >30 kg/m^2), altered mental status, the presence of comorbid disease, evidence of hypovolemia (BUN >20 mg/dl or increasing, HCT >44 % or worsening of hemoconcentration, elevated creatinine, and decreased urine output), and the presence of pleural effusions or pulmonary infiltrates on CXR (Table 17.5). The presence of any of these factors should alert the practitioner to the potential for the early deterioration of apparent mild disease to moderately severe or severe disease and should prompt early aggressive monitoring and judicious guided resuscitation.

ICU Management

Management in the First 24–48 h

Patients with severe acute pancreatitis may have a torrential course, especially in the first few days of their disease process. Decisions that occur in the initial resuscitation phase can have lasting repercussions on disease progression, the development of organ failure, and the occurrence of local and systemic complications. Early appropriate resuscitation may prevent the progression of disease and development of necrotizing pancreatitis. However, over-resuscitation may contribute to the development of secondary abdominal compartment syndrome in patients that are already prone to intra-abdominal hypertension. Renal replacement therapy may play a role in ameliorating the inflammatory state in severe acute pancreatitis and decreasing intra-abdominal pressure, even in those who do not have significant acute kidney injury.

Initial Resuscitation

During the early pro-inflammatory phase of SAP, an intense capillary leak develops due to the release of cytokines and inflammatory mediators from pancreatic and interstitial cellular injury. This leads to the extravasation of protein-rich fluid from the intravascular space into the pancreas and peripancreatic tissues and in more severe cases into the peritoneal cavity (ascites), pleural spaces (pleural effusion), and lung parenchyma (extravascular lung water) [102].

Early adequate IVF resuscitation may interrupt the cascade of events that leads to pancreatic necrosis by providing macro- and microcirculatory support [103]. Hemoconcentration appears to serve as a surrogate marker of plasma volume status and failure to adequately resuscitate. Patients who present with significant hemoconcentration and an elevated HCT (≥44–47 %) or who fail to have their admission HCT decrease at 24 h have an increased risk of developing severe disease [104]. This is at least in part due to decreased perfusion pressure in an edematous abnormal pancreas leading to microcirculatory changes that result in pancreatic dysoxia and necrosis [102, 105]. This hemoconcentration and decreased perfusion pressure may also lead to organ dysfunction that may worsen to failure [106]. The association between organ failure, development of pancreatic necrosis, severity of disease, and mortality illustrates why judicious aggressive intravenous resuscitation is extremely important in these patients.

Volume of Resuscitation

Despite expert opinion [18, 102, 103, 107] and indirect clinical evidence [104, 106, 108] to the importance of early aggressive plasma volume expansion, there are only a few studies in which it had been directly evaluated [109, 110], and the optimal strategy remains unclear [111, 112]. Additionally, there is suggestion that overly aggressive fluid resuscitation may worsen outcomes and lead to more intensive care unit transfers, respiratory complications, as well as an increased

association with pancreatic necrosis and infection, persistent organ failure, and increased hospital length of stay and mortality [113–118]. However, it remains unclear whether the high-volume requirements in these studies are causative of worsened outcomes or simply serve as a surrogate marker of severity of disease.

The amount of fluid sequestration that occurs in the first few days of acute pancreatitis has been reported in several studies and may help to guide fluid therapy volume goals. The reported mean fluid sequestration at 48 h was 3.7 L (liters) in mild and 5.6 L in severe pancreatitis in a retrospective series from Ranson in 1978 and formed the basis for the well-described 6 L fluid sequestration criteria [119]. A more recent study evaluated the median fluid sequestration after hospitalization for acute pancreatitis in those without necrosis (3.2 L, range 1.4–5 L), with necrosis (6.4 L, range 3.6–9.5 L), and with persistent organ failure (7.5 L, range 4.4–12 L) and showed a clear relationship between the severity of disease and receipt of addition volume resuscitation [113, 120].

Though aggressive volume resuscitation remains the recommendation of many [102, 103, 109], the proposed volumes recommended (250–500 mL/h for 48 h) in several published resuscitation strategies would lead to the routine administration of 6–12 L of fluid in the first 24 h [102, 120, 121]. Unfortunately, by the time many patients with acute pancreatitis are hospitalized or transferred, extensive fluid shifts, hypovolemia, and hemoconcentration are often already present [120, 122], and there is a suggestion that the cycle of events leading to irreversible pancreatic necrosis is already established [123]. This coupled with the association of worsened outcomes with large volumes of fluid administration suggests that a more tempered and guided approach seems prudent [113–118].

Given the similarity of these patients to those who present with severe sepsis, a resuscitation management approach that is similar to that set out in the Surviving Sepsis Campaign, rather than a predetermined fluid administration, is appropriate [124]. A volume bolus of 20–30 mL/kg followed by a maintenance rate of 1.5–3 mL/kg per hour was used when evaluating two types of fluid in a recent randomized controlled prospective trial in acute pancreatitis resuscitation and is a reasonable starting point [110]. Frequent re-evaluation for adequacy and end points of resuscitation are important, but it is far from clear what markers should be used [111, 112, 120].

Guidance of Resuscitation

Although laboratory markers of hemoconcentration (HCT, BUN, and creatinine) and their worsening can be predictive of the development of severe pancreatitis, their use to assess adequacy of volume resuscitation is not granular enough to offer any real guidance. Resuscitation using a heart rate (HR) goal has the potential for significant error, as these patients frequently have an elevated HR from SIRS independent of their overall volume status. Utilizing a urine output goal of 0.5–1 mL/kg per hour is reasonable and easy to obtain [110, 123, 125], but continued oliguria despite volume loading may be more reflective of renal function than volume status in patients who frequently present with renal dysfunction. Measuring serum lactate, and $ScvO_2$ levels may offer assistance in monitoring resuscitation [126, 127], but have not been specifically studied in pancreatitis [120].

Though central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), and mean arterial pressure (MAP) are frequently utilized, their limitations are well known and compounded by acute pancreatitis patients on positive-pressure ventilation and who often have intra-abdominal hypertension (IAH) in the early acute phase [120, 122, 128]. There is increasing interest in using invasive and noninvasive measures of stroke volume variation (SVV) and pulse pressure variation (PPV) to evaluate volume responsiveness in the critically ill on mechanical ventilation. Unfortunately PPV seems most useful at its extremes and most patients fall into a gray zone (4–17 %) where it remains poorly predictive of volume responsiveness [129]. Additionally SVV is at its most accurate when the patient has a normal cardiac rhythm, is not spontaneously breathing, and is ventilated at a larger (≥8 mL/kg) than standard tidal volume currently used in practice [130, 131].

The ability of bedside ultrasound to evaluate inferior and superior vena cava diameter and collapsibility is useful to assess volume responsiveness although mechanical ventilation and higher levels of PEEP may decrease its utility [132, 133]. There is increasing evidence that intensivist performed limited transthoracic echocardiography compares well with information obtained from pulmonary artery catheters, is better able to assess volume status than invasive measures of stroke volume variation, and may help guide volume resuscitation, titration of vasopressors, diuresis, and diagnose cardiac abnormalities (right and left ventricular dysfunction) that may alter management [127, 134–136].

Resuscitation Fluid Type

The type of fluid used for acute resuscitation is as contentious an issue as the amount of volume needed. Unfortunately there is little published data to guide fluid choice in acute pancreatitis and decisions must be extrapolated from other disease processes [110, 111, 137]. Crystalloid remains the mainstay of volume resuscitation, and the main choices available to clinicians include normal saline and buffered solutions that have composition closer to that of plasma, such as lactated ringers and Plasma-Lyte. There is growing

literature that suggests resuscitation with saline results in worsened renal function, increased need for renal replacement therapy, and worsened mortality, likely related to hyperchloremic acidosis, the effects on the renin-angiotensin system, and reduction in renal artery blood flow that high sodium chloride loads impose [138–140]. When one considers the large volume of resuscitation fluid that is often administered to these patients, an alternative choice to saline seems wise. The available literature suggests that, compared to normal saline, resuscitation with lactated ringers in acute pancreatitis reduces SIRS and C-reactive protein and may decrease intra-abdominal hypertension and lower requirement for mechanical ventilation when coupled with hydroxyethyl starch [110, 137]. Though some may be reluctant to administer potassium-containing solutions to patients who have acute kidney injury [111], given the available data about high-volume saline infusion, the low amount of potassium in these fluids, and several available treatment strategies for management of hyperkalemia, this hesitation seems unwarranted.

Many practitioners feel that colloidal solutions should play a role in the treatment of severe acute pancreatitis [111]. The only available study that has evaluated the use of colloid in acute pancreatitis compared lactated ringers with lactated ringer and hydroxyethyl starch and found that the patients who received both fluids had decreased intra-abdominal hypertension and a reduction in the use of mechanical ventilation [137]. However, given the available literature that links the use of hydroxyethyl starch with acute kidney injury, need for renal replacement therapy, red blood cell transfusion, and mortality, its use outside of controlled studies cannot be recommended [141–144]. There has been enthusiasm for the use of albumin in sepsis and severe acute pancreatitis [111, 145–147]. Its use in critically ill patients with sepsis requiring volume resuscitation has been shown to be safe when compared to saline crystalloid resuscitation, although in smaller volumes than those required for SAP resuscitation [146, 147]. When used as a part of resuscitation in its dilute (4–5 %), but not concentrated, form, there is evidence of improved mortality in patients with severe sepsis [145, 146, 148]. In contrast, recent work suggests that there is no mortality benefit to albumin resuscitation in sepsis [149–151]. However, the mortality analysis of these studies was mainly swayed by the inclusion of research that evaluated albumin resuscitation in its concentrated form (including one multicenter trial only published as an abstract) [152], when prior work showed that a mortality benefit wasn't realized when using concentrated albumin compositions [145].

There are animal studies that suggest that early resuscitation with hypertonic saline (HTS) in acute pancreatitis may positively impact cytokine expression and improve pancreatic microcirculation, cardiac contractility, and peripheral tissue perfusion, as well as reduce lung injury and edema [120, 153–155]. However, caution is warranted when interpreting these studies; as to date most literature has failed to show a significant mortality benefit to HTS resuscitation [156]. Additionally, overutilization could result in significant hyperchloremia and an increased morbidity, occurrence of acute kidney injury from hyperchloremia or hypertonicity, need for renal replacement therapy, and accelerated mortality [138, 139, 157, 158].

Vasopressor and Inotropic Support

Patients presenting with severe acute pancreatitis have a significant SIRS state that is similar to severe sepsis and they may be accompanied by profound vasodilatation [159]. Additionally, cardiac dysfunction, either as a response to SIRS or as decompensation of preexisting comorbid conditions, is not uncommon [159]. The early addition of vasopressor and inotropic support in acute pancreatitis patients with these findings, in a strategy similar to that suggested by the Surviving Sepsis Campaign International Guidelines, may be beneficial [124].

Intra-abdominal Hypertension and Abdominal Compartment Syndrome

The development of intra-abdominal hypertension (IAH) is a frequent finding in patients with moderate and severe acute pancreatitis and may be seen in up to 80 % of these patients [126, 160–162]. The subsequent development of abdominal compartment syndrome (ACS) has been associated with a mortality rate of 50–75 % in SAP patients [163]. IAH is defined as intra-abdominal pressures (IAP) ≥12 mmHg and abdominal compartment syndrome (ACS) as sustained IAP ≥20 mmHg that is associated with new organ dysfunction or failure [164]. IAH is seen in the early phase of severe acute pancreatitis related to a combination of the development of retroperitoneal edema, acute peripancreatic fluid collections, ascites, and ileus [126]. It may be exacerbated by overly aggressive fluid resuscitation, and there is some suggestion that the addition of colloids may help to ameliorate this [120, 126, 137, 164]. IAH in critically ill patients has been repeatedly shown to be associated with morbidity, organ failure, and mortality, although it remains unclear whether its treatment improves patient outcomes [164]. Similarly, the development of IAH and subsequent ACS in patients with severe acute pancreatitis is associated with worsened outcomes, including increased pancreatic infection, septic shock, multi-organ dysfunction syndrome (MODS), and mortality [160, 165].

Although the treatment of IAH without ACS has not been proven to improve patient outcomes, its association with worsened outcomes and mortality in acute pancreatitis

Table 17.6 World Society of the Abdominal Compartment Syndrome IAH/ACS Medical Management Algorithm [164]

	Step 1	Step 2	Step 3	Step 4
Evacuate intraluminal contents	Place nasogastric and/or rectal tube	Minimize enteral nutrition	Consider colonoscopic decompression	If: IAP is > 20 mmHg, new organ dysfunction is present, and IAH/ACS is refractory to medical management, consider surgical abdominal decompression
	Begin prokinetic agents	Administer enemas	Discontinue enteral nutrition	
Evacuate Intra-abdominal space occupying lesions	Abdominal ultrasound to identify drainable lesions	Abdominal Computed tomography to identify lesions	Consider surgical evacuation of lesions	
		Percutaneous drainage of fluid collection and ascites		
Improve abdominal wall compliance	Ensure adequate sedation & analgesia	Consider reverse trendelenberg position	Consider neuromuscular blockade	
Optimize fluid administration	Avoid excessive fluid resuscitation	Resuscitate using hypertonic fluids and colloids	Consider hemodialysis/ ultrafiltration	
	Attempt zero to negative fluid balance by the third day	Fluid removal with diuresis once stable		
Optimize regional perfusion	Goal-directed fluid resuscitation	Hemodynamic monitoring to guide resuscitation		

suggest that a strategy to decrease its effects is warranted. Approaching its treatment in a stepwise approach, as suggested by the clinical practice guidelines of the World Society of the Abdominal Compartment Syndrome (Table 17.6), seems prudent [164]. These include escalating treatment strategies to evacuate intraluminal contents and intra-abdominal space-occupying lesions, improve abdominal wall compliance, optimize fluid administration, and improve regional perfusion. Additionally, there is evidence that suggests the use of continuous renal replacement therapy in the early phase of acute pancreatitis, independent of volume management and treatment of acute kidney injury, may help to reduce IAH and the development of organ failure [120, 166–169].

Continuous Renal Replacement Therapy

Since intense cytokine and inflammatory mediator production is thought to be a main contributor to both local pancreatic and distant organ injury, there has been interest in pro-inflammatory cytokine removal using continuous veno-venous hemofiltration (CVVH) and hemodiafiltration (CVVHD) [120]. There are several studies that have shown that a short course of high-volume hemofiltration (HVHF) in vasopressor-dependent severe sepsis reduces vasopressor requirements, improves organ function, and decreases mortality [170–172], and there are multiple studies that have demonstrated decreased levels of serum cytokines when CVVH is utilized in severe acute pancreatitis [166, 168, 173–176]. Additionally, CVVH may help to reduce IAH and its secondary effects [166–169]. There is suggestion that the use of CVVH decreases the need for surgical interventions in patients with acute pancreatitis [177], and it has also been demonstrated to decrease APACHE II and SOFA scores, as well as appearing to improve organ failure and clinical outcomes [175, 176, 178–180]. There is minimal data suggesting an improvement in mortality [180], in part because so much of the research is in non-controlled case series. CVVH appears to have its greatest effect when started before the appearance of acute kidney injury [180]. Whether continuous renal replacement therapy can be effective in treating severe acute pancreatitis and its optimal form, timing of institution, dose, and duration await further well-controlled trials. While it cannot be routinely recommended in the treatment of severe acute pancreatitis at this time, it may help to improve outcomes in the future [120, 181].

Strategy for Management in the First 24 h

Given the above discussion and lack of definitive research, a pragmatic approach seems appropriate. It would be reasonable to begin resuscitation of patients with acute pancreatitis with a small volume bolus (250–500 mL) of HTS. This should be followed by a bolus of a balanced buffered crystalloid solution at 20–30 mL/kg and subsequent maintenance at a rate between 1.5 and 3 mL/kg per hour. Further resuscitation should be given as boluses and guided by end points

such as urine output, lactate, $ScvO_2$, SVV and PVV, ultrasound assessment of IVC/SVC collapsibility, and bedside echocardiography. The addition of dilute albumin to those who are requiring volumes of resuscitation >4 L remains volume responsive and hypoalbuminemic is safe and may offer benefit. The addition of vasopressors and/or inotropes for patients that are no longer volume responsive, are found to be significantly vasodilated, or have cardiac dysfunction, should be strongly considered as further volume loading may be harmful.

Intra-abdominal hypertension is common in patients with severe acute pancreatitis and they are at risk to develop ACS. IAP should be measured on admission to the ICU. If the IAP is elevated >12 mmHg, it should be followed at regular intervals (every 4–6 h) or continuously. When elevated, IAP should be treated in a stepwise approach. Specific attention to adequate sedation and analgesia and carefully guided fluid resuscitation in these patients is extremely important. The potential development of ileus, ascites, and intra-abdominal fluid collections should be aggressively investigated and treated with nasogastric and rectal decompression, prokinetic agents, and interventional trans-abdominal drainage when necessary. A course of neuromuscular blockade should be considered when ACS is present, sedation and analgesia are adequate, and there are potentially medically treatable conditions that can decrease the IAP. For patients in whom no response to therapy or neuromuscular blockade is seen, surgical decompression should be strongly considered.

CRRT appears to be effective in decreasing IAP and preventing and treating IAH. This seems to be both related to its ability to achieve a negative fluid balance and independent of it. It is also able to decrease cytokine levels and may improve organ failure, clinical outcomes, and mortality. CRRT should be considered as part of the treatment strategy to achieve negative fluid balance in managing patients with IAH when acute kidney injury or hemodynamics prevent diuresis and may be entertained as a primary modality to prevent the development of IAH in severe cases of acute pancreatitis. Though it cannot be routinely recommended on the basis of available literature, early institution of HVHF in patients who appear to be developing an early malignant course of severe acute pancreatitis can be considered in order to improve outcomes given their overall poor prognosis.

Management in the First Week

(Early ICU Strategies for Complication Prevention and Improving Outcomes)

The resuscitation of acute pancreatitis and close monitoring for the development and treatment of IAH often continue several days into the disease process. However, overall attention turns to a supportive phase that focuses on treating developed organ failure, providing nutritional support, limiting extra-pancreatic infections, and preventing the development of secondary infection of sterile (peri)pancreatic necrosis and local pancreatic complications. Specific treatment of organ failure is beyond the focus of this chapter and is covered elsewhere in this text. The main areas that have been studied to limit worsening of pancreatitis during this early phase include nutritional support, the use antibiotics and probiotics to reduce the incidence of infected necrosis, and specific interventional treatments to reduce recurrent episodes of pancreatitis.

Nutritional Support

In the past it was considered necessary to rest the pancreas and maintain patients in an NPO status until resolution of clinical symptoms, normalization of pancreatic enzymes, and resolution of pancreatic inflammation on imaging studies [18, 107, 182]. This dogmatic belief does not appear to be supported by current data, and there is evidence that early gastric feeding in mild cases of pancreatitis may shorten the course of the disease and reduce the risk of food intolerance [18, 183–185]. Additionally, early oral feeding with a soft or a low-fat solid diet has been shown to be safe and associated with shorter hospital stays in mild acute pancreatitis [183, 186–188].

Enteral Nutrition

Multiple studies have shown that early enteral nutritional support in severe acute pancreatitis leads to an improvement in SIRS, a reduction in organ failure, and decreases in extra-pancreatic infectious complications, infected necrosis, morbidity, local complications, need for surgical intervention, hospital length of stay, and mortality [189–195]. Enteral nutrition appears to have its greatest impact when instituted within 48 h of admission [191]. It is thought that the reduction in pancreatic infection and other infectious complications is due to enteral nutrition's ability to maintain the gut mucosal barrier, preventing its disruption and subsequent translocation of bacteria [194, 195]. The prevention in secondary infections of pancreatic and peri-pancreatic necrosis likely explains much of the reduction in surgical interventions, hospital length of stay, and mortality. However, mechanisms by which early enteral nutrition may decrease the SIRS response and organ failure remain unclear.

In contrast, early institution of total parenteral nutrition has been associated with pancreatic and extra-pancreatic infections, central venous line-related complications, and worsened mortality when compared to early enteral nutrition [18, 189, 194, 195]. Its use should be reserved for patients who fail to tolerate enteral nutrition after 7 or more days of treatment.

Table 17.7 Summary of meta-analyses evaluating the use if prophylactic antibiotics in acute necrotizing pancreatitis

Year	1st author	Included trials	Total patients	Decrease in infected necrosis	Mortality benefit
1998	Golub	8	514	Not tested	Yes
2001	Sharma	3	160	No	Yes
2006	Heinrich	5	288	No	Yes
2006	Villatoro	5	294	No	Yes
2006	Mazaki	6	329	No	No
2006	Xiong	6	338	No	No
2007	Dambrauskus	10	1,279	Yes	Yes
2007	**De Vries**	**6**	**397**	**No**	**No**
2008	**Hart**	**7**	**429**	**No**	**No**
2008	**Xu**	**8**	**540**	**Yes**	**No**
2008	**Bai**	**8**	**467**	**No**	**No**
2009	**Jafri**	**8**	**502**	**No**	**No**
2010	**Villatro**	**7**	**404**	**No**	**No**
2010	**Bai**	**9**	**519**	**No**	**No**
2011	**Wittau**	**14**	**841**	**No**	**No**

Bolded meta-analyses consistently show no mortality benefit or decrease in the rate of infected necrosis

Location of Enteral Feeding

Nasojejunal feeding has been routinely utilized in patients with SAP to minimize stimulation of the pancreas. However, recent comparisons of nasogastric and nasojejunal feeding in patients with predicted severe acute pancreatitis have caused this practice to be questioned [196, 197]. Unfortunately this work is clouded by the inclusion of patients who received duodenal feeding in the jejunal feeding group. It is known that duodenal feedings with low-fat elemental formulas are stimulatory in nature and that feeding 20 cm and further beyond the ligament of Treitz results in a progressive loss of pancreatic secretory stimulation [198–200]. Furthermore, the development of functional (gastric ileus) or mechanical (pancreatic inflammation and acute fluid collections) gastric outlet obstruction is not uncommon in patients with severe acute pancreatitis and impacts their ability to tolerate gastric enteral nutrition regardless of its stimulatory effect [200]. Considering the significant improvement in outcomes associated with the early institution of enteral nutrition, these factors should be taken into account when considering in which anatomic location to begin feeding.

Antibiotics and Probiotics in the Prevention of Infected Necrosis

When compared to pancreatic necrosis that remains sterile, those who develop infected necrosis have a higher rate of mortality that in some series approaches 69 % [18, 107]. While it is generally believed that infected pancreatic necrosis occurs later in the course of the disease, there is data that suggests that over a quarter of cases occur within the first 14 days [91, 193, 201]. Given the excess mortality associated with infected pancreatic necrosis strategies that may prevent its development are extremely important.

Prophylactic Antibiotics

There was great enthusiasm for the use of prophylactic antibiotics for prevention of the development of infected pancreatic necrosis based on series published in the 1980s. However, the data of many of these studies was questioned given their poorly designed nature. There were several randomized trials in the 1990s that continued to suggest a positive effect for prophylactic antibiotics [202–205]. Since that time there have been multiple studies that have repeatedly failed to demonstrate any benefit of the prophylactic use of antibiotics [206–209]. Multiple meta-analyses, including the well-designed prospective randomized trials published since 1993, have failed to demonstrate a mortality benefit or a consistent decrease in pancreatic infections (Table 17.7) [210–213]. Additionally, early prophylaxis with broad-spectrum antibiotics has been associated with the subsequent development of resistant bacterial infections (including MRSA and multi-drug-resistant *Pseudomonas* and *Acinetobacter*) and fungal infections [208, 214–216]. Although it is possible that a subset of patients in whom some type of antibiotic prophylaxis may be of benefit exists, the current literature does not support the routine administration of prophylactic antibiotics to prevent infection of pancreatic necrosis or to improve outcomes.

Probiotics

Some clinical trials have suggested a benefit of probiotics in critically ill patients, and several studies suggest that they can enhance intestinal barrier function and stimulate the production of antimicrobial peptides such as bactericidal/permeability-increasing protein [217]. Given the role that intestinal bacterial translocation is thought to play in the infection of pancreatic and peripancreatic necrosis, there has been interest in its possible prevention with the use of probiotics [217, 218]. Multiple early studies showed improvements in bacterial translocation, infected pancreatic necrosis, and the need for surgical intervention in these patients [219]. These were followed with the publication of the randomized, double-blind, placebo-controlled PROPATRIA trial in 2008 which demonstrated no differences in infectious complications and showed a significantly increased mortality in patients who were treated with probiotics [220]. This has resulted in a decline in interest in the use of probiotics in SAP and in critically ill patients in general. However, there were significant issues with the design of the trial, including the administration of the probiotic [219]. Probiotics in the study were administered as a bolus directly into the small bowel with a combination of soluble and insoluble fiber. It has been proposed that the administration of large volumes of soluble fiber and probiotics into the small bowel led to local fermentation, stasis, localized acidosis, and bowel wall injury [219]. Further analysis suggested that the main mortality difference in the study appears to be related to bowel ischemia and transmural necrosis and perforation near the site of probiotic delivery [219, 221]. This coupled with the results of further RCTs and meta-analysis that demonstrate no adverse effects of probiotic administration [217] calls into question the results of the PROPATRIA trial. Though probiotics cannot be currently recommended for use in the prevention of infected necrosis in severe acute pancreatitis, they appear to be safe, and further clinical trials are warranted.

The Role of Acute Endoscopic Therapy

Gallstones are one of the leading causes of acute pancreatitis [18, 28–30]. Generally most of the gallstones that cause acute pancreatitis pass through into the duodenum [222]. In a small number of patients continued choledocholithiasis or ampullary edema can cause severe acute pancreatitis and/or cholangitis related to ongoing pancreatic and biliary tree obstruction. In these cases the use of ERCP and ES to remove the obstruction could reduce the risk of progression and has been an area of keen interest.

There have been several studies that demonstrated that the early (within 24–72 h) routine use of ERCP in acute gallstone pancreatitis reduces the risk of progression to severe disease and decreases the complication rate in patients with predicted severe disease, without affecting mortality [223, 224]. However, further studies and meta-analysis, while showing a morbidity and mortality benefit when ERCP is performed in the setting of acute cholangitis and biliary obstruction, have failed to demonstrate any benefit in progression of disease, complications, or mortality in their absence [225–227]. Ongoing choledocholithiasis and biliary obstruction can be reliably diagnosed with MRCP and endoscopic ultrasound (EUS), rendering the use of ERCP unnecessary in establishing the diagnosis [18, 59]. When coupled with the potential risk for the development of post-ERCP pancreatitis in 2–10 % of cases [18], ERCP and ES should not be used in the absence of demonstrated biliary obstruction or cholangitis to prevent the progression of disease of severe acute pancreatitis.

Although up to 40 % of patients with acute pancreatitis will develop some type of a peripancreatic or pancreatic fluid collection, only a small number of patients will go on to develop a pancreatic fistula [228]. Although a high-quality pancreatic protocol CT can suggest the presence of a fistula in severe acute or non-improving moderate pancreatitis when acute fluid collections fail to resolve, MRCP can diagnose and characterize an active leak without the administration of contrast-enhancing agents or invasive tests [228–231]. The use of ERCP and placement of pancreatic duct stents have been shown to be effective as part of a multidisciplinary treatment strategy for pancreatitis-induced pancreatic fistula and fluid collections [228]. However, its early prophylactic use for the prevention of persistent fluid collections in the case of acute ductal disruption has not been investigated.

The routine use of early index hospitalization cholecystectomy has been shown to decrease the incidence of recurrent gallstone pancreatitis in mild cases of disease [232–236]. However, the risk of operating on patients with SAP early in the disease course, and the technical difficulties that can result in increased complications when surgery is delayed 1 or 2 weeks, typically results in delays of cholecystectomy until later times during prolonged hospitalization, as part of the surgical management of pancreatic necrosis, or until well after discharge [18, 237]. Unfortunately, these delays put the patient at an increased risk of recurrent episodes of acute gallstone pancreatitis while they are recovering from severe disease [237]. Although not supported in all reviews [235], there have been multiple studies that have demonstrated a protective effect of ERCP/ES against recurrent pancreatitis [232, 233, 237]. Given these findings, ERCP/ES should be considered after the resolution of the initial acute phase of severe gallstone-induced pancreatitis when cholecystectomy is going to be significantly delayed.

The third leading cause of acute pancreatitis is idiopathic; however it is likely that most of these cases are related to biliary microlithiasis [27, 31, 32]. When considering the data regarding the prevention of recurrent gallstone pancreatitis by ERCP/ES, its use should be considered with IP as well.

However, when cholecystectomy in IP was performed in the absence of stones, sludge, or significantly elevated liver enzymes, it was not preventative of recurrent episodes of acute pancreatitis [238]. Given these findings the routine use of ERCP/ES in the absence of these findings cannot be recommended. The administration of ursodeoxycholic acid decreases the viscosity of and sediment in bile and has been shown to decrease recurrence of microlithiasis-induced and idiopathic pancreatitis [32, 33, 239]. It offers a noninvasive alternative that may play a role in reduction of symptoms and recurrence of disease in SAP or in those with IP that do not fit criteria for endoscopic therapy.

Management of Hypertriglyceridemia-Induced Pancreatitis

Hypertriglyceridemia is likely the third leading cause of acute pancreatitis accounting for at least 1–10 % of all cases [34–37]. It is present in more than half of acute pancreatitis cases in pregnancy, and it likely plays a role in the pathogenesis of alcohol-induced acute pancreatitis [27, 38, 39]. Serum triglyceride (TG) levels greater than 1,000 mg/dL are generally considered necessary to cause acute pancreatitis [18, 21, 27], and acute pancreatitis seen in patients with lower levels should be investigated for other causes. Secondary causes of HTG include common endocrine disorders (hypothyroidism, type II diabetes, Cushing's syndrome), certain medications (glucocorticoids, thiazide and loop diuretics, β-adrenergic blockers, estrogens, cholestyramine, antiretrovirals, and others), alcohol intoxication, chronic kidney disease, nephrotic syndrome, and acute hepatitis. However, the levels of HTG needed to produce acute pancreatitis generally require an underlying familial hyperlipidemic disorder [240, 241]. Because secondary causes often play a role in significant elevation of HTG levels in patients with familial hyperlipidemic disorders, they should be aggressively sought out and treated as part of the management strategy in HTG-SAP.

The underlying pathophysiologic mechanism of HTG causing pancreatitis remains unclear, but likely includes some combination of direct acinar cell and pancreatic capillary injury combined with impaired blood flow related to chylomicron-induced increased viscosity of blood [35]. Whether or not early treatment changes outcomes is unclear as severe HTG quickly decreases to levels in which the likelihood of further pancreatic injury is low within 48 h of the onset of pancreatitis [35, 40]. Given the burden of morbidity and mortality associated with SAP, it seems prudent to rapidly reduce TG levels if they may be inducing ongoing injury or ischemia.

The mainstays of TG management, dietary modification, and fibrates have little role in the acute management of patients with severe acute pancreatitis due to HTG. However, their institution should be considered when enteral nutrition is started. Additionally, careful consideration of the type of enteral nutrition and fat composition is important. In instances where TPN becomes necessary, the use of intralipids should be avoided or very carefully monitored [35]. For patients requiring sedation, agents other than propofol should be considered.

Both heparin and insulin infusions have been utilized for reduction of TGs in the treatment of HTG acute pancreatitis [35, 241]. Insulin has been shown to increase the production and activity of peripheral lipoprotein lipase (LPL) and thus decrease levels of TGs [35, 241, 242]. While it is unclear whether the routine use of insulin is helpful, it is particularly useful in patients with poorly controlled diabetes-precipitated HTG-AP who present with both HTG and hyperglycemia [243]. Heparin infusion increases serum LPL activity resulting in an initial decrease in TG. Unfortunately, this effect is transient due to depletion of LPL on the surface of endothelial cells, and TG levels later rise [35, 241, 242]. This combined with the possibility of hemorrhage into areas of pancreatic necrosis [244] has led to a significant decrease in the use of heparin for HTG management.

There has been enthusiasm for the use of plasmapheresis to reduce levels of TG. The available studies demonstrate its ability to decrease serum TG between 49 and 80 % after a single session [245–251]. This could significantly limit the ability of HTG to cause further injury in cases of severe acute pancreatitis. However, the lack of randomized and controlled trials and the unknown optimal start time, duration, and technique, combined with its lack of availability, limit its routine use [35].

Overall Management Strategy in the First Week

Management in the first week of severe acute pancreatitis includes the completion of goal-oriented resuscitation and ongoing support of any developing or non-transient organ failure. Additionally, continued monitoring of IAP is necessary as fluid shifts and ongoing resuscitation needs may lead to the delayed development of ACS.

Early enteral nutrition has been the only therapy shown to consistently improve outcomes and decrease infectious risks and mortality in pancreatitis and it should be aggressively started within 48 h of onset of disease. It is unclear whether the location of delivery of enteral nutrition impacts worsening of disease, but given that early enteral nutrition is so important, it must be administered someplace where it will be tolerated. While gastric and duodenal feeding is reasonable, frequent assessments for tolerance are necessary and those unable to tolerate should have early conversion to jejunal feeds. Considering the multiple competing interests in these

patients, it may be better to just begin with jejunal feeding to assure adequate delivery early in the disease process.

Antibiotics given prophylactically do not reduce morbidity, local complications, pancreatic infections, or mortality. Infection of pancreatic necrosis in the first week, though possible, is extremely uncommon. However, extra-pancreatic infections are common, related to ICU management and the inflammatory state, and should be investigated aggressively. The use of antibiotics should be reserved for treatment of strongly suspected or proven extra-pancreatic and pancreatic infections.

Whether there is any role of probiotic in the management of SAP is unclear, although when administered appropriately they do not negatively affect outcomes. Their use should be reserved for clinical trials or if other clear indications for administration in the critically ill become available.

The acute use of endoscopic therapy with ERCP/ES should be reserved for cases where cholangitis or ampullary obstruction is present. As ERCP/ES has been shown to reduce recurrence of gallstone pancreatitis, it should be considered after the early acute phase of management in patients with gallstone-induced SAP and in cases of idiopathic pancreatitis when biliary microlithiasis or sludge is identified, when early cholecystectomy is unable to be performed. There may be a role for prevention of pancreatic collections, pseudocysts, and fistula with early pancreatic stent placement when ductal disruption is diagnosed, but further investigation is needed.

Patients who present with HTG-induced AP should have potential secondary causes evaluated and managed. The acute management of HTG-AP patients with type 2 diabetes and hyperglycemia should include an insulin infusion. Plasmapheresis should be considered in patients presenting with severe acute pancreatitis and TG levels >1,000 mg/dL. In severe cases of HTG-AP, insulin and glucose infusion should be considered in nondiabetic patients when plasmapheresis is unavailable.

ICU Management After the First Week

(Identification and Management of Local Complications)

After the first week of severe acute pancreatitis patients often remain critically ill related to persistent organ failure, need for mechanical ventilation, and renal replacement therapy support. Management includes ongoing support for organ failure and continued enteral nutritional support. Continued vigilance in evaluation for extra-pancreatic infections associated with ICU care (VAI, CR-BSI, CAUTI) is necessary as they are common in this patient population and their development significantly impacts morbidity and mortality [18]. It is during this later phase of the disease process that local complications of acute pancreatitis begin to occur and contribute to worsened outcomes. Any patient that has failure to improve or an acute decompensation after previously improving should be carefully investigated for the development of infected necrosis or other local complications.

Management of Sterile and Infected Necrosis

Pancreatic and peripancreatic necrosis occurs in about 15 % of patients with acute pancreatitis [252]. However, the likelihood of having pancreatic necrosis goes up significantly in patients who present with SAP and persistent organ failure. In the past open necrosectomy was the treatment of choice, early debridement was considered to be important to improve outcomes for symptomatic sterile necrosis, and immediate urgent debridement was felt to be mandatory in cases of infected necrosis [18, 107, 253]. However, carefully done retrospective studies have demonstrated that reoperation rates, morbidity, and mortality are significantly improved when surgical debridement of infected necrosis can be delayed to more than 28–30 days [201, 254, 255]. While patients with fulminant severe acute necrotizing pancreatitis in the first week of disease who are deteriorating despite maximal medical and intensive care unit therapy are sometimes offered early surgical therapy for sterile necrosis, these patients' prognosis remains poor and does not appear to be improved with surgical intervention, with the possible exception of surgical decompression for ACS [7, 201, 252].

Classification and Diagnosis

Acute (peri)pancreatic fluid collections and acute necrotic collections may occur early after the development of acute pancreatitis. However, the appearance of necrosis is often delayed until several days (up to 5) after presentation [13, 58, 59, 74, 96, 252]. When present for greater than 4 weeks without resolution, necrosis may organize into a liquid and necrotic collection, become encapsulated, and is termed walled-off necrosis (Fig. 17.1) [13, 252]. Pseudocysts (Fig. 17.2) are uncommon after acute pancreatitis and are fluid collections that persist for more than or develop after 4 weeks, lack significant non-liquid material, and are encapsulated [13, 252]. They may cause symptoms related to compression and rarely lead to pseudoaneurysm and hemorrhage (Fig. 17.3).

Contrast-enhanced CT is the standard imaging test to detect pancreatic and peripancreatic necrosis, determine its extent, and diagnose local complications. MRI is likely equivalent to CT for the diagnosis of necrosis, even in the absence of intravenous contrast. It has the advantage of improved imaging of the biliary and pancreatic ducts and can diagnose retained stones and disruptions, as well as avoid exposure to radiation [252]. As they are rarely required to make the diagnosis of acute pancreatitis, and severity can be

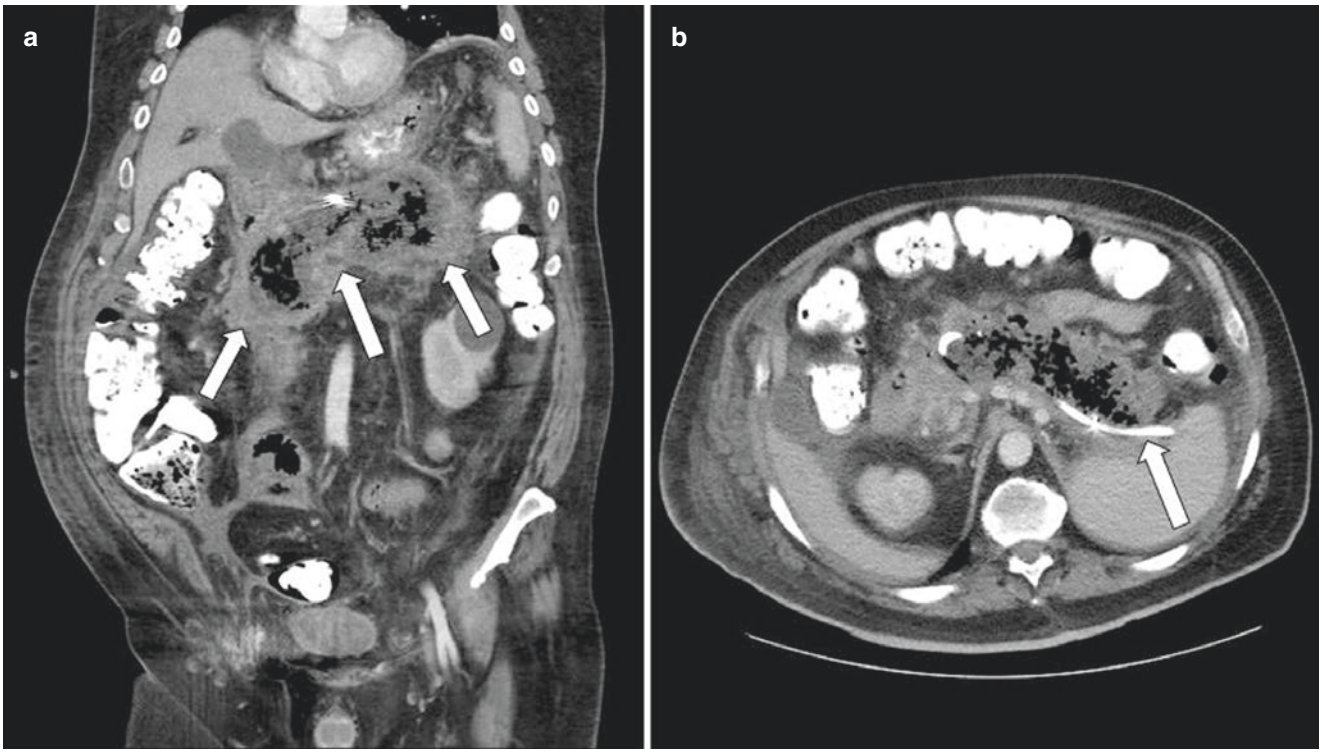

Fig. 17.1 (**a**) Area of walled-off necrosis (WON) characterized by a thickened organizing wall (*arrows*) surrounding a collection of fluid and necrosis that usually occurs more than 4 weeks after the onset of necrotizing pancreatitis. The presence of gas within the necrosis suggests infection, which in this case was previously drained. (**b**) A drain (*arrow*) can be seen traversing the left retroperitoneum and flank in anticipation of a video-assisted retroperitoneal debridement/necrosectomy (VARD)

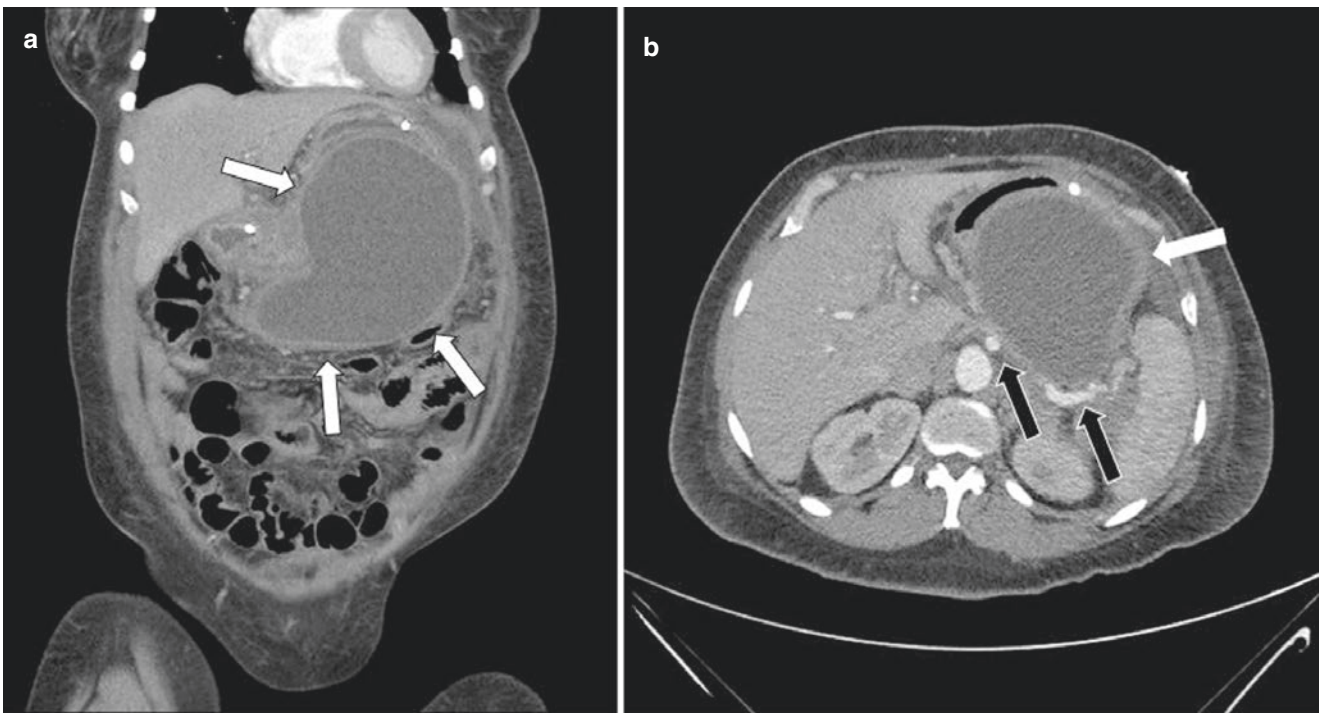

Fig. 17.2 Coronal (**a**) and axial (**b**) views of a large pancreatic pseudocyst, characterized by a well-formed encapsulated wall (*white arrows*) surrounding a fluid collection. They are uncommon after acute pancreatitis but when present typically develop more than 4 weeks after the acute episode. They may cause early satiety or nausea related to compression of the stomach and duodenum and are frequently associated with pain. The proximity to mesenteric, peripancreatic, and splenic vessels (*black arrows*) may lead to hemorrhage due to compression and erosion into the vessels

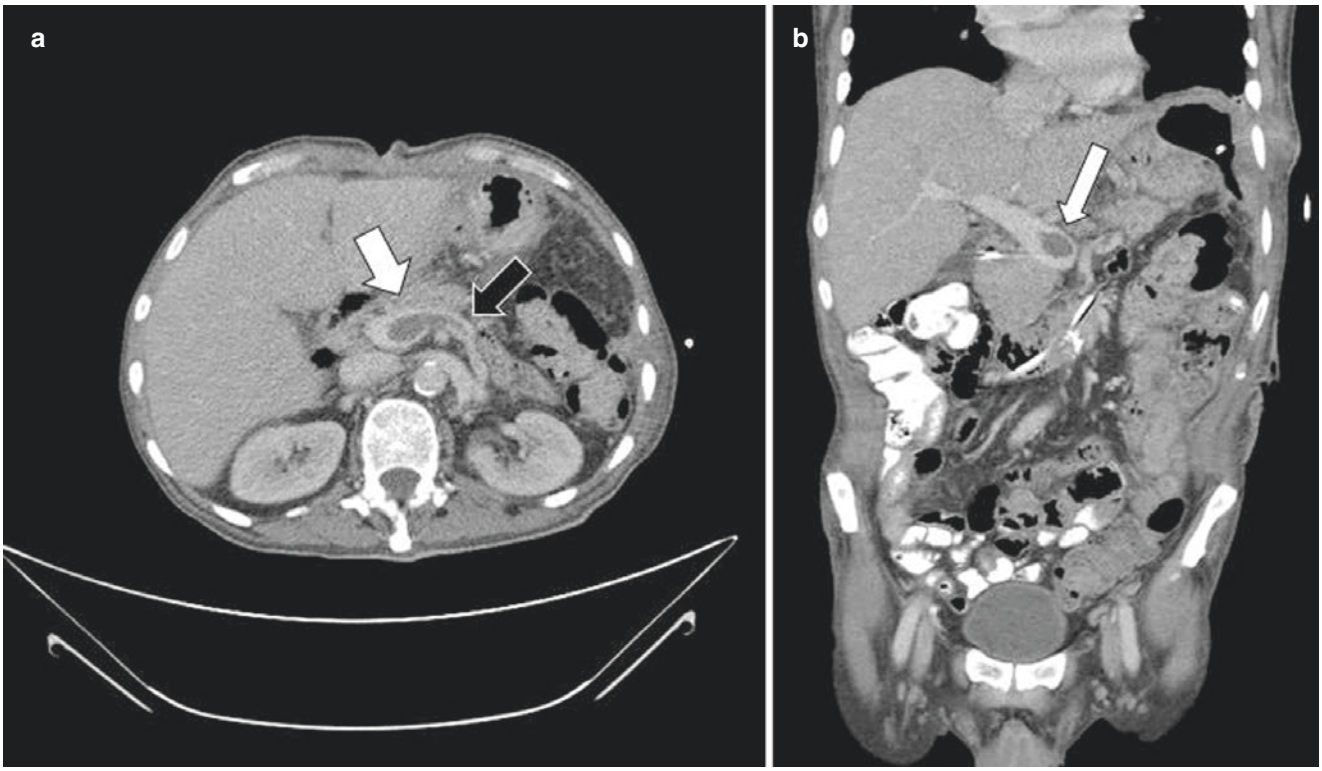

Fig. 17.3 Portosplenomesenteric thrombosis secondary to acute pancreatitis. (**a**) Axial view demonstrating nearly occlusive thrombus in the portal vein (*white arrow*) with extension into the splenic vein (*black arrow*). (**b**) Coronal view of thrombus within the portal vein (*arrow*)

predicted equally well with other methods, pancreatic imaging studies should not be routinely utilized in the early phase of acute pancreatitis. Instead they should be reserved for making the diagnosis of necrosis and local complications of severe acute pancreatitis.

Noninfected asymptomatic pancreatic and extra-pancreatic necrosis does not require intervention and generally resolves over time [18, 252]. Most patients with symptomatic sterile necrosis (gastric outlet obstruction or biliary obstruction) will be manageable with supportive care. Although some may require intervention, they are generally treatable with percutaneous or endoscopic drainage therapies [252]. In contrast, some type of intervention will be required in nearly all cases of infected necrosis, although there are reports of successful treatment with antibiotics alone [13, 252, 256, 257].

Infection of pancreatic and peripancreatic necrosis is rare in the first week after the development of acute pancreatitis. Though its development peaks between the second and fourth weeks [252], up to a quarter of all cases of infected necrosis may occur within 14 days, and infection may occur at any time during the course of the disease [193]. Diagnosis of infection should be strongly considered in patients who develop a worsening or new onset of SIRS, sepsis, or organ failure after the first week of the disease [107, 121, 252, 258]. This is particularly true if the patient was previously improving and evidences a precipitous decline. Additionally, chronically infected necrosis may be present in up to 40 % of patients who are persistently unwell (ongoing inability to tolerate oral feedings, persistent pain, nausea, or vomiting,and persistent low-grade fever) [254]. When any of these develop, the patient should be carefully investigated with cultures, radiologic evaluation, and when indicated interventional evaluation. Often the causative infections will be extra-pancreatic and hospital acquired and can have a significant impact on mortality rates [18]. Infection should be strongly considered when there is gas documented in necrotic collections on abdominal imaging, especially when coupled with the correct clinical scenario.

Utility of Fine Needle Aspiration

CT-guided fine needle aspiration (FNA) to diagnose infected pancreatitis has been used for the past several decades. Unfortunately, in up to 25 % of cases FNA may not identify all of the causative organisms of infection [259], and the false-negative rate may be as high as 25 % [254]. Given the frequent misleading results, the ability to diagnose most cases of infected necrosis with clinical scenario and imaging studies, the potential for treatment with antibiotics alone, and the opportunity for potentially definitive minimally invasive percutaneous or endoscopic drainage, the role of FNA has been diminishing [252]. The current role for FNA is likely limited to cases of suspected necrosis that are not

responding to initially selected antibiotic therapy and have no area amenable to indwelling external drainage.

Antibiotic Therapy for Infected Necrosis

When a patient is suspected of having infected necrosis and has significant clinical deterioration, antibiotics should be started without delay in advance of interventional treatment or diagnostic techniques. Few intravenous antibiotics have the ability to penetrate into pancreatic and peripancreatic necrosis. Ones that have been shown to penetrate in clinical trials (carbapenems, high-dose cephalosporins, quinolones, metronidazole) should be selected for initial empiric therapy [18, 102, 260–262]. For patients that develop infected necrosis later in the course of disease (3–4 weeks) and who have received previous treatment for extra-pancreatic hospital-acquired infections, coverage for fungal infection, MRSA, and resistant gram-negative organisms should be considered [208, 214–216]. There is suggestion that infected necrosis can be successfully treated with antibiotics alone or as a bridge to allow more successful intervention after the demarcation and liquefaction of necrosis, in stable patients [256, 257, 263, 264]. However, patients with suspected infected necrosis who have severe sepsis, develop clinical deterioration, or fail to respond to antibiotic therapy require interventional therapy [252].

Interventional Treatment for Infected Necrosis

Several series have shown that most cases of infected pancreatic necrosis are amenable to, and nearly 50 % of patients can be managed with, antibiotics and percutaneous therapy alone [92, 252, 265, 266]. There does not appear to be a worsened mortality when percutaneous therapy is utilized as primary management, and it has the benefit of a lower complication rate than open and other minimally invasive techniques of management. Percutaneous drainage of pancreatic or peripancreatic necrosis can be achieved via a transabdominal or retroperitoneal approach (Fig. 17.1b). The retroperitoneal approach is preferred in order to avoid peritoneal contamination, enteric injury and subsequent fistula, and to facilitate a step-up approach to minimally invasive necrosectomy when indicated [252, 266]. There is suggestion that a dedicated interventional radiology team and a multidisciplinary approach are needed to achieve the good outcomes seen in several studies as multiple catheters and frequent catheter exchanges are often necessary [265, 266]. The optimal number and size of catheters remain unknown, but one study suggested that a single 14-French drain was adequate for most patients [92]. When percutaneous management alone is unsuccessful, further minimally invasive techniques are available. These include minimally access retroperitoneal necrosectomy and endoscopic necrosectomy.

Minimally invasive retroperitoneal necrosectomy (MARPN) is generally achieved with video assistance and is referred to as video-assisted retroperitoneal debridement (VARD). Several series comparing a step-up approach to VARD after percutaneous drainage versus open surgical debridement have shown decreased morbidity, including a reduction in postoperative organ failure, bleeding events, enterocutaneous fistula, enteric perforation, pancreatic fistula, incisional hernia, and development of pancreatic exocrine and endocrine insufficiency [92, 267, 268]. Some studies suggest a longer hospital course and no difference in mortality in patients treated with MARPN, while others demonstrate reductions in both mortality and hospital length of stay [268]. Overall the need for open necrosectomy for infected necrosis can be reduced from more than 90 % to less than 10 % in centers experienced with percutaneous drainage and MARPN [252]. Unfortunately, the disadvantage of both percutaneous drainage and MARPN/VARD is the greater than 20 % development of pancreaticocutaneous fistula that may have difficulty with closure related to associated disruptions in the pancreatic duct [252].

Various reports of endoscopic drainage for pancreatic pseudocysts have been described for over a quarter century, but the first report of endoscopic transluminal necrosectomy for walled-off necrosis (Fig. 17.1a) was in 2000 [269]. The procedure generally requires endoscopic ultrasound (EUS) guidance for success and to decrease complications [252]. When compared to open and MARPN techniques, it has the potential benefits of a decreased inflammatory response and a decreased risk of external pancreatic fistula due to the nature of its internal drainage. In one series comparing it to surgical necrosectomy (VARD or open), there was a statistically significant reduction in new post-intervention organ failure and pancreatic fistula and a non-statistically significant reduction in mortality [270]. However, the procedure is limited by the availability of expertise, the presence of WON within 2 cm of the gastric or duodenal wall, the size and complexity of the necrotic fluid collections, and the frequent need for multiple repeated procedures [252]. A combination of endoscopic and percutaneous approaches is often feasible and may decrease the need for multiple interventions, the number of drains required, the number of CT scans, the time to drain removal, and length of hospitalizations [252].

Given the overall improvement in morbidity and the potential improvement in mortality that minimally invasive techniques offer, open necrosectomy is reserved for cases that fail these management techniques or when they are not available. Necrosectomy is performed in an organ-sparing non-resectional blunt fashion to avoid removal of normal pancreatic tissue in order to decrease the incidence of pancreatic endocrine and exocrine insufficiency and to minimize the risk of bleeding and fistula. There are four basic available

techniques for management after initial open necrosectomy: open packing and serial surgical debridement with subsequent closure, open packing and serial dressing changes until closure by secondary intent, closed packing and drainage, and closed drainage and continuous lavage [9]. The available data suggests that closed packing or continuous lavage is superior to open techniques and results in a decreased incidence of bleeding events, pancreatic and enteric fistula, and ventral incisional hernia [9, 254].

Disconnected Pancreatic Duct Syndrome and Pancreatic Fistula

Up to 40 % of patients with pancreatic necrosis will have disconnected pancreatic duct syndrome [252]. These disruptions can lead to persistent or recurrent pancreatic and peripancreatic fluid collections and the development of pancreatic ascites or pancreaticopleural fistula. Additionally they can contribute to the development of pancreaticocutaneous fistulas in patients who have undergone interventional drainage. The diagnosis is made by either direct evaluation of the duct through ERCP or MRCP, identification of amylase-rich fluid collections, or persistent drainage of pancreatic fluid through externalized catheters or drains [252, 271, 272]. Though small bridgeable disruptions may be treated with external drainage and endoscopic placement of pancreatic stents across the area of disruption, true disconnected duct syndrome generally requires either internal transmural drainage into the GI tract or distal pancreatectomy [252]. Internal drainage may be achieved either endoscopically or surgically. Although endoscopic internal drainage is less invasive, it generally requires that transmural stents be left in place indefinitely as routine removal leads to recurrent pancreatic fluid collections in up to 40 % of patients [252, 273]. Overall, endoscopic transmural drainage appears to be most successful when it is accompanied by placement of a bridging transpapillary pancreatic stent [274]. Surgical alternatives include distal pancreatectomy and internal drainage of either the duct (Roux-en-Y pancreaticojejunostomy) or walled-off fluid collection (cyst gastrostomy or cyst jejunostomy). When possible, internal drainage is preferred over distal pancreatectomy due to decreased operative blood loss and the preservation of pancreatic parenchyma that may minimize the development of endocrine and exocrine insufficiency.

Gastrointestinal Complications of Severe Acute Pancreatitis

The most common GI manifestations of severe acute pancreatitis, gastric ileus and gastroduodenal outlet obstruction, are generally self-limited and manageable with nasogastric drainage, placement of distal naso-enteric feeding access, and when necessary drainage of pancreatic fluid collections.

Colonic complications are rare (3.3 %) in acute pancreatitis, but may occur in up to 15 % of cases of severe acute pancreatitis [275]. Complications of the colon include necrosis, fistula, and stricture, all of which significantly increase morbidity in this patient population. The development of colonic necrosis is associated with a mortality of 54 % [275]. While most cases of necrosis are diagnosed in the fourth week (median: 25 days), there are multiple reports of its development within the first few days of severe acute pancreatitis [275, 276]. The transverse colon and splenic flexure are most commonly affected, due to their proximity to the body and tail of the pancreas. The most common pathogenic mechanism is thought to be a combination of (1) hypotension and inflammatory-induced mesenteric vascular thrombosis with resultant ischemia at watershed areas and (2) direct retroperitoneal spread of pancreatic enzymes to the mesocolon and colon leading to colitis and transmural necrosis [276–279]. Erosion of a pseudocyst or walled-off necrosis into the colon is a less common etiology [280]. The diagnosis is frequently obscured by the ongoing inflammatory process in fulminant cases of severe acute pancreatitis [275, 281]. Patients with worsening clinical status despite aggressive therapy in the first week of severe acute pancreatitis, and patients with secondary decompensation thereafter, should increase clinical suspicion and aggressive investigation with CT and fluoroscopic imaging should follow. Surgical resection and proximal diversion remains the mainstay of therapy. Overall, gastrointestinal perforation and fistula are far more common as a result of interventional therapy and open debridement in the management of necrosis then as a primary result of severe acute pancreatitis [282].

Vascular Complications of Acute Pancreatitis

Up to 25 % of patients with acute pancreatitis will develop arterial or venous vascular complications, most occurring in those with severe disease [283]. While most cases of venous thrombosis will have a benign clinical course [284], the development of arterial pseudoaneurysm and hemorrhage is associated with significant morbidity and a 40–90 % mortality [285].

Portosplenomesenteric Venous Thrombosis

Portosplenomesenteric venous thrombosis (PSMVT) is the most common vascular manifestation of acute pancreatitis present in up to 22.6 % of cases [286]. Though it is rare in the absence of necrosis, it occurs in over 50 % of cases

where pancreatic necrosis is present [284]. Thrombosis is most common in the splenic vein (86 %), followed by the portal (36 %) and superior mesenteric veins (27 %), and it may be present in more than one location (Fig. 17.3) [284]. The occurrence of venous thrombosis in acute pancreatitis is likely related to a combination of factors, including the release of procoagulant inflammatory mediators, vascular spasm, and compression from (peri)pancreatic edema and acute fluid collections [287]. Although PSMVT may be acutely associated with ischemia and infarction of the bowel, spleen (which may lead to spontaneous rupture), or liver and chronically associated with left-sided (sinistral) portal hypertension, complications related to its presence are uncommon [284, 286, 288]. Resolution without anticoagulation is infrequent, and when vascular thrombosis is complete, delays in anticoagulation after the first week of diagnosis result in a significant decrease in recanalization (69 % vs. 25 %) [284, 287, 289]. Despite the low rate of resolution of PSMVT with delays in treatment, early anticoagulation in critically ill patients with severe acute pancreatitis seems unwise given the risk of hemorrhagic complications and the infrequent rate of complications due to thrombosis. However, patients should be evaluated for treatment at the earliest possible time as the subsequent development of left-sided port-venous hypertension may lead to gastric varices and acute GI bleeding events in up to 12.3 % [286].

Hemorrhage and Pseudoaneurysm

Life-threatening hemorrhage after acute pancreatitis is rare affecting only 1–3 % of patients [9]. Massive hemorrhage is usually the result of a ruptured arterial pseudoaneurysm (Fig. 17.4), but may also occur due to diffuse bleeding from necrosis, hemorrhage from pseudocysts, and erosion into small peripancreatic veins (or more rarely, erosion into the portosplenomesenteric venous system) [9, 285, 290]. Additionally, some patients develop GI hemorrhage related to erosion of acute pancreatitis into the GI track.

The incidence of pseudoaneurysm formation after acute pancreatitis has not been well established but is within a range of 1.3–10 % in most case series [285]. They occur either due to arterial wall autodigestion and arteritis from proteolytic enzymes released during acute pancreatitis or from direct extension and erosion of pseudocysts into the arterial tree (Fig. 17.4) [9, 285]. Pseudocysts are a significant risk factor as up to 40 % of patients with pseudoaneurysms have concomitant pseudocysts [291]. Large pseudoaneurysms are most often the result of pseudocyst erosion into a vessel with resultant decompression into the pseudocyst [292, 293]. Pseudoaneurysm formation is uncommon prior to the third week of acute pancreatitis, and patients may not present with symptoms until years after their acute disease process is completed [285, 294, 295]. The most commonly affected mesenteric vessels are the splenic (50 %), gastroduodenal (20–22 %), and pancreaticoduodenal (10–25 %) arteries, and the remainder occur in the superior mesenteric and hepatic arteries [285, 296]. The most useful tool for diagnosis is computed tomography angiography (CTA), as it is rapid and readily available and has a sensitivity of more than 95 % [285]. However, small pseudoaneurysms may only be visible on digital subtraction angiography (DSA) and patients presenting with retroperitoneal, peripancreatic, intra-abdominal hemorrhage, or gastrointestinal bleeding with a negative CTA should have further investigation with DSA [285].

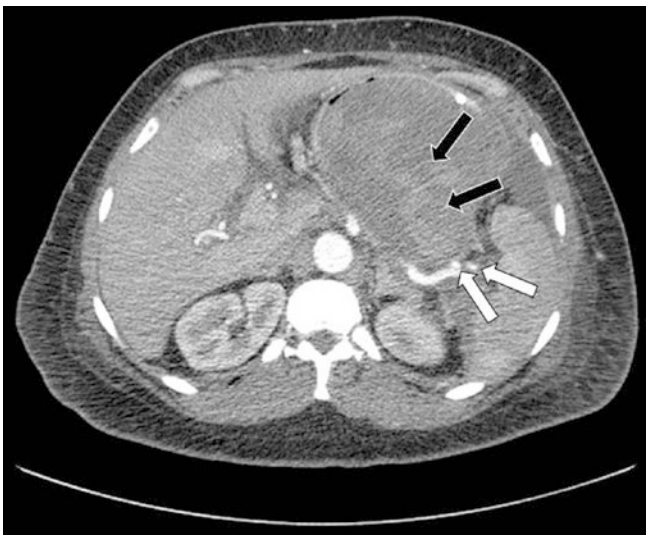

Fig. 17.4 Development of pseudoaneurysms (*white arrows*) of the splenic artery with secondary hemorrhage (*black arrows*) into a large pseudocyst. Most pseudoaneurysms due to severe acute pancreatitis can be controlled with interventional techniques and embolization with an overall improvement in outcomes compared to open surgical management

Rupture of pseudoaneurysms associated with acute pancreatitis have a high morbidity and a reported historic mortality between 40 and 90 % [285]. Mortality rates are higher when pancreaticoduodenal arteries are involved, likely related to their rich collateral blood supply and difficulty with definitive catheter-based treatment [285, 297]. In the past, pseudonaeurysms were surgically repaired or resected with rates of mortality reported between 10 and 50 % [285]. The availability of interventional catheter-based techniques has seen an improvement in the outcomes in these cases and has become the current first-line therapy [285]. These techniques, which may include embolizaition (coil, balloon, or foam) and covered stent placement, have a success rate of between 80 and 100 % and are associated with a reduction of mortality to around 10 % [285, 298–300]. Complications of embolization may occur in up to 25 % of

patients and include splenic infarction, coil migration, and intestinal necrosis [285, 296, 299]. Recurrent hemorrhage may occur in approximately 12 % of those who undergo interventional treatment and 37 % of those who undergo surgical repair [296]. When it occurs, repeat angiography as either primary therapy or as a bridge to surgical intervention is warranted. Occasionally, patients may be too unstable to pursue angiography, and emergent surgical therapy becomes necessary. When the appropriate expertise is available, resuscitative endovascular balloon occlusion of the aorta (REBOA) may be life saving for the patient in extremis from hemorrhage and offers a bridge to either interventional or surgical therapy [301].

Strategy for Management After the First Week

Patients with severe acute pancreatitis will continue to require nutritional support and management of organ failure, after the first week in the ICU. They should begin to show gradual resolution in SIRS and recovery of organ dysfunction. However, when a patient fails to improve, is persistently unwell, or has a clinical decompensation after a period of improvement, aggressive investigation into the possibility of a hospital-acquired non-pancreatic infection or a local complication of pancreatitis is imperative. Cultures and investigation to rule out typical non-pancreatic infections should be performed, and a careful investigation for local complications with a CT of the abdomen and pelvis with oral and IV contrast should occur. In cases where hemorrhage is suspected, the study should be protocolized as a CTA.

Most cases of symptomatic sterile necrosis can be managed with supportive care. Patients will often require nasogastric decompression and naso-enteric feeding access for nutritional support. Occasionally percutaneous drainage can facilitate the resolution of gastroduodenal obstruction, but should be carefully considered when necrosis is sterile as secondary infection can occur.

When significant deterioration occurs and there is a strong clinical suspicion of infected necrosis, broad-spectrum antibiotics with good pancreatic penetration should be started without delay for diagnostic studies. Otherwise, antibiotics should be reserved for cases where CT features are consistent with infected necrosis or cultures from necrosis are positive. Given the high false-negative rate and imprecision of FNA, its use should be reserved for cases of suspected infected necrosis that are not responding to initially selected antibiotics and have no areas amenable to drainage.

Infected necrosis with associated fluid collections or walled-off necrosis that is not responding to antibiotics should undergo percutaneous drainage. In general, a left retroperitoneal approach should be utilized, if anatomically possible, to facilitate a possible step-up approach to a VARD. Up to 50 % of patients will be manageable with percutaneous drainage and antibiotics alone. Those who fail to initially improve with drainage and appropriate antibiotic therapy should be considered for repeat percutaneous drainage or upsizing of drains. When possible, surgical therapy should be delayed until the fourth week to decrease morbidity and mortality. Nearly all outcomes appear to be improved when a minimally invasive approach to debridement (VARD or endoscopic necrosectomy) is used. Open necrosectomy is warranted when a minimally invasive approach is not anatomically possible or local expertise is not available, and outcomes appear best with closed rather than open techniques.

Persistent pancreatic and peripancreatic fluid collections after the first week or the presence of pancreatic ascites or pancreaticopleural fistula should raise the suspicion of disconnected pancreatic duct syndrome. Patients should be evaluated with either MRCP or ERCP and if diagnosed a transpapillary pancreatic stent should be considered. Definitive management may require internal drainage or distal pancreatectomy if fluid collections persist and develop into a pseudocyst.

The most common gastrointestinal manifestations of severe acute pancreatitis are gastric ileus and gastroduodenal outlet obstruction which are generally manageable with supportive care. Colonic complications, while rare, almost always require surgical intervention. Colonic necrosis and perforation tend to occur in the fourth week, though they may develop acutely in the first week of the disease. Patients with clinical deterioration should undergo CT, but the diagnosis may be obscured by the local inflammatory process and infected necrosis and may require the addition of fluoroscopic studies to establish its presence. There should be a strong clinical suspicion of erosion and colonic peroration in patients who develop gastrointestinal hemorrhage. Progressive fibrosis and stricture with obstruction tend to occur much later in the disease process. The mainstay of treatment of all colonic complications is resection and proximal diversion, though these cases are often technically challenging related to the intense local inflammatory process in the mesentery.

CTs performed to evaluate for local complications should be carefully scrutinized for vascular complications. PSMVT is relatively common, and patients should be considered for treatment with anticoagulation due to the potential for the subsequent long-term development of sinistral hypertension, gastric varices, and gastrointestinal hemorrhage. When possible, treatment should be started early in cases of total occlusion as the rate of recanalization decreased significantly for delays in treatment. However, many patients with severe acute pancreatitis will have a significant risk of hemorrhage early in the disease process. Given the overall low complication rate with PSMVT, a careful risk-benefit analysis should occur in each patient, and frequently therapy will need to be delayed.

Patients with clinical evidence of acute hemorrhage who are stable or who have sequelae of recent (peri)pancreatic hemorrhage on CT should undergo CTA to evaluate for the development of pseudoaneurysms. Patients with acute hemorrhage who have hemodynamic compromise that improves with resuscitation and patients with negative CTA with signs of peripancreatic hemorrhage should undergo angiography. Most pseudonaeurysms can be interventionally treated with embolization or covered stent isolation with improved morbidity and mortality compared to open surgical techniques. Patients with hemodynamic compromise secondary to pancreatic hemorrhage who do not respond to resuscitation may require acute surgical intervention. The use of REBOA in these patients may be lifesaving as a bridge to surgical or interventional therapy.

Summary

Pancreatitis is the most common gastrointestinal disease process requiring hospital admission and severe cases continue to have a high morbidity, mortality, and cost of care. The initial aspect of management is predicting which patients with acute pancreatitis will go on to develop severe forms of the disease. Unfortunately, most of the severity indices and classification systems used to assist in this process are either imprecise or require several days to complete, at which point severe disease is apparent. There are however a number of features that can be evaluated at presentation (Table 17.5) and can be helpful in identifying those at risk for severe disease. The subsequent ICU management of severe acute pancreatitis can be divided into phases that correspond with the pathophysiologic stages of severe disease.

Care in the first 24 h is focused on prevention of the development of pancreatic necrosis and persistent organ failure and mitigation of the overall disease process. Carefully guided resuscitation, avoidance of over-resuscitation, monitoring for and treatment of the development of intra-abdominal hypertension and abdominal compartment syndrome, and acute support for organ failure are the key features.

The first week of treatment is characterized by support for organ failure, continued monitoring of IAH, and specific therapies to minimize the risk of the development of local complications. The only therapy that has been shown to minimize the development of infected pancreatic necrosis, decrease local complications, and improve outcomes and mortality is early enteral nutritional therapy, which should be started within the first 48 h. There is currently no role for prophylactic antibiotics or probiotics to prevent the development of infected pancreatic necrosis. Routine endoscopic therapy in the first few days does not change the acute phase of the disease process or improve outcomes, except for patients presenting with ampullary obstruction or cholangitis. However, after the initial acute phase, ERCP and ES should be considered to prevent recurrence for patients with biliary causes of pancreatitis in whom early cholecystectomy is not possible. Patient with severe acute pancreatitis should be investigated for elevated triglycerides within the first 2 days, and therapy should be instituted when they are >1,000 mg/dl.

The subsequent weeks of ICU care are characterized by ongoing nutritional support, treatment for persistent organ dysfunction, and vigilant monitoring for the development of local complications and infection. Patients who fail to improve or have an acute decline in their status should be carefully investigated for their development. Modern minimally invasive techniques of percutaneous drainage, angiography, VARD, and endoscopic therapy have improved morbidity and mortality and supplanted open surgical management in most cases. Open surgical treatment still plays a role for the treatment of abdominal compartment syndrome nonresponsive to medical management; pancreatic necrosis with severe clinical deterioration in the first week of the disease; infected pancreatic necrosis not amenable or responding to minimally invasive therapy; colonic necrosis, perforation, or stricture; and acute hemorrhage with hemodynamic compromise.

Though morbidity and mortality remain high in patients with severe acute pancreatitis, it is likely that an organized, protocolized approach to their management can improve outcomes.

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Hepatic Failure

18

Mario Rueda and Pamela A. Lipsett

Acute Liver Failure

Definition, Epidemiology, and Causes

Acute liver failure (ALF) refers to the rapid deterioration of liver function that is seen in previously healthy patients. Its defining characteristics include the development of coagulopathy, with an international normalized ratio (INR) >1.5, as well as alteration of mental status (encephalopathy). It occurs in individuals without preexisting cirrhosis and with an illness of no more than 26 weeks duration.

There are some minor differences that are associated with duration of symptoms, and therefore ALF can be further subdivided into hyperacute (less than 7 days), acute (7–21 days), or subacute (more than 21 days and less than 26 weeks). Hyperacute and acute liver failures are more commonly associated with cerebral edema, while patients with subacute failure can present with ascites, portal hypertension-related bleeding, and renal failure.

Approximately 2,300 patients experience ALF in the United States [1]. Half of these cases are associated with drug toxicity, most of them related to acetaminophen. Viral hepatitis accounts for one fifth of the cases, the remaining being different metabolic and vascular disorders (Table 18.1) [2].

Clinical Manifestations

The rapid compromise of hepatic physiologic function results in clinical features that can affect several organ systems and can be variable in their presence and intensity.

Neurologic System

Nonspecific complaints such as fatigue, malaise, lethargy, nausea, vomiting, headache, and anorexia are frequently present in patients with liver failure. As a defining characteristic, patients with ALF present with various degrees of encephalopathy, ranging from slight confusion to coma. In order to characterize the severity of the impairment, several grading scales have been described [3]. Most commonly used is the West-Haven criteria (Table 18.2) [4]. For moderate to severe cases of encephalopathy, the Glasgow Coma Scale can also be used.

The mechanism by which these changes occur has not been fully identified; however, there are some generally

Table 18.1 Causes of acute liver failure

Medications	Acetaminophen (paracetamol)
	Tetracycline
	Troglitazone
	Isoniazid
	Aspirin
Toxins	*Amanita* mushrooms
	Lepiota helveola
Infectious	Hepatitis A
	Hepatitis B
	Hepatitis C (very uncommon)
	Cytomegalovirus
	Epstein-Barr virus
Metabolic	Acute fatty liver of pregnancy
	Wilson's disease
	Reye's syndrome
Vascular	Budd-Chiari syndrome
	Portal vein thrombosis
	Veno-occlusive disease
	Ischemic hepatitis
Parenchyma replacement or loss	Breast cancer
	Melanoma
	Small cell lung cancer
	Hepatectomy
	Necrosis

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Table 18.2 West-Haven criteria for grading hepatic encephalopathy

Grade I	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade II	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
Grade III	Somnolence to semistupor but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade IV	Coma (unresponsive to verbal or noxious stimuli)

accepted theories that revolve around impaired detoxification of substances normally cleared by the liver.

- Ammonia
- The metabolism of nitrogen-containing compounds in the gastrointestinal system results in the production of ammonia. In its normal state, the liver converts this neurotoxic product into glutamine and urea. Impaired liver function results in elevated blood ammonia. Astrocytes contain the enzyme glutamine synthetase in their endoplasmic reticulum as a means of handling excessive ammonia. Accumulation of glutamine within the astrocytes results in cell swelling which leads to a series of events that result in a neuroinhibitory state [5].
- False Neurotransmitters
- The failing liver results in the production of false neurotransmitters. These molecules may interfere with normal brain functioning and have a net inhibitory effect [6].
- Amino Acid Imbalance
- Patients with hepatic failure have decreased plasma levels of the branched-chain amino acids (BCAA) valine, leucine, and isoleucine while experiencing increased levels of aromatic amino acids (AAA) phenylalanine, tryptophan, and tyrosine. This is thought to be related to increased muscle catabolism and therefore increased BCAA metabolism as well as decreased breakdown of AAA by the compromised liver. The end result is an imbalance that leads to an increased influx of AAA in the brain which has an inhibitory effect in the nervous system [7].
- GABA receptor
- Thought to be mediated by inflammatory cells, neurosteroids are produced by myelinated glial cells. This results in positive modulation of GABA receptors that in turn enhance the inhibitory tone [8].

Besides the astrocyte swelling that is seen with the accumulation of glutamine explained above, overall neurologic dysfunction results in loss of autoregulation of intracranial pressure as well as reduced cerebral blood flow. The result of these changes may result in further neurologic derangement and compromise [9].

Besides hepatic encephalopathy, patients with ALF can also present with cerebral edema. There is an overlap with the clinical features that are seen with encephalopathy and include nausea, vomiting, headache, and agitation. In advanced cases which can progress to brain herniation, hypertension, bradycardia, changes in pupillary exam or reflexes, as well as respiratory depression can be seen [10].

Table 18.3 Respiratory complications seen in acute liver failure

Infectious	Upper respiratory infections
	Pneumonia
Noninfectious	Pulmonary edema
	Pleural effusion
	Pneumothorax
	Hepatopulmonary syndrome
	Acute respiratory distress syndrome
	Acute lung injury
	Depressed central respiratory drive

Respiratory System

Patients with ALF may present with nonspecific respiratory symptoms including dyspnea on exertion, orthopnea, anxiety, and air hunger. The affecting processes involved are very broad and can range from a simple pleural effusion to acute respiratory distress syndrome (ARDS) [11]. The spectrum of respiratory pathology that is seen can be grouped in to two major categories: infectious and noninfectious (Table 18.3).

Pulmonary edema can be of cardiogenic or noncardiogenic etiology. The prevalence of pulmonary edema appears to be higher in those patients with cerebral edema, suggesting the accumulation of osmotic substances within the lung parenchyma and outside the vasculature [12]. Molecular imbalance and injury to endothelial cells, accompanied by a decrease in oncotic pressure, may play a role in the development of this disease.

Hepatopulmonary syndrome can be seen in both ALF and chronic liver failure. It is thought to arise from microscopic shunting from arteriovenous dilations that occur in the pulmonary vasculature [13]. The precise mechanism is unknown; however, it is thought that the elevated levels of nitric oxide seen in patients with liver failure may mediate the abnormal vasodilation that occurs in the pulmonary parenchyma. The result is an overperfusion with maintenance of ventilation; a VQ mismatch occurs that ultimately leads to hypoxemia [14].

Cardiovascular and Hematologic System

As part of the pathophysiology associated with ALF, there is low systemic vascular resistance and a hyperdynamic

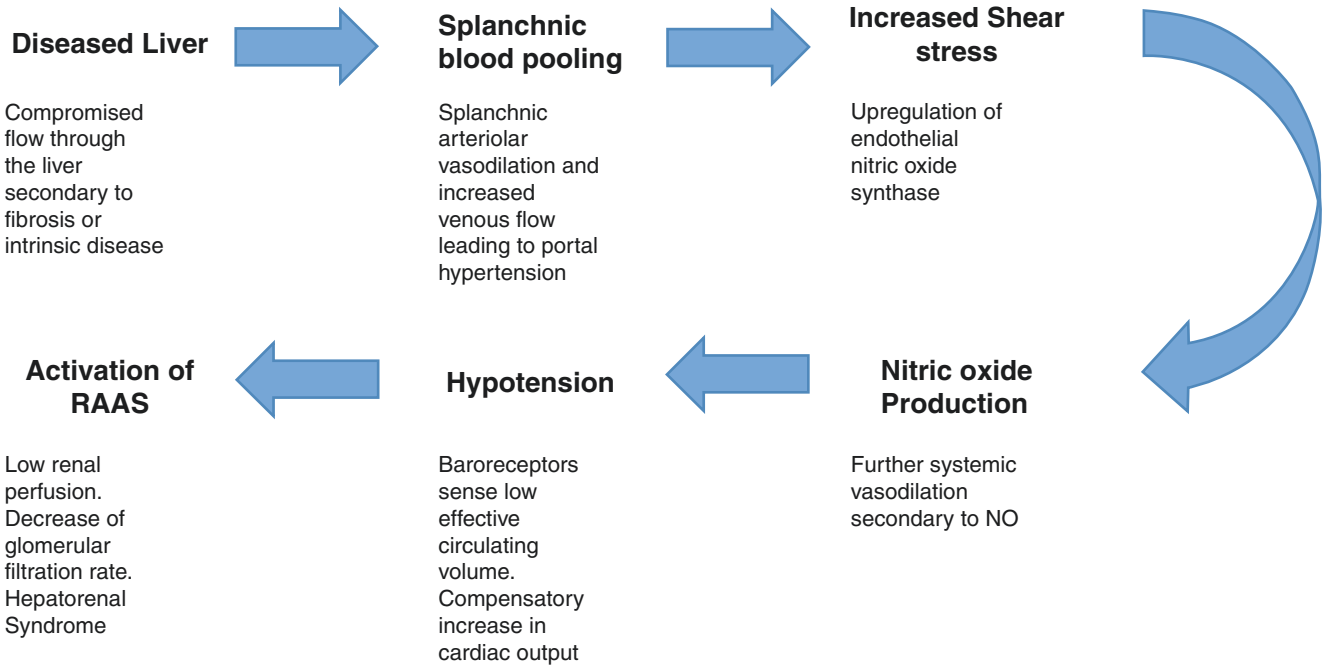

Fig. 18.1 Physiologic changes that occur in patients with liver failure

circulation with elevated cardiac output. The pathophysiology is multifactorial but vasoactive substances are thought to mediate the process [15]. While the underlying pathophysiology may differ, hemodynamic variables appear very similar to those seen in sepsis and septic shock.

In the failing liver, there is an increase in splanchnic blood pooling that is associated with the increased resistance of flow through the liver. This results in increased shear stress in the splanchnic circulation that causes upregulation of endothelial nitric oxide synthase (eNOS) and ultimately nitric oxide (NO) production [15, 16]. There is further systemic vasodilation causing a low effective circulating volume and relative hypotension despite an overall elevated intravascular volume. The systemic baroreceptors are unloaded and there is a compensatory increase in cardiac output as well as activation of the renin-angiotensin-aldosterone system (RAAS) that may ultimately affect the renal system (Fig. 18.1) [15].

Patients with ALF usually present with varying degrees of coagulopathy. As the liver fails, there is decrease in the synthesis of factors involved in both coagulation and anticoagulation, specifically fibrinogen, prothrombin, protein C, protein S, and factors V, VII, VIII, IX, X, and XI. The end result is an increased in prothrombin and activated partial thromboplastin times as well as elevation of INR [17].

Overt bleeding is not typically seen, as there is a decrease in both coagulation and anticoagulation factors. However, mucosal bleeding from the oropharynx or the gastrointestinal mucosa can be frequently seen. This is compounded by the underlying platelet dysfunction that can occur in patients with liver failure.

Gastrointestinal and Endocrine Systems

Right upper quadrant pain, gastrointestinal bleeding, ascites, nausea, and vomiting can be seen in patients with ALF. These symptoms are nonspecific and can be multifactorial.

Patients with acute viral or autoimmune hepatitis may experience liver parenchyma inflammation as part of the normal response to infection. This leads to an increase in the overall volume of the liver. The liver capsule may be unable to accommodate acute volume changes, and stretching of it results in activation of pain receptors and right upper quadrant pain. Discomfort in this area can also be related to direct trauma causing bleeding.

Abdominal distention may be associated with ascites. The neurohumoral alterations are seen with ALF leading to excessive sodium retention and ultimately plasma volume expansion. This, combined with a decrease in the overall circulating proteins due to compromised liver function, leads to overflow of fluid into the peritoneal cavity [18]. Tense ascites can result in compromise of respiratory, renal, and cardiovascular function due to direct compression of the diaphragm and vasculature.

As part of its normal physiologic function, the liver is responsible for gluconeogenesis as well as glycogen storage. As liver function worsens, these two key metabolic functions are compromised. In up to 40 % of patients, hypoglycemia is seen and treatment is warranted [19].

Renal System and Electrolytes

Acute kidney injury can be present in 30–70 % of patients with ALF [20, 21]. The etiology can be variable: prerenal azotemia, drug toxicity, and acute tubular necrosis have all been implicated. Hepatorenal syndrome, especially type 1, has also been associated with the progression of this disease. Acute kidney injury can be divided into oliguric vs. anuric failure, with the latter making fluid management difficult in the critical care setting [15].

Accompanying this derangement we can also see electrolyte disturbances: hyperkalemia, hyperphosphatemia, hypophosphatemia, hypercalcemia, and hypomagnesaemia that can lead to secondary arrhythmias and mental status changes [22].

Lactic acidosis can be seen in patients with ALF. The accumulation of tissue lactate is multifactorial. The effective blood pressure is usually lower in those patients with liver failure. This causes a generalized tissue hypoxia that leads to the production of lactate. The compromised liver is unable to uptake and process the lactate, leading to its accumulation [23–25]. In addition, acute kidney injury can further contribute to the underlying acidosis due to failure of fixed acid clearance [22].

Infectious Disease

Kupffer cells can be found around the hepatic sinusoids. Because of their location, they are constantly exposed to gut bacteria and endotoxins. They play a key role in clearing these pathogens and in maintaining normal homeostasis. In patients with liver failure, their function is impaired, and there is an increased susceptibility to develop Gram-positive and Gram-negative bacterial infections as well as possible fungal and viral infections [26].

Hepatic encephalopathy has been linked to an increased incidence of infection [27]. Although the mechanism behind this has not been clearly elucidated, it is thought that CNS depression alters the immune system modulation. In ALF, there is also a change in the production as well as clearance of different cytokines in patients with liver failure and compromised neutrophil function. These problems will lead to decreased bacterial opsonization and clearance. These alterations ultimately contribute to the immunologic impairment [26–28].

Up to three quarters of patients with ALF will develop a bacterial infection. The organisms that are most commonly seen include Gram-negative-bacteria, *Streptococcus*, *Staphylococcus*, and *Candida*. They may develop a systemic inflammatory response syndrome (SIRS) that will be undistinguishable from noninfectious conditions including necrotic hepatocytes from the failing liver [29–31].

Other Systems

Jaundice and pruritus are common complaints of patients with ALF. Although not specific to liver failure, the presence of both symptoms should raise suspicion of compromised excretion of bilirubin by hepatocyte failure.

A normal by-product of the metabolism of heme, bilirubin is usually excreted in bile and urine. The liver is responsible for conjugating glucuronic acid with bilirubin in order to make a soluble compound. As a result, conjugated bilirubin passes into the colon and is eventually eliminated. In the failing liver, there is a severe compromise of the ability to metabolize and excrete bilirubin secondary to the undergoing cell necrosis. There is buildup of unconjugated bilirubin in the blood resulting in eventual deposition of these molecules in mucous membranes, skin, and conjunctiva, what is known as jaundice [32]. Because of the yellow color of the pigment, the physical appearance of the patient changes, directly correlating with bilirubin levels.

Besides bilirubin, there is also accumulation and deposition of bile acids in the skin. This has been associated with pruritus. Other mechanisms that may explain this symptom include the endogenous opioids theory which proposes that the liver failure patient has elevated opioid levels secondary to decrease clearance and metabolism. These molecules activate the mu opioid receptor which may produce pruritus [33–35].

Workup and Initial Management

As explained throughout this chapter, the management strategies for patients with ALF are different from those of patients that have chronic liver failure with an acute decompensation. It is imperative to determine what form of failure the patient is experiencing. For those with ALF, early recognition and transfer to a transplant center will improve outcomes and mortality.

On initial presentation, a patient's mental status will be affected to different degrees; however it may deteriorate further. Getting a thorough history during the first encounter is therefore important as it can elucidate the possible cause of the acute failure.

The intensivist should review all medications that the patient ingested in the last 7 days. Specific questions about ingestion of acetaminophen should be asked. Dietary intake should also be explored, playing close attention to any exposure to mushrooms. Exact time of ingestion is key in order to determine treatment and further steps in management.

Social history should also be reviewed in detail. Recent travel to viral hepatitis endemic areas as well as contact with other patients that have required hospital visits should be evaluated. Focus on alcohol and drug use, sexual behaviors, and vaccination status can help determine the causative mechanism for the liver failure.

Past medical history plays a key role in determining if the patient has chronic liver disease or if they are experiencing an acute failure. A history of hepatitis, ascites, jaundice, asterixis, and gynecomastia and family history of a metabolic

Table 18.4 Laboratory exams that should be part of the initial evaluation of patients with acute liver failure

Infectious	White blood cell count
	Hemoglobin and hematocrit
	Platelet count
	Hepatitis A IgM
	Hepatitis B surface antigen
	Hepatitis B surface antibody
	Hepatitis B core antibody IgM
	Hepatitis B e antigen
	Hepatitis C antibody
Coagulopathy	Prothrombin time
	Activated thromboplastin time
	INR
	Type and screen
Renal and metabolic	Serum electrolytes (Na, K, Cl, CO2, Mg, PO4, Ca)
	Glucose
	BUN and creatinine
	AST
	ALT
	Alkaline phosphatase
	Total bilirubin
	Direct bilirubin
	Albumin
	Amylase
	Lipase
	Arterial blood gas
	Serum lactate
	Ammonia
	Ceruloplasmin
Toxin	Acetaminophen level
	Toxicology screen
Autoimmune	ANA
	ASMA
	Immunoglobulin levels

disorder favor chronic liver disease with an acute exacerbation. History of malignancy and lack of screening for colorectal cancer should also make the intensivist suspicious for metastatic malignancy. Physical exam may disclose important findings that can elicit cause. An effort to identify the clinical manifestations described previously should be done.

Laboratory values that should be routinely obtained are listed in Table 18.4.

When testing for hepatitis B, it is important to evaluate for immunity (hepatitis B surface antibody), infectivity (hepatitis B e antigen), and the presence of an acute infection (hepatitis B core antibody IgM). Although hepatitis C can cause ALF, it is usually associated with chronic liver failure [36].

BUN and CO2 can usually be lower than reference values in patients with ALF. This is secondary to poor muscle mass as well as a respiratory alkalosis experienced by these patients. Presentation with concomitant renal failure will alter most serum electrolytes.

Elevation of liver enzymes can be indicative of acute hepatitis and ALF. However, values that are within reference range may be markers of poor prognosis as it may be reflective of decreased effective liver mass [26, 34].

Workup should be started on presentation, even if patient is going to be transferred to a liver center. Early identification of the etiology and early treatment can significantly improve outcome. It can also identify those patients that will need liver transplantation in order to treat their disorder.

If during the history and physical assessment a cause can be clearly identified, treatment should be started empirically. Waiting for laboratory values can be detrimental and result in further deterioration of the patient. Consultation with hepatology/gastroenterology, transplant surgery, and the intensivist should be done upon determination of liver failure of any cause.

Management

The development of ALF has very different etiologies as well as presentations. As such, the management may differ from patient to patient. Identification of the causative agent and treatment of it is important. However, supportive care in the intensive care unit is critical for ensuring a positive outcome.

Patients that have evidence of encephalopathy will require intensive care unit (ICU) admission and management while those with no neurologic derangement can be followed on a regular ward with close monitoring. Patients should have frequent checks of their coagulation parameters, arterial blood gases, complete blood counts, metabolic panels, serum aminotransferases, alkaline phosphatase, and bilirubin levels. Derangements warrant further investigation. Hemodynamic monitoring, precise fluid management, and monitoring for infections are all essential.

Encephalopathy, Cerebral Edema, and Intracranial Hypertension

The grade of hepatic encephalopathy guides the management and treatment of the neurologic system in ALF. This is because intracranial hypertension (ICH) and cerebral edema characterize the severity of patient presentation. Those with mild forms (grades I and II) very rarely develop these devastating complications while 25–35 % of patients with grade III and 65–75 % of those with grade IV present with ICH [11].

For those patients with grades I and II, frequent neurologic assessments should be performed to follow possible neurological progression. Maintaining the patient in a quiet environment helps minimize agitation. Sedation should be minimized; however, if needed minimal doses of short-acting

benzodiazepines should be used [37]. For patients who present with or develop grade III and IV neurological symptoms, securing an airway should be the first treatment strategy followed by mechanical ventilation. For sedation, propofol should be used since there is evidence that it decreases cerebral blood flow and allows for frequent ongoing neurological assessment [38].

Intracranial pressure (ICP) monitoring devices are used in some ICUs in patients with ALF and grade III or grade IV encephalopathy [39]. The main reason for its use is the early identification of ICH and subsequent treatment. Also, not all patients present with Cushing's trial of systemic hypertension, bradycardia, and irregular respirations. Several trials have shown that ICP monitoring can be performed safely and successfully be used to manage ICH [40–42]. However, no trial has demonstrated a survival benefit. Bleeding has been associated with the placement of monitors; however, recent literature reports that there is a decrease prevalence of this particular complication. The incidence of bleeding after placement of ICP monitor device has been less than 1 % [43].

CT scan of the brain should be considered in those patients with an acute mental status change and those with coagulopathy in order to rule out intracranial bleed. This imaging modality does not diagnose cerebral edema or ICH in all patients, and therefore, it is not needed in every case of encephalopathy. Patients at risk of encephalopathy should also have the head of their bed elevated at 30° [44], minimize ET suctioning, and minimize pain as these factors can lead to ICH [37].

For those patients with elevated ammonia levels (greater than 75 ug/dL) and ALF, administration of lactulose can lower the incidence of cerebral edema and decrease mortality [45]. Prior to prescribing this drug, the route of drug administration must be considered as the patient's ability to tolerate PO intake may be compromised. Other compounds studied include L-ornithine L-aspartate but have failed to demonstrate any survival improvement [46].

Phenytoin has been proposed as a possible prophylactic measure to prevent cerebral edema. An initial study that involved evaluation of brain at autopsy showed that patients who were treated with prophylactic phenytoin had a decrease in cerebral edema [47]. Follow-up trials were unable to replicate these results and more importantly, there was no survival improvement when this agent was used prophylactically [48].

The administration of intravenous mannitol has been shown to transiently decrease cerebral edema and may be helpful in cases in which ICH is <60 mmHg [49]. A dose of 0.5–1 g/kg may be beneficial and it may be repeated if serum osmolality is below 320 mOsm/L. The use of hypertonic saline has also been suggested. There is a lower incidence of ICH in patients with ALF that are treated with hypertonic if it is used to achieve a serum sodium level between 145 and 155 mEq/L [50]. Use of hypertonic saline can be limited by renal failure. A newer treatment technique that has been proposed to prevent ICH is hypothermia. It is thought to mediate this benefit by preventing hyperemia [51]. Concerns regarding the use of hypothermia in the treatment of ALF include worsening coagulopathy and compromise of hepatocyte recovery [52].

Hyperventilation and use of corticosteroids have been proposed as a management option to reduce ICP. The former may achieve this goal via vasoconstriction. However, trials suggest that although there is a delay in the onset of cerebral herniation, there is no reduction in the incidence of cerebral edema and no survival benefit [53]. Hyperventilation should only be used after all other resources have failed.

Respiratory Management

While hypoxemia in patients with ALF arises from many causes, it is treated with supplemental oxygen. If the patient has grade III or IV hepatic encephalopathy, a definite airway should be established. During intubation, *cis*-atracurium is the agent of choice since it does not increase ICP [54].

Pleural effusions can be observed and may or may not be contributing to hypoxemia or other respiratory problems. The use of diuretics should be carefully considered as these patients are usually in a very delicate hemodynamic state. Overuse of diuretics can precipitate renal failure [34].

Hepatopulmonary syndrome (HPS) has been traditionally resistant to medical therapies [15]. Oxygen supplementation for hypoxemia is recommended. Transjugular intrahepatic portosystemic shunt (TIPS) has been reported to improve HPS; however, it is not currently recommended as its outcomes are variable [55, 56]. Liver transplantation is the only therapy that has been shown to improve oxygenation and decrease oxygen requirement [57]. The diagnosis of HPS should prompt immediate referral to a transplant center.

Cardiovascular and Hematologic Management

Decreases in blood pressure lead to compromised renal and brain perfusion. It is imperative to be attentive to blood pressure and heart rate values in order to ensure adequate hemodynamics and, most importantly, adequate perfusion. Patients with ALF should be resuscitated initially with crystalloid before considering vasoactive agents.

The generally accepted goal mean arterial pressure is 65 mmHg [58]. If after adequate volume resuscitation the patient is still hypotensive and not meeting blood pressure goals, vasopressors should be considered. Norepinephrine should be initiated and titrated to effect [59]. For resistant hypotension consideration to vasopressin should be given, although it should be used with caution as it has been associated with cerebral vasodilation and increased ICH [60, 61]. Terlipressin has also been suggested as adjuvant treatment but it is currently not available in the United States [60]. Other causes of hypotension resistant to vasopressor therapy

should also be entertained including adrenal failure and severe acidosis.

During liver transplantation, ICH and hemodynamics improve immediately after hepatectomy, probably secondary to removal of vasoactive cytokines. Hepatectomy can improve these derangements for up to 48 h [62]. Hepatectomy is currently recommended only as a last resort and when a liver graft in the process of being delivered to the transplant institution [37].

Despite the derangements of coagulation laboratories in patients with ALF, their coagulation status remains in equilibrium and overall hemostasis. In the absence of bleeding, no correction of laboratory parameters should be performed [63]. Transfusion should be discouraged because treatment with FFP may precipitate pulmonary problems including hypoxia, and transfusion also prevents the use of INR as a marker of hepatocyte recovery [37].

If an invasive procedure is planned or if there is evidence of significant bleeding, correction of coagulopathy should be done. FFP can be used for this purpose; however, careful volume management should also be achieved. The use of plasmapheresis and recombinant activated factor VII (rFVIIa) can help in the correction of coagulopathy. rFVIIa has been proposed as it effectively corrects derangements without volume overload [64]. However, administration does carry the risk of myocardial infarction and portal vein thrombosis [65]. ALF has also been associated with vitamin K deficiency and it should be administered routinely in these patients [66].

Thrombocytopenia has also been reported in patients with ALF. Platelets should not be administered in the absence of bleeding. If the patient has platelet counts that are greater than 10,000/mm^3, no prophylactic transfusion should be given [67]. If an invasive procedure is planned, platelets between 50,000/mm^3 and 70,000/mm^3 have been proposed, and in those bleeding, the intensivist should consider transfusion if platelets drop below 50,000/mm^3 [67, 68].

Gastrointestinal and Endocrine Management

Bleeding from intestinal mucosa is rare but has been reported in patients with ALF. Histamine-2 receptor blockers have been used in critically ill patients as prophylaxis of gastrointestinal (GI) bleeding with great success [69]. Also, proton pump inhibitors (PPI) have contributed to the reduced incidence of upper GI bleeding in patients with liver dysfunction [70]. It is therefore recommended that ALF patients are started on prophylaxis while in the ICU.

Nutrition can be compromised in patients with ALF; therefore, enteral feedings should be started early unless there are contraindications. There is no evidence that using branched-chain amino acid formulas has benefits over other enteral tube feeds [71]. Protein supplementation should not be restricted but rather limited to 60 g per day in most patients. If gastrointestinal feeding is contraindicated, parenteral nutrition may be considered. There is also evidence that the risk of GI bleeding is reduced in patients that are on enteral feeding [72].

Hypoglycemia should be actively treated in patients with ALF. The intensivist should consider adding dextrose to crystalloids in the form of D5. If hypoglycemia is severe, central replacement with D20 concentration should be used. Frequent glucose checks should be performed in order to assess the response to glucose administration. Improvement and eventually weaning can be achieved in those patients that experience hepatocyte recovery.

Right upper quadrant pain can be treated with narcotics. Judicious doses should be used as metabolism of medications can be compromised with the failing liver [37]. The management of ascites will be discussed with chronic liver failure.

Renal Management

Close urine output monitoring is paramount in patients with ALF. Hemodynamic changes and alterations in the cardiovascular system make the kidneys susceptible to injury. Insertion of a urinary catheter should be performed upon determination of hepatic failure.

Besides serum electrolytes, measurement of urinary sodium and creatinine is necessary. High or normal urine sodium may indicate the presence of acute tubular necrosis, while a low urine sodium may indicate prerenal azotemia or hepatorenal syndrome. Several electrolyte derangements may occur and correction should be attempted. Accumulation of lactate may result from tissue hypoxia and combined with renal failure may cause life-threatening acidosis.

Renal replacement therapy may be necessary in these patients. When indicated, continuous dialysis should be used as studies have shown that it provides cardiovascular as well as intracranial pressure stability when compared to intermittent dialysis [73].

Infectious

The development of an infection in a patient with ALF has been associated with worsening encephalopathy and cerebral edema. Also, the presence of bacterial or fungal infections may compromise any attempts at performing a liver transplantation. Because of the impact that it has, prophylactic antimicrobials have been proposed as a prevention strategy for these patients [74].

Prophylactic antibiotics have been used and shown to decrease the incidence of infections in patients with ALF. In a prospective control trial by Rolando N et al., patients with fulminant liver failure were randomized to receive either selective parenteral and enteral antimicrobials vs. no treatment until clinically indicated. 104 patients were included in this study. Thirty-four percent of those patients randomized

to receive prophylactic antibiotics developed an infection compared to 61 % of those that were treated when clinically indicated ($p<0.005$). However, this did not translate into a survival benefit [75]. It is currently recommended that if no prophylactic antibiotics are used, periodic sputum, urine, and blood cultures are performed to determine if there are bacterial infections [37].

The use of antifungals has also been studied [76]. It is routine practice of the authors to use prophylactic enteric fluconazole in patients that are expected to be in the ICU for more than 3 days, given that there is a decrease in fungal infections in high-risk critically ill surgical patients [77].

It is paramount to perform an infectious workup to any patient with liver failure that develops a change in mental status as it may be a change precipitated by infection.

Specific Management

Acetaminophen Toxicity

The most common cause of ALF in the United States is acetaminophen (paracetamol) toxicity [78]. Over-the-counter availability and the fact that it can be found in combination with other medications make it the cause of voluntary or involuntary overdoses that compromise liver function and may result in fulminant liver failure.

Acetaminophen is usually taken orally and absorbed via the gastrointestinal system. Its half-life is usually 2–4 h with one exception being extended release preparations in which it is increased to more than 4 h. Total doses should not exceed 4 g per day. Ingesting doses less than 7.5 g per day is unlikely to result in acute toxicity; however, it can vary depending on underlying liver function [79].

The metabolism of acetaminophen is performed in the liver. Most of the compound, approximately 90 %, is conjugated with sulfate or glucuronide and excreted in the urine. Five percent of the remaining medication is excreted unchanged in the urine. The remaining acetaminophen is subject to metabolism by the cytochrome P450 pathway. It is converted into N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive and toxic compound that is immediately conjugated with hepatic glutathione and excreted in the urine.

When glutathione levels drop below 20 % physiologic levels, NAPQI forms covalent bonds via cysteine groups with hepatic molecules and proteins, leading to irreversible hepatocyte damage. A decrease in glutathione levels, enhanced cytochrome P450 activity secondary to medication use, acetaminophen overdose, or decreased liver function from chronic disease make patients more susceptible to developing toxicity.

The clinical presentation of acetaminophen toxicity can be divided into four different stages (Table 18.5).

Stage I includes a series of nonspecific GI symptoms that start shortly after ingestion. No liver abnormality can be seen. During stage II, there is usually transaminitis with a high AST/ALT ratio. Stage III is characterized by the clinical evidence of liver failure and, in some patients, renal failure. Mortality is higher at this stage. Those patients that survive this stage progress to stage IV in which there is normalization of most of their lab derangements.

Because patients may not show symptoms up to 24 h after ingestion, it is very important to obtain a detailed history. Standard workup should be initiated as discussed previously. Contacting poison control will help coordinate efforts to treat and eventually transfer patient to a liver center [37].

In order to determine the severity of the poisoning, a serum acetaminophen concentration (4 h post ingestion or later) should be plotted against time on the modified Rumack-Matthew nomogram (Fig. 18.2) [80, 81]. Patients with acetaminophen levels below the treatment line can be discharged home after psychiatric and social evaluation. All other patients should be admitted to the intensive care unit [82].

For those patients that ingested a single dose of acetaminophen of more than 7.5 g less than 4 h prior to presentation, administration of activated charcoal should be considered. Review of several small studies demonstrated that activated charcoal was the best available option to reduce absorption [83–85]. Also, there is a decreased risk of developing liver injury if charcoal is given prior to other forms of treatment [85]. If patient has an unstable airway, charcoal should not be administered until the airway is controlled.

The antidote of choice for acetaminophen toxicity is N-acetylcysteine (NAC). The exact mechanism of action is unclear; however, it appears to restore glutathione levels

Table 18.5 Clinical stages of acetaminophen toxicity

Stage	Onset	Symptoms	Laboratory values
Stage I	0–24 h	Nausea, vomiting, malaise	Elevated acetaminophen levels
Stage II	24–72 h	RUQ pain, nausea, vomiting	Elevated AST, ALT, ALP, total bilirubin, lactate, and creatinine
Stage III	72–96 h	Encephalopathy, jaundice	Elevated AST, ALT, ALP, total bilirubin, PT, INR, PTT, lactate, and creatinine
			Hypoglycemia
Stage IV	5 days	Improvement in confusion, resolution of GI symptoms	Normalization of above values

[86, 87]. Indications for administration include a serum acetaminophen level above the treatment line, ingestion of more than 7.5 g, serum acetaminophen level >10 mcg/mL if time of ingestion is unknown, evidence of liver injury, and a history of acetaminophen ingestion regardless of time of ingestion [86–88].

Oral and IV administration of NAC have been studied and both appear effective [86]. The main factor determining the mode of treatment should be the mental status of the patient. If the patient is confused or has evidence of encephalopathy, oral administration should be avoided. If the oral protocol is used, a loading dose of 140 mg/kg should be given followed by 17 doses of 70 mg/kg given every 4 h. If IV NAC is used, a loading dose of 150 mg/kg is given over 1 h. A second dose of 50 mg/kg is then given over 4 h and finally a third dose of 100 mg/kg is given over 16 h.

An alternative to NAC is hemodialysis. This method effectively removes acetaminophen [89]. However, because of the effectiveness of NAC, it should be reserved for cases in which the antidote is not available.

Acetaminophen toxicity is best managed in a multidisciplinary setting with assistance from hepatology and surgery teams.

Amatoxin Intoxication

Ingestion of poisonous mushrooms can lead to lethal emergencies including ALF. *Amanita phalloides*, *Amanita bisporigera*, *Amanita verna*, and other mushroom species may cause ALF. These mushrooms do not express repulsive smells or tastes, and they can be found throughout midsummer in moist oak forests.

Alpha-amanitin is the amatoxin responsible for liver failure. After gastrointestinal absorption, enterohepatic circulation is responsible for transportation into the liver, where via active transport it concentrates in hepatocytes. The toxin will bind to RNA polymerase and inhibit protein synthesis, ultimately leading to apoptosis [90].

The clinical presentation of patients that ingest amatoxin includes an initial asymptomatic period of a few hours. This is followed by gastrointestinal symptoms that include abdominal pain, nausea, vomiting, and diarrhea that can be bloody. Liver enzymes will be elevated and will continue to increase. One to two days after ingestion, the second phase of the presentation begins with an apparent recovery with continuing elevation of AST and ALT. In severe poisonings, coagulopathy and possible DIC and renal failure may ensue. The last phase includes ALF and typically starts 3 days after ingestion. Hypoglycemia and multi-organ failure can be seen.

Workup of a patient with suspected amanita ingestion should proceed as indicated earlier in this chapter. Detection of amatoxin can be performed in urine samples using enzyme-linked immunoassay (ELISA); this test is not readily available in all institutions and awaiting results should not preclude supportive treatment [91].

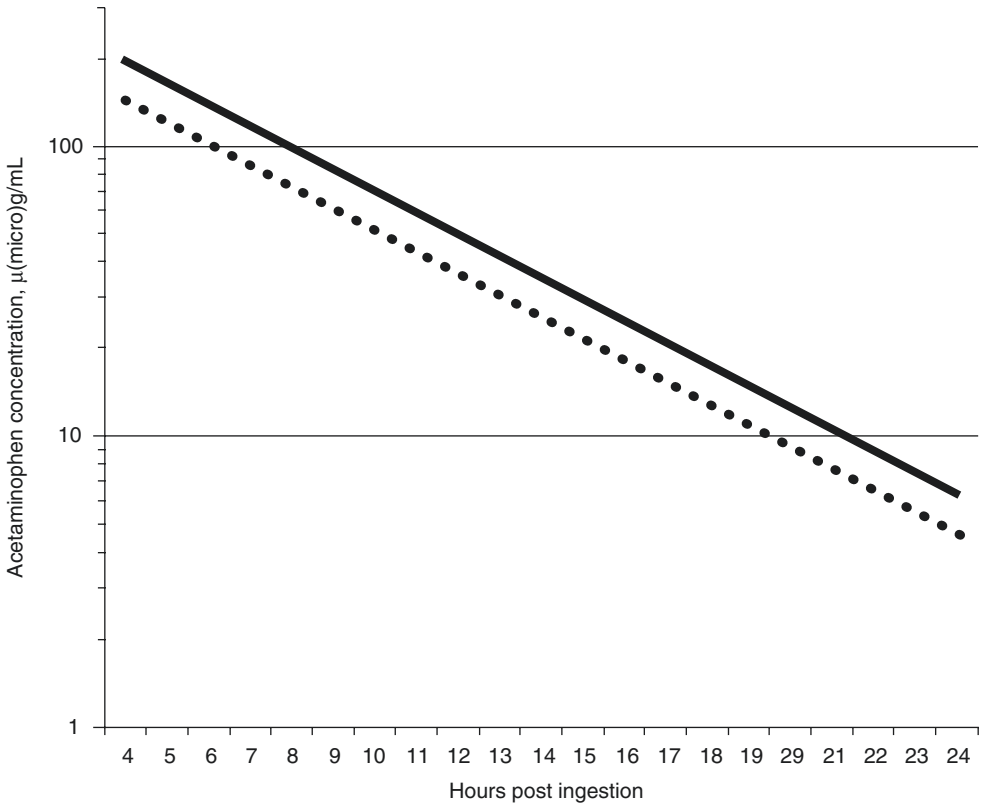

Fig. 18.2 Modified Rumack-Matthew nomogram. The *X axis* represents the number of hours after ingestion of acetaminophen and the *Y axis* the concentration of the medication in the blood. Levels are measured at least 4 h after ingestion. The *solid line* represents concentrations that are toxic. The *dotted line* represents a 25 % reduction in the toxic levels and it accounts for possible errors in acetaminophen assays. If the level is above the *dotted line*, NAC therapy should be started. If below, the patient can be safely discharged after medical evaluation (Data from Rumack and Matthew [80] and Rumack [81])

Supportive treatment should be started immediately after presentation. In addition, an effort to minimize toxin absorption should be attempted. Activated charcoal can bind amatoxin, and if given in repeated doses, it can reduce mortality significantly by increasing elimination via gastrointestinal tract [37].

Medications that can inhibit uptake of this toxin have also been described. These include penicillin G and silymarin. The former is given as a continuous infusion and has been show to decrease mortality [92, 93]. The latter is a more potent inhibitor and is available in IV and PO formats. Silymarin has been shown to minimize damage to hepatocytes [92, 94, 95].

NAC has also been used in the treatment of amatoxin intoxication. Mortality appears to improve with implementation of protocols very similar to those of acetaminophen toxicity [92, 96].

Wilson's Disease

Wilson's disease poses a different presentation from frank ALF. It normally occurs in the background of chronic liver disease that has been unrecognized. Treatment varies when presentation of this disease is acute, and this will be the focus of this section.

A genetically recessive disease, it is estimated that 2–3 % of ALF cases are related to Wilson's disease [97]. The majority of copper that is ingested is transported into the liver where it is incorporated into enzymes and copper-binding proteins (ceruloplasmin). Excess copper is combined with apometallothionein and excreted into bile. In Wilson's disease, the incorporation into ceruloplasmin is compromised and copper is accumulated in the liver. As the disease progresses, other organs are affected. Besides parkinsonian movements and tremors, Kayser-Fleischer rings, psychiatric alterations, and renal problems, Wilson's disease will present with liver disease: cirrhosis, chronic failure without cirrhosis, and acute liver failure.

Laboratory workup should include serum ceruloplasmin, which is usually low, as well as serum copper level (above 200 mcg/dL) [97]. In patients with evidence of ALF, low transaminases, low alkaline phosphatase, hypokalemia, glycosuria, hypophosphatemia, and renal tubular acidosis, the diagnosis of Wilson's disease should be considered.

In patients with acute failure, the aim should be to remove copper. Hemodialysis and peritoneal dialysis can successfully achieve this goal [98]. Albumin dialysis and the molecular absorbent recirculating system (MARS) device have also been used with promising results [99, 100]. Penicillamine, zinc, and other medications used for treatment of Wilson's disease do not play a role in ALF.

Viral Hepatitis

The development of ALF from viral hepatitis may occur after acute infection; Ostapowicz et al. estimated that the etiology of 12 % of those patients that were diagnosed with ALF was viral hepatitis [101]. Most of the clinical deteriorations that are seen in patients with this etiology of disease are related to chronic liver infection. ALF is more common with hepatitis B but it can also present in patients with hepatitis A, C, and E [34].

Presentation of viral hepatitis is described in four phases. Phase 1 is characterized by lack of symptoms but changes in laboratory studies that may be suggestive of viral hepatitis. Phase 2 marks the development of symptoms that include nausea, vomiting, abdominal pain, arthralgias, and possible fevers. The next phase includes clinical characteristics of ALF including right upper quadrant pain, becoming icteric, and possible coagulopathy. The last phase, 4, leads to the normalization of laboratory values and resolution of symptoms.

Diagnosis of viral hepatitis relies on serum laboratories. Acute hepatitis A is diagnosed by the presence of IgM antibody against the hepatitis A virus. Presence of IgG implies previous infection and resolution.

Hepatitis B has several important antigens and antibodies. Hepatitis B surface antigen (HBsAg) is usually found in patients with acute infection. A second antigen, associated with infectivity, is hepatitis B e antigen. The first antibody that can be detected in patients acutely infected and that indicates acute presentation of disease is IgM anti-HBcAg. Resolution of acute infection and recovery results in IgG antibodies against this antigen. Finally, anti-HBsAg appears in the serum several months after infection, indicating resolution. They will also be found in patients with hepatitis B vaccine.

IgG anti-hepatitis C virus has been used to diagnose exposure to this viral infection. It can usually be found in the serum several months after an acute infection and contrary to anti-HBsAg, it does not confer immunity to Hepatitis C. Use of ELISA and RIBA testing for diagnosis has fallen out of favor. HCV RNA PCR assays were developed in order to detect the presence of the virus. It has been successful in not only establishing the diagnosis but also the presence of an acute infection.

Treatment of acute hepatitis A is limited to supportive care as there are no medications that improve outcome. Hepatitis B treatment usually follows the same principles as most antiviral therapy is directed toward treatment of chronic disease. However, recent studies have suggested that acute hepatitis B may benefit from administration of lamivudine [102]. Finally, acute hepatitis C has been treated with IFN therapy with resolution of HCV RNA after several months of treatment [103].

Ischemic Hepatitis

Low perfusion pressure to the liver may result in clinical manifestations of ALF known as ischemic or hypoxic hepatitis. It is an uncommon cause of liver failure, with a prevalence of 1 per 1,000 hospital admissions [104]. This can be a direct

consequence of global hypoperfusion, hemodynamic instability, direct vascular occlusion during surgical procedures, hepatic artery disease (occlusion, dissection, thrombosis) in patients with portal vein thrombosis, or hepatic sickle cell crisis [105]. Hepatocytes in zone 3 become ischemic and eventually necrotic leading to liver insufficiency.

Prognosis of ischemic hepatitis is poor. Raurich et al. described an in-hospital mortality of 61.5 % in all patients that were diagnosed with this disease process. In those patients with concomitant septic shock and those that experienced cardiac arrest, mortality rates were higher, at 83.3 % and 77.7 %, respectively. Risk factors for mortality included an elevated INR, need for renal replacement therapy, and diagnosis of septic shock. Non-survivors were more likely to be on vasopressors and to require mechanical ventilation [106].

Patients with hepatitis secondary to shock present with several symptoms related to their hemodynamic instability including altered mental status, respiratory distress, severe hypotension, and renal failure. Patients with a history of cardiac compromise may present with nausea, vomiting, right upper quadrant pain, and malaise. Up to 14 % of patients with septic shock will also have ischemic hepatitis, presenting with fevers and severe hypotension [106].

Laboratory examination reveals elevated aminotransferase levels, usually above 1,000 IU/L. The ratio of serum alanine aminotransferase to LDH less than 1.5 suggests ischemic hepatitis [107]. If hypoperfusion is chronic in nature, synthetic function may be preserved and coagulation studies may be normal; however, in acute cases, there is severe derangements that continue to progress with time. If ischemic hepatitis is suspected, a right upper quadrant ultrasound with Doppler should be immediately performed as it may reveal the etiology of the insufficiency.

There is no specific treatment for ischemic hepatitis. Management is centered around restoring cardiac output and reestablishing hepatic perfusion. Appropriate resuscitation is necessary. Excessive fluid administration may lead to vascular congestion which can in turn compromise perfusion of hepatocytes and aggravate the presentation. Judicious use of diuretics should be exercised as diuresis may exacerbate hypoperfusion and therefore liver failure. Intensivists should rule out ischemic hepatitis in any patient that presents with septic shock and has elevated aminotransferases [106]. Prompt recognition of hypoperfusion state may lead to early intervention and possible better outcomes.

Chronic Liver Disease

Definition, Epidemiology, and Causes

Continuous hepatic injury that persists for more than 6 months is considered chronic liver disease (CLD). The liver parenchyma suffers continuous inflammation and potential destruction. The hepatic insult does not only result in damage but also in attempts of repair. Ultimately this leads to a broad spectrum of clinical manifestations including fibrosis, cirrhosis, and hepatocellular carcinoma. These changes are accompanied by alterations in serum liver function tests and can include physical exam finding suggestive of physiologic alterations.

Table 18.6 Causes of chronic liver disease

Infectious	Chronic hepatitis B
	Chronic hepatitis C
	Brucellosis
	Syphilis
	Echinococcosis
	Schistosomiasis
Drugs and toxins	Alcohol
	Amiodarone
	Isoniazid
	Methotrexate
Metabolic (acquired and genetic)	Nonalcoholic fatty liver disease (NAFLD)
	Hemochromatosis
	Wilson's disease
	α1-Antitrypsin deficiency
Vascular	Right heart failure
	Veno-occlusive disease
	Hereditary hemorrhagic telangiectasia
Other	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Autoimmune hepatitis

In the United States, the most common causes of cirrhosis leading to liver transplantation are alcoholic liver disease, chronic viral hepatitis, and nonalcoholic liver disease (Table 18.6) [108]. This last etiology has increased significantly in incidence. Most patients are generally asymptomatic until decompensation occurs, making the calculation of prevalence difficult. Approximately 49,500 deaths in 2010 where associated with CLD [109].

Clinical Manifestations

Patients with CLD may present with compensated or uncompensated hepatic failure. The former may be asymptomatic prior to evaluation, but patients usually report nonspecific symptoms such as weight change, fatigue, and lack of appetite. Those patients with an acute decompensation may show signs of active bleeding, confusion, and skin changes. Because of the broad spectrum of the disease, presentation will vary between different patients. Due to similar underlying pathophysiology, symptoms and findings may be similar to those described previously during the acute liver failure presentation.

Nervous System

Patients with CLD may present with varying degrees of hepatic encephalopathy. Classification and underlying pathophysiology are similar to those described previously in the ALF section. An acute exacerbation with an underlying chronic liver dysfunction can cause rapid progression from confusion to coma.

Respiratory System

Shortness of breath, dyspnea, and other nonspecific respiratory symptoms may also be reported. As with acute dysfunction, the etiology may be of infectious, metabolic, or of cardiac etiology. Hepatopulmonary syndrome can also play a role in underlying hypoxemia [15]. The mechanisms that lead to the respiratory derangements in CLD are similar to those described in acute liver compromise.

Cardiovascular and Hematologic System

Figure 18.1 explains the molecular mechanism behind the underlying decreased effective perfusion pressure seen in patients with liver failure. As a result, patients will have a lower than baseline blood pressure, with some of them transitioning from hypertensive to normotensive.

The cardiac output in patients with liver disease is usually high; however it is important to understand that myocardial cells are actually depressed from exposure to the changes in cytokines and other molecules. There is a slightly elevated heart rate that compensates for the depression and overall results in increase cardiac output, in a normal-sized man, often in the range of 10–12 L/min [15].

Patients with CLD may present with anemia, leukopenia, thrombocytopenia, and coagulopathy [110]. The pathophysiology behind anemia is multifactorial, and it may include episodes of gastrointestinal bleeding associated with portal hypertension and coagulopathy. There may also be nutritional deficiencies such as folate deficiency that can lead to compromised production of red cells and vitamin K deficiency that can lead to decreased production of coagulation factors [17]. Aplastic anemia, hypersplenism, and hemolysis may contribute to the anemia experienced by patients with chronic failure [111].

Thrombocytopenia is associated with portal hypertension: an enlarged spleen can sequester the majority of the circulating platelet mass and lead to a decrease platelet count. It has also been described that patients with liver disease have decreased levels of thrombopoietin that will also lead to thrombocytopenia [112].

Gastrointestinal and Endocrine Systems

Patients experiencing CLD can present with abdominal distention and pain, anorexia, nausea, and vomiting. Physical exam may also show ascites, hypogonadism, hypersplenism, and evidence of gastrointestinal (GI) bleeding such as hematemesis, hematochezia, and melena. GI bleeding can be the result of mucosal injury and thrombocytopenia or a more severe and life-threatening event such as variceal hemorrhage. An umbilical hernia may be seen when ascites becomes prominent.

For those patients with CLD, there are significant changes in the hemodynamics of the portal vein. The hepatic microcirculation, sinusoids, undergoes constriction secondary to architectural changes that compromise the lumen of these systems. Furthermore, there is active contraction of myofibroblasts and active smooth muscle secondary to cytokine changes (increased levels of intrahepatic ET-1) that cause even more restriction in the radius of these sinusoids [113, 114]. These changes lead to an increase in portal pressure.

A second factor that impacts the pressure of the portal vein is the increased in blood flow in the portal vein. As shown in Fig. 18.1, there is a splanchnic arteriolar vasodilation that leads to increase venous outflow and, therefore, increased flow that results in further increases of portal pressure and eventually portal hypertension (PHT) [15].

The elevated blood pressure and flow are partially relieved by decompressing the inflow into the portal vein into systemic collaterals. The esophageal submucosal veins are a preferred method of decompression and may result in esophageal varices. As flow increases so does the vessel radius [115]. This ultimately leads to an increase in wall tension that may end up in rupture and variceal bleeding [114, 116].

Ascites is also closely related to PHT. In fact, patients without evidence of PHT do not develop ascites even in the presence of cirrhosis. The threshold for formation of ascites appears to be 12 mmHg at the level of the portal vein [117]. As a response to this increase in pressure, there is splanchnic vasodilation leading to a decrease in effective arterial blood volume that is mediated by several molecules including nitric oxide (NO). There is subsequently an activation of the renin-angiotensin-aldosterone system that increases renal sodium retention and plasma expansion that ultimately leads to accumulation of fluid in the peritoneal cavity [118]. The low levels of circulating protein secondary to liver compromise may also favor the formation of ascites.

On physical exam, we can find evidence of PHT by placing a stethoscope over the epigastrium. If there are collateral connections between the portal system and the umbilical vein, a murmur can be auscultated. This finding is known as Cruveilhier-Baumgarten murmur.

Dizziness, diaphoresis, and overall malaise may be reflective of underlying hypoglycemia. Patients with CLD undergoing an acute exacerbation may see decreased levels of circulating glucose with corresponding changes in neurologic exam.

Male and female patients with CLD can report abnormalities related to infertility, impotence, and in the case of women chronic anovulation. Physical exam may show evidence of

testicular atrophy in men, while ultrasound and other imaging may show atrophic ovaries and uterus. There are several possible mechanisms that explain these findings. The increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) observed in some patients suggest the primary dysfunction of the testicles or ovaries. An alternative mechanism suggests suppression of the hypothalamic-pituitary function. The dysfunction may be secondary to decreased clearance of estrogen, testosterone, prolactin, and other substances [119, 120].

Male patients with CLD may complain of loss of male pattern pubic hair, chest and axillary hair loss, and gynecomastia. This finding is thought to be related to an overall increase in estradiol: the adrenal glands produce and increase quantities of androstenedione that undergoes aromatization into estrone and eventually to estradiol [120].

Renal System

Similar to patients with ALF, patients with CLD can present with renal pathology. These may manifest as decreased urine output, arrhythmias, generalized body edema, and overall malaise. Most of the changes are associated with the underlying liver dysfunction.

In hospitalized patients with CLD, it is estimated that approximately 10 % of them will develop hepatorenal syndrome (HRS). The pathophysiology of HRS follows the development of PHT. As explained in Fig. 18.1, there is dilation of the splanchnic circulation, leading to a decrease in perfusion pressure. The response is cardiac compensation as well as activation of the renin-angiotensin-aldosterone system. There is also vasoconstriction mediated by the sympathetic nervous system. These changes ultimately lead to low renal perfusion and a significant decrease of the glomerular filtration rate [16].

Electrolyte abnormalities can accompany the changes that are seen on the renal system. Hyperkalemia, hyperphosphatemia, and hyponatremia can be detected in serum electrolytes. Symptoms may be variable and depend not only on severity of derangement but acuity. Dizziness, weakness, and palpitations may be reflections of these abnormalities.

Infectious Disease

CLD leads to acquired immune deficiency and makes these patients prone to developing infections. The mechanism by which the immune response is compromised includes the deficiency of serum complement [121] as well as the compromised activity and function of phagocytes such as macrophages, PMNs, and Kupffer cells [122, 123]. Certainly, the presence of fevers should make the intensivist suspicious for an infectious process and further investigation is warranted in order to determine additional symptoms that may guide further treatment. However, patients who present with decompensated liver failure may have an infection causing the decompensation. Thus, suspicion for the presence of infection should be high, and the threshold for obtaining cultures is low in any patient with liver failure who is acutely ill.

Abdominal pain that worsens and fevers should raise the suspicion for spontaneous bacterial peritonitis (SBP) in those patients with evidence of ascites. Up to 30 % of these patients may develop SBP [124]. Patients with cirrhosis have an increased intestinal permeability as well as altered intestinal motility. This may lead to the bacterial overgrowth and infection of ascites [125]. The most common organism seen is *Escherichia coli*; however, other organisms have also been described [126]. Typically SBP is monomicrobial and a polymicrobial infection should prompt consideration of a perforated viscous.

Other Systems

Similar to ALF, skin and urine color can change in patients with CLD. The increase in bilirubin secondary to compromised liver function leads to the accumulation in the skin leading to jaundice as well as dark appearance of urine. These changes are usually undetectable if the serum bilirubin is less than 2 mg/dL.

Another change that can be appreciated in the skin of patients with CLD includes palmar erythema. It is thought to be the consequence of altered sex hormone metabolism which may lead to capillary vasodilation [127].

Careful examination of the skin can also reveal vascular lesions characterized by the presence of a central arteriole with surrounding smaller vessels. These are called spider angiomata and their appearance is related to an increase in estradiol levels. The number as well as size of these lesions is related to the severity of liver disease although they are not specific for it [128].

As an additional route to decompress the portal vein during PHT, the umbilical vein may open leading to shunting into abdominal wall veins. These vessels engorge significantly making them very easy to identify during physical exam. This finding is known as caput medusa.

Workup and Initial Management

Initial workup and management of patients with CLD should begin with a thorough history. Onset of symptoms and identification of disease progression helps determine the pathophysiologic manifestations of the disease. Previous medical diagnosis including viral hepatitis should be assessed. A thorough review of all medications that the patient takes can help identify potential additional mechanisms of liver injury. Hospitalizations and transfusions should be reviewed.

Social history including exposure to high-risk behaviors such as intravenous drug use and alcohol abuse should be performed. Family history of liver disease and personal

history of malignancy (including oncologic treatment and surveillance studies) also play a key role in the development of disease and should be explored.

A complete physical exam should be performed and an attempt to determine if any of the clinical manifestation discussed previously are present. The exam should include neurologic, rectal, and skin exam. Assessment of vital signs in order to identify possible hypotension, hypoxemia, as well as end-organ perfusion should be performed.

There is no serologic test that can diagnose CLD accurately. Laboratory abnormalities that are identified could be related to ALF or another etiology with some degree of liver dysfunction. Besides serologic tests, evaluation of the degree of liver fibrosis and additional characteristics of CLD can be investigated with radiologic studies.

The initial serologic studies that are performed as well as initial management are similar to those described in Table 18.4 in the ALF section. In addition, studies from ascitic fluid should also be performed when it is desired to identify etiology of fluid and possibility of infection. After paracentesis with removal of 50 mL of ascites in a sterile fashion, the intensivist should send the fluid for cell count, cytology, albumin, total protein, triglycerides, amylase, adenosine deaminase, as well as culture [129]. This should be accompanied by a serum albumin in order to calculate the serum-ascites albumin gradient (SAAG). This is done by subtracting the albumin in the ascitic fluid from the serum value. Based on such studies, the etiology of ascites can be determined (Table 18.7).

Imaging studies that are routinely used include ultrasonography (US), CT scan, and magnetic resonance imaging (MRI). US can help identify morphologic changes such as nodularity. With Doppler US, patterns of flow as well as possible occlusions can be identified. CT and MRI are able to identify nodularity and changes in volume of liver mass (hypertrophy or atrophy) as well as assess the portal vasculature [130]. Evaluation of collateral circulation, varices, and tumors can also be performed. Since US does not use contrast, this can be very helpful in those patients with renal compromise [131, 132].

If after a thorough workup, the diagnosis of CLD cannot safely be established, liver biopsy should be considered. Identifying changes consistent with CLD may be very beneficial as it may prevent delays in therapy and potential worsening of the patient [133–135]. Surgery and interventional radiology teams should be involved in order to determine the safest and least invasive method that can render a diagnosis.

Table 18.7 Ascitic fluid studies and etiology of disease

Chylous ascites	Triglycerides
Peritoneal tuberculosis	Adenosine deaminase
Pancreatic ascites	Amylase and protein
Spontaneous bacterial peritonitis	Cell count
	Culture
Malignant ascites	Cytology
SAAG >1.1 g/dL	Portal hypertension
SAAG <1.1 g/dL	Nephrotic syndrome
	Tuberculosis
	Pancreatic ascites
	Malignancy

Suspicious findings for CLD should prompt consultation with hepatology/gastroenterology and transplant surgery in order to determine if the patient will benefit from additional therapies and workup including possible transplantation.

Evidence of encephalopathy, compromised ventilation, hypotension, hypoperfusion, active bleeding, sepsis, and SBP should prompt admission to the ICU. Consideration of additional hemodynamic monitors such as an arterial line and central access may be considered in every patient. A Foley catheter should be placed in all patients with hemodynamic instability or with poor renal function but avoided in those with anuria to prevent a urinary tract infection.

It is also helpful to classify the severity of liver disease. The Child-Turcotte Pugh (CTP) classification divides patients into three groups based on serum labs and clinical presentation. It can help in determining possible surgical treatments or additional therapies [136, 137]. This specific scoring system is presented in Table 18.8.

Another classification system that is used for the allocation of organs in the Unites States is the model for end-stage liver disease (MELD). It consists of a formula that will assign a score to a patient and that accurately predicts mortality within 3 months. The formula is based on three laboratory values (bilirubin, INR, and creatinine) and it is modified by etiology. The formula is shown below [138]:

$$\mathrm{MELD} = 3.78\times\ln\left(\text{serum bilirubin}\left(\frac{\text{mg}}{\text{dL}}\right)\right)+11.2\times\ln\left(\text{INR}\right)+9.57$$
$$\times\ln\left(\text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)\right)+6.43\times\text{etiology}$$

Table 18.8 Child-Turcotte-Pugh (CTP) classification

	Points		
Measurement	1	2	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	1–2	2–3	>3
Ascites	Absent	Slight	Moderate
Encephalopathy grade	None	1 and 2	3 and 4
PT	1–4	4–6	>6
or			
INR	<1.7	1.7–2.3	>2.3

If the disease process is alcohol, 1 is assigned to etiology. If the liver failure is secondary to a cholestatic process, 0 is assigned instead. Several factors can modify the calculated MELD score for allocation purposes, and these include dialysis and the presence of hepatocellular carcinoma.

The CTP and MELD system have been compared in several studies in order to determine which provides a better answer to prognosis for patients. Although some studies show superiorities of MELD, others show no difference and good predictions with both systems [139–142]. A systematic review, suggested that the MELD was better for predicting 3-month mortality but otherwise the systems were similar [143]. Because of its use with United Network for Organ Sharing (UNOS) lists for allocation of organs, MELD has become more popular.

Management

Encephalopathy

Hepatic encephalopathy (HE) is a diagnosis of exclusion, and therefore, an effort to identify other etiologies of altered mental status should be performed. It is also necessary to determine the precipitating event leading to the neurologic derangement which includes bleeding, renal failure, electrolyte abnormalities, changes in diet, and changes in medication [144].

Treatment principles are similar to those described in the ALF section. They should be based on supportive care, attempts to correct precipitating factors, minimizing GI nitrogen intake, and establishment of therapy.

Admission to an ICU is important as patients with HE need constant neurologic assessments for progression or resolution. For grade III and grade IV HE, establishment of definite airway should be the first step in management. Laboratory studies are key in order to identify possible precipitating events.

A decrease in nitrogen production as well as nitrogen delivery should be attempted with medication. The most common therapy used is lactulose, which reduces the absorption of ammonia. Twenty-five milliliter should be given twice a day and should be titrated to achieve two soft bowel movements [145].

Rifaximin has also been used as an add-on therapy to lactulose. It is an antibiotic with activity against Gram-positive and Gram-negative aerobes and anaerobes. The usual dose is 400 mg three times a day. Trials have shown benefit in the treatment of HE when rifaximin is used in addition to lactulose [146]. Another antibiotic that has been use is neomycin. This alternative treatment has been used for the treatment of overt hepatic encephalopathy [147]. However, because it has been associated with complications such as ototoxicity and nephrotoxicity, neomycin is used less commonly today [145].

An assessment of nitrogen intake by assessing a patient's diet is also very important. If a patient's HE is unresponsive to the therapies described above, oral branched-chain amino acids (BCAA) should be considered in an attempt to reduce the hepatically metabolized nitrogen load. A recent meta-analysis showed that BCAA-enriched formulations may be beneficial in some patients with HE and CLD [71]. The daily protein intake should be 1.2–1.5 g/kg/day as severe restriction may be detrimental in the catabolic state of CLD [145].

Ascites

The first step in management of a patient with CLD and ascites should be sodium restriction to no more than 2,000 mg per day [129]. This should also be accompanied by oral spironolactone and possibly furosemide in order to perform natriuresis while maintaining normokalemia. Spironolactone inhibits sodium reabsorption in the distal tubule and collecting ducts but it can lead to gynecomastia and hyperkalemia. Furosemide is a loop diuretic and inhibits the luminal Na-K-2Cl symporter causing natriuresis and also hypokalemia when used alone. Combination therapy has been used more effectively in achieving sustained results. If the serum sodium is less than 125 mmol/L, fluid restriction to no more than 1.2 L per day should also be done [148].

For those patients that are not responsive to diuretic therapy, serial paracenteses can be performed in order to relieve symptoms [149]. In carefully selected patients, transjugular intrahepatic portosystemic shunt (TIPS) should be considered. Trials have demonstrated that there is better control of ascites and overall survival with this procedure; however, there is worsening hepatic encephalopathy [150]. Referral to a transplant center should be done for patients with refractory ascites.

Tense ascites with respiratory compromise and abdominal discomfort can also be the initial presentation of patients

with CLD. Prior to sodium restriction, paracentesis should be performed. For large volume (>5 L) removal, albumin replacement should be done [151]. Replacement of 6–8 g of albumin per L of fluid removed has been shown to improve survival [129].

Replacement after paracentesis has remained a controversial topic. In one study performed by Gines et al., patients with tense ascites were randomized to receive albumin or no replacement. Those that did not receive albumin had more changes in serum electrolytes, plasma renin, and creatinine but had no survival advantage [152]. There has been no study up to date demonstrating decreased survival in patients without replacement when compared to albumin [153].

In a meta-analysis by Bernardi et al., 1,225 patients from 17 trials were analyzed. Albumin was shown to be superior to other plasma expanders, with an infusion between 5 and 10 g of albumin per liter removed [154].

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, and nonsteroidal anti-inflammatory agents should be avoided in patients with CLD and ascites: prostaglandin inhibition can severely affect renal hemodynamics as well as natriuresis.

It is important to evaluate patients with ascites for ventral and umbilical hernias. For those patients with ascites, hernia repair should only be attempted after medical treatment of ascites. For those with refractory ascites, repair should be deferred until after liver transplantation. If the patient has an incarcerated or strangulated hernia, emergency repair is warranted, but special attention to the ascites postoperatively must be made.

Spontaneous Bacterial Peritonitis

The diagnosis of spontaneous bacterial peritonitis (SBP) is established with studies sent from ascitic fluid revealing one of the following three findings:

1. Leukocyte count of more than 500 per mm^3
2. Polymorphonuclear count of more than 250 per mm^3
3. Positive bacterial culture

The causative organism is usually a Gram-negative enteric bacteria; if more than one organism is identified, secondary peritonitis should be considered. *Escherichia coli* and *Klebsiella* are responsible for more than 50 % of the cases [155]. Therapy is tailored based on the most likely causative agent.

If the patient has not been on empiric antibiotics prior to presentation, an intravenous third-generation cephalosporin should be started, preferably cefotaxime 2 g every 8 h. If the patient has been exposed prior to this medication, coverage should be based on hospital antibiogram [129]. Therapy should be started if there is a high suspicion for infection while cultures are pending.

The recurrence rate of SBP can be as high as 70 % and therefore prophylaxis is advocated. Long-term antibiotic therapy, norfloxacin 400 mg daily, is recommended [156]. Trimethoprim/sulfamethoxazole can be used as a second-line agent for those patients with sensitivities [129].

Variceal Hemorrhage

The presence of esophageal varices in patients with CLD warrants prophylactic therapy. The most effective medication has been propranolol that inhibits stimulation of the beta-2 venodilator receptors seen in varices. It should be started at low doses, 5 mg orally twice a day, and titrated to reduction of pulse rate by 25 %. If patients cannot take propranolol, isosorbide mononitrate can be used. If the patient is unable to tolerate medical therapy, esophagogastroduodenoscopy (EGD) and variceal banding should be performed [157].

Three principles govern the management of an acute variceal bleed: stabilization and resuscitation, identification and treatment of bleeding, and prevention of recurrence. If a patient presents with evidence of GI bleeding, immediate type and cross should be performed, and if needed, transfusion of untyped and uncrossed blood should begin. Waiting for laboratory values to show anemia may worsen the overall clinical condition of the patient.

Upper GI bleeding in a patient with presumed CLD prompts urgent endoscopy to identify possible bleeding esophageal or gastric varices. If during endoscopy, no varices are seen, repeat evaluation should be done in 3 years. If varices are identified but not bleeding, follow-up endoscopy should be done after 1 year. If active bleeding is encountered and it appears to involve esophageal varices, an attempt at controlling the bleeding varices should be done. Banding followed by sclerotherapy are the two most common methods of achieving control. If after appropriate attempts bleeding does not stop, a Sengstaken-Blakemore tube should be inserted. TIPS and surgical shunts should be considered if all previous methods fail. TIPS has shown improved outcomes [129]; however, it is associated with HE [157]. Surgical shunts carry a high morbidity and should be considered a last resort.

CLD patients with GI bleeding are at risk of developing bacterial infections. Some advocate the use of ceftriaxone for 7 days while patients are GI bleeding [158, 159]. If the patient stabilizes and tolerates oral intake, changing to norfloxacin is reasonable.

Hepatorenal Syndrome

The diagnostic criteria for hepatorenal syndrome (HRS) are shown in Table 18.9.

HRS is a diagnosis of exclusion and it is important to rule out other etiologies including prerenal azotemia, intrinsic renal disease, and post renal failure. In order to diagnose HRS, all major criteria in Table 18.9 must be met. Minor

criteria are not required; however, they provide supportive evidence that the pathophysiology is consistent with HRS. Identification of precipitating event is also instrumental in the management of HRS as additional therapy can be instituted.

When performing large volume (>5 L) paracentesis, it is recommended to replace volume with albumin (see ascites section above) as this procedure may lead to HRS. Evaluation for possible SBP as well as workup for GI bleeding should be considered as they are well-established risk factors for the development of this syndrome.

There are two manifestations of HRS: type I and type II. The former shows a rapid decline in renal function with either an initial creatinine of greater than 2.5 mg/dL or a 50 % reduction in the creatinine clearance. Type II usually leads to moderate renal failure that progresses slowly and is manifested as diuretic-resistant ascites [160].

Liver transplantation is the preferred treatment for patients with HRS. Any patient with evidence of this syndrome should be referred to a liver transplantation center in order to be listed for transplantation [161]. Bridging with pharmacotherapy is necessary in most patients as there is rapid decompensation, especially in those with type I HRS.

The basic principle behind the management of HRS is reversal of renal vasoconstriction and splanchnic vasodilation. Dopamine, fenoldopam, and prostaglandins have been used in an attempt to cause direct renal vasodilation [15]. Results of several trials have not favored any of these agents as none have improved outcome [160–162].

Splanchnic vasoconstriction, in an attempt to reduce portal blood flow and decrease pressure, has been attempted with vasopressin, ornipressin, terlipressin, norepinephrine, and midodrine [15]. Ornipressin, with some promising results, resulted in an increase rate of ischemic events [163]. Terlipressin in combination with albumin has shown the most promising results, with improvements in renal function although its use has not been approved in the United States [164]. Norepinephrine and vasopressin have been used with improvement of renal function and successful bridging to transplantation [60].

Hemodialysis may be required in the treatment of these patients, especially those with type 1 disease. Those patients that are hospitalized in an ICU should receive continuous dialysis rather than intermittent as it minimizes changes of abrupt hemodynamic changes and further compromise of these frail patients [73].

Table 18.9 Criteria for diagnosis of hepatorenal syndrome

Major criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension
Low glomerular filtration rate
Serum creatinine >1.5 mg/dL
or
24 h creatinine clearance <40 mL/min
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs
Absence of GI fluid losses
Absence of renal fluid losses in response to diuretic therapy
No sustained improvement in renal function after diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander
Proteinuria <500 mg/day
No obstructive uropathy, parenchymal renal disease, microhematuria
Minor criteria
Urine volume <500 mL/day
Urine sodium <10 mEq/L
Urine osmolality greater than plasma osmolality
Urine RBCs <50/high-power field
Serum sodium concentration <130 mEq/L

Liver Transplantation

Patients with ALF and CLD may benefit from liver transplantation. This therapeutic option should be considered when medical therapy has failed and when there is progression of disease. Referral to transplant center should occur once the patient has experienced ascites, variceal hemorrhage, HRS, and HE. Consultation with hepatology and transplant surgery teams ensures early consideration for transplantation. Table 18.10 presents poor prognostic factors from the King's College Criteria that may suggest that the need for transplantation is increased.

Prior to transplantation, a thorough evaluation is performed on patients regardless of etiology. This includes assessment of cardiac function, possible occult malignancy, identification of infection, contraindications to chronic steroid therapy, and appropriate social support.

The rapidly progressive nature of ALF designates that these patients are currently listed as Status 1 by the United Network for Organ Sharing (UNOS) [165]. Approximately

Table 18.10 King's College criteria that suggests poor prognosis

Non-acetaminophen
INR greater than 6.5 or
Three of the following five criteria:
Patient age of less than 11 or greater than 40
Serum bilirubin of greater than 300 μmol per liter
Time from onset of jaundice to the development of coma of greater than 7 days
INR greater than 3.5
Drug toxicity, regardless of etiology of ALF
Acetaminophen
Arterial pH <7.3
INR greater than 6.5
Creatinine greater than 300 μmol per liter
Encephalopathy (grade III or IV)

40 % of patients with ALF will undergo liver transplantation, 25 % of them will improve with supportive care, and 35 % will not survive their presentation; of those that have a liver transplant performed, the 3-year survival is approximately 75 % [165]. Patients with failure secondary to viral hepatitis usually have better outcomes than those with drug reactions or metabolic causes. Also, patients with ALF have worst outcomes when compared with patients with CLD.

The 1-year survival for patients with CLD that undergo liver transplantation is 90 % [166]. Timing is not standard and is usually dependent on severity of MELD. Living donors have been used secondary to decrease in organ availability and it has been successful. This therapy has not been studied in patients with ALF.

Other Therapies

Liver replacement therapies (LRT), also known as liver dialysis, have been studied and used as a bridging therapy to transplant [167–170]. Several methods have been developed and they can be grouped into artificial and bioartificial devices. Regardless of the mode of action, they attempt to clear toxins that are free and protein bound, as well as to regenerate or replace proteins that are affected by the liver failure process.

Among the artificial methods, the most studied is the molecular adsorbent recirculation system (MARS). It effectively clears several toxic compounds and causes a dramatic improvement in serum laboratories and in some symptoms such as pruritus [171]. Unfortunately, this has not translated into clinical benefits [172].

Biologic methods include devices with porcine hepatocytes and with human hepatoblastoma cells [167, 171–173]. Their theoretical advantage is the production of proteins and compounds produced by a normal liver as well as detoxification functions. As opposed to artificial systems, technology is not readily available. The results from different trials have been promising, showing improvement in survival to transplantation and normalization of serum laboratories [167].

An alternative to liver transplantation is hepatocyte transplantation. This consists of injecting human hepatocytes into the portal vein with an attempt to restore hepatic function [174]. It has been principally used to correct errors of metabolism, and trials have shown improvement in encephalopathy and ammonia and serum laboratories in patients with ALF that undergo this therapy [175]. More trials are needed in order to establish the role of this treatment option.

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Abdominal Compartment Hypertension and Abdominal Compartment Syndrome

19

Patrick Maluso and Babak Sarani

Introduction

Intra-abdominal hypertension (IAH) and its most severe manifestation, abdominal compartment syndrome (ACS), represent different endpoints on a spectrum of illness. At the most basic level, cellular dysfunction due to IAH and ACS results from the same underlying physiology as compartment syndromes in general, namely, derangement in perfusion arising from an increase in pressure within the fixed volume of an anatomic compartment. The abdomen and pelvis form one such compartment, bounded by the abdominal wall, the diaphragm, the back, and the peritoneal reflection at the bony pelvis. As with other forms of compartment syndrome, if the pressure within the fixed abdominal compartment is elevated, physiologic derangements will occur as a result of impaired capillary and venous blood flow. The resultant metabolic acidosis can be accentuated as a result of impaired respiratory function from upward pressure on the diaphragm preventing adequate expansion of the lungs and therefore ventilation. Common impairments seen in ACS include decreased venous outflow from the splanchnic circulation with resultant malperfusion of the intestines, decreased glomerular blood flow resulting in acute kidney injury, and decreased cardiac return as a result of compression of the inferior vena cava.

The exact incidence of ACS is poorly defined. Reports following major operation or severe injury range between 10 and 35 % [1–3]. The incidence of ACS in non-injured, critically ill patients is also poorly described, but the few reports that exist demonstrate the same incidence as trauma and surgical patients [3, 4]. As might be expected, the incidence of IAH is significantly higher and ranges between 30 and 70 % in either group. The presence of either IAH or ACS is associated with a significant increase in mortality in either group.

Definition and Causes of IAH/ACS

In 2013, the World Society of the Abdominal Compartment Syndrome (WSACS) published an updated consensus statement on IAH and ACS [5]. In this statement, they provide clinical definitions and pressure measurement guidelines to assist clinicians in the diagnosis and treatment of IAH/ACS. Intra-abdominal pressure (IAP) is defined as the abdominal pressure measured at end expiration in the supine position without contraction of the abdominal wall musculature. Measurement of the IAP allows for calculation of the abdominal perfusion pressure (APP), which is derived by subtracting IAP from the systemic mean arterial pressure (MAP). Whereas normal IAP ranges between 2 and 7 mmHg, the WSACS statement defines IAH as a sustained IAP greater than 12 mmHg. IAH is further subdivided into grades I–IV, as described in Table 19.1.

ACS is the primary pathological endpoint in IAH and is associated with end-organ dysfunction or failure in the setting of a sustained IAP >20 mmHg (IAH grades III and IV) with or without an APP <60 mmHg. It is important to note

Table 19.1 Grading and treatment of intra-abdominal hypertension

Grade	Intra-abdominal pressure	Treatment(s)
I	12–15 mmHg	Sedate patient, diurese, paracentesis, loosen abdominal closure device
II	16–20 mmHg	Sedate patient, diurese, paracentesis, loosen abdominal closure device
III	21–25 mmHg	Pharmacologically paralyzed patient, loosen abdominal closure device, decompressive laparotomy
IV	>25 mmHg	Decompressive laparotomy

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Table 19.2 Risk factors for intra-abdominal hypertension

Decreased abdominal wall compliance
Large torso burn
Large ventral hernia repair
Prone positioning
High-volume fluid resuscitation
Septic shock
Hemorrhagic shock, particularly when resuscitated using crystalloid solutions
Large surface area burn
Pancreatitis
Increase abdominal content
Tense ascites or hemoperitoneum
Large neoplasm
Severe ileus
Pancreatitis

that factors such as obesity can affect patients' baseline IAP; a 2001 prospective study of IAP in hospitalized patients found a strong correlation between increased IAP and increased BMI [6]. Wilson et al. similarly found that anesthetized bariatric surgical patient's baseline IAP increased by 0.14 mmHg per every unit of BMI but that none of the patient's baseline fell within the range of IAH. The average baseline IAP in the study was 9 ± 6 mmHg and the average BMI was 48 kg/m^2.

Although it is difficult to predict which patients will develop IAH, certain broad categories of illness and therapy put patients at higher risk. Clearly, conditions that decrease abdominal wall compliance such as burns, abdominal wall operations (especially ventral herniorrhaphy), and prone positioning can predispose patients to IAH [7, 8]. Conditions that require large-volume fluid resuscitation such as sepsis, burns, and trauma have also been implicated in IAH [1, 9, 10]. Finally, conditions in which intra-abdominal contents are increased such as tense ascites, large tumors, hemoperitoneum, severe ileus, and pancreatitis can also lead to IAH (Table 19.2) [5, 11, 12]. While this list is by no means comprehensive, it illustrates the broad categories of illness and treatment that may predispose patients to IAH or ACS. Moreover, an understanding of the pathophysiology that can predispose to IAH is important in recognizing at-risk patients, especially since it can affect patients without primarily abdominal pathologies.

Aggressive, crystalloid-based resuscitation is highly associated with development of both IAH and ACS and subsequent mortality [13]. In hemorrhaging patients, the incidence of ACS and mortality decreases as the volume of biologically active colloid, including red blood cell and plasma transfusion, increases and the volume of crystalloid fluid decreases [14]. Similarly, in non-injured, critically ill patients, although mortality is not changed, resuscitation with crystalloid is associated with a greater risk of developing IAH and ACS than resuscitation with colloid [15].

Diagnosis: Physiologic Markers of ACS

Regardless of the method used for measurement of IAH or ACS, a protocol for initiation of IAP measurements or appropriate clinical suspicion is a key first step. An understanding of the physiologic derangements resultant from IAH and their subsequent clinical effects is critical in the early recognition of the organ system dysfunction that heralds IAH and impending ACS. This understanding should necessarily inform decisions to measure IAP and ultimately to treat ACS before more permanent damage or death has occurred. At the least, intra-abdominal pressure should be measured in patients with two or more of the risk factors noted in Table 19.2 [16].

Cephalad pressure on the diaphragm due to IAH has a direct effect on pulmonary compliance [17]. This decreased compliance affects pulmonary function by a progressive decrease in tidal volume, residual volume, and functional residual capacity. These effects are accentuated with increasing IAP [18]. Patients with ACS will not be able to breathe spontaneously and will require mechanical ventilation. In mechanically ventilated patients, the effects of IAH can be recognized by the resultant increase in peak inspiratory and mean airway pressures [19]. The changes in compliance and subsequent hypoventilation manifest initially as hypercapnic respiratory failure but can progress to hypoxemia as well. The blood gas derangements usually correct promptly with treatment (namely, abdominal decompression) [20, 21].

The hemodynamic effects of IAH/ACS center on decreased venous return to the heart due to compression of the inferior vena cava from the IAH itself as well as transmitted intrathoracic pressures (ITP). Increasing IAP has the additional effect of increasing systemic vascular resistance by compression of the aorta and splanchnic circulation, thereby increasing afterload and decreasing stroke volume. Moreover, transmitted increases in IAP increase end-diastolic pressures, thereby decreasing cardiac filling, an effect that is exacerbated by hypovolemia [20, 21]. Taken together, these hemodynamic derangements cause a net decrease in cardiac output with resultant hypotension [22].

Renal function is also commonly adversely affected in ACS and is manifest by oliguria with IAP above 15 mmHg and anuria with IAP above 30 mmHg. The mechanism of acute kidney injury is multifactorial, resulting both from prerenal and intrarenal processes. IAP of 20 mmHg or more has been shown to increase renal vascular resistance by 555 % in a canine model [23]. The decreased cardiac output described above certainly has effects on renal blood flow, contributing to prerenal failure; however, IAH has also been shown to be an independent cause of renal impairment [24]. IAH is associated with a decrease in renal plasma flow and glomerular filtration rate, attributable to renal arterial, venous, and parenchymal compression [25]. These derangements lead to

increased activation of the renin-angiotensin-aldosterone hormone signaling cascade with resultant increase in systemic vascular resistance which, in turn, feedbacks into the already-described imbalance in cardiac output [26].

The hepatobiliary system is especially sensitive to increased IAP, even after controlling for cardiac output. An increase of only 10 mmHg in abdominal pressure can cause a significant decrease in hepatic venous, arterial, and microcirculatory blood flow [27]. Impaired hepatic function manifests as an increased plasma lactate level which is not attributable solely to cardiac output derangements, suggesting reduced hepatic clearance [28]. This functional decrease in serum lactate clearance confounds the use of lactate levels as a resuscitative endpoint in patients with IAH. In addition, the rising lactate levels lower the serum pH, which can result in further myocardial depression as well as arteriole dilation thereby leading to additional lowering of the systemic blood pressure and worsening cellular respiration.

As discussed above, serum lactate elevations in IAH are multifactorial and are also partly attributable to the effects of increased IAP on bowel perfusion. In a porcine model, IAP of 20 mmHg caused significant impairment of mesenteric blood flow with a concomitant decrease in mucosal blood flow and drop in mucosal pH, indicating significant bowel ischemia [29]. Other studies have also shown decrease in bowel mucosal oxygen levels in the setting of IAH [30]. The bowel ischemia seen in IAH not only results in interstitial edema thereby contributing to development of ACS but is also a key pathologic feature that leads to further physiologic decompensation. By impairing mucosal blood flow even in the setting of normal mean arterial pressures, IAH has been shown to cause translocation of intraluminal bacteria after as little as 60 min of IAP over 25 mmHg [31]. This bacterial translocation may contribute to septic shock if ACS is not treated quickly.

Diagnosis: Measurement of Abdominal Pressure

In a series of 110 consecutive ICU patients who had undergone abdominal surgery, clinical estimation of IAP by an intensivist was compared with direct measurement of IAP and was found to have only 60.9 % sensitivity for detecting IAP >18 mmHg [3, 32]. Because of the unreliability of clinical examination alone in diagnosing IAH, objective measurement of IAP is key in the management of critically ill patients in whom IAH or ACS are suspected. Multiple methods of measurement of IAP, both direct and indirect, have been described.

Direct measurement of IAP, while theoretically most accurate, is necessarily invasive and therefore not broadly useful as a screening apparatus for identifying patients with IAH. Means of direct measurement include the use of intraperitoneal pressure transducers and measurement of pressures through peritoneal dialysis catheters or ascites drainage catheters.

Indirect measurement techniques include measurement of peak ventilator pressures (although this is complicated by concerns of lung and chest wall compliance), central venous, intravesical, rectal, and intrauterine pressures. Among indirect measurement techniques, measurement of bladder pressures is generally considered the gold standard for diagnosis of IAH due to its ease and minimally invasive nature [5, 16]. This technique should be performed while patients are fully supine, as patient position can affect pressure readings. IAP should be measured at end expiration with the abdominal wall musculature fully relaxed, conditions which are hard to replicate consistently without the use of chemical sedation and mechanical ventilation. In order to measure intravesical pressures, 20 ml of sterile water or saline is instilled into the bladder, and a manometer zeroed at the level of the midaxillary line is used to record the pressure transmitted from the abdomen, through the bladder wall, and into the column of fluid. The procedure must be done under sterile conditions and with sterile fluids in order to prevent contamination of the catheter system and therefore iatrogenic urinary tract infections. In one prospective trial of serial IAP measurements via intravesical pressures, instillation of volumes greater than 50 cc was shown to artificially increase the measured IAP [33]. There is a commercially available product which connects to the urinary catheter and may decrease the probability of technical error in measuring abdominal pressure, but the procedure can also be carried out by inserting a needle connected to a pressure transducer into the sampling port of a urinary catheter.

While measurement of intravesical pressures remains the gold standard for objective measurement of IAP, this technique may not be feasible in a certain subset of patients, such as those with a history of cystectomy and those with traumatic bladder injury or pelvic hematoma/intra-abdominal packing that would make measurement either unreliable or contraindicated. For situations such as these, a variety of other measurement strategies have been described. Several authors have suggested the use of inferior vena cava pressure monitoring via a standard central venous catheter. Studies evaluating this technique have demonstrated good correlation between IVC pressures and other validated methods [34]. Another method involves measurement of gastric pressures via a naso- or orogastric tube but is complicated by contractions of the migrating motor complex, which may confound results of intermittent readings. A related technique involving the use of a continuously monitored gastric manometry balloon has been validated in vivo by comparison with insufflation pressures during laparoscopic cholecystectomy [35]. The continuous method of measurement

negates the confounding effects of the migrating motor complex contractions; however, it is unclear whether enteral feeding may confound the measurements. Other novel techniques involving the use of specialized catheters (for intravesical, rectal, intrauterine use) with embedded microchips have been described but are less cost-effective than the simpler techniques described above [36].

Whereas the majority of studies on the topic use absolute IAP as an endpoint for analysis, some retrospective studies have found that APP may be a more clinically useful endpoint in the diagnosis and treatment of IAH. In their review of 144 patients treated for IAH, Cheatham et al. found that APP was superior to other commonly used endpoints such as serum lactate or urine output in predicting patient survival [37]. According to their data, an APP of less than 60 mmHg is predictive of the need for urgent intervention and is useful as both a resuscitative endpoint and a predictor of need for surgical decompression. Another study of cirrhotic patients with septic shock found that APP less than 55 was associated with mortality and also found that this value was more predictive of survival than other traditional measures of end-organ perfusion, such as central venous oxygen saturation, serum lactate level, and MAP [38].

Treatment

Once the diagnosis of ACS has been made, appropriate treatment strategies are based on rapid relief of the intra-abdominal pressure in order to restore perfusion to the abdominal viscera and resolve the derangements in cardiopulmonary function. Although the definitive management of ACS is surgical decompression of the abdomen, lower-grade IAH may be amenable to nonsurgical measures (Table 19.1). Lower-grade IAH that is exacerbated by abdominal wall tension (e.g., third-spacing of fluids or a tight abdominal wall repair following ventral herniorrhaphy) may be improved by neuromuscular blockade (NMB). In one prospective study, patients with IAH were given a short trial of NMB using cisatracurium and experienced an average 4 mmHg decrease in IAP; however, the response was short-lived and showed no effect on the patients' urinary output. Similarly, the patient's APP did not increase, suggesting the limited clinical utility of NMB for IAH and further suggesting that it is ineffective for true ACS [39].

For selected patients in whom IAH is due to acutely increased intraperitoneal fluid volumes, such as patients with tense ascites, paracentesis has been shown to be effective in avoiding decompressive laparotomy. In a case series of burn patients, paracentesis using a peritoneal dialysis catheter avoided laparotomy and effectively relieved IAH [40]. Other studies have shown the efficacy of paracentesis for relief of IAH due to massive ascites in cirrhotic patients. With drainage of ascites, Savino et al. showed a decrease of 10 mmHg IAP with concomitant improvement in cardiac index, urinary output, and creatinine clearance [41]. In patients for whom IAH is largely due to free fluid within the peritoneal cavity, percutaneous drainage may have at least a temporizing role, if not a definitive one, in the management of IAH.

While other therapies discussed have limited roles in the temporization and management of IAH and should be attempted where appropriate, ACS with its inherent organ system dysfunction merits urgent definitive management with decompressive laparotomy in most cases [16, 42]. However, laparotomy carries many risks which should be carefully weighed against the patient's clinical situation before the decision is made to proceed. Consideration of patients' fitness for travel to an operating room, especially with regard to their need for high-level positive-pressure ventilation not amenable to transport without a ventilator, should inform decisions as to the setting for operation. While the intensive care unit is capable of managing pulmonary and physiologic changes after decompression, it is often difficult to control surgical bleeding, and maintenance of a sterile environment is more difficult. Post-decompression physiological changes must also be anticipated when attempting laparotomy. A sudden rapid increase in pulmonary compliance can lead to respiratory alkalosis if ventilator settings are not adjusted post-decompression. Ideally, vasopressor doses can be rapidly titrated down following decompression, because venous return to the heart and cardiac output should improve almost instantly.

Management of the Open Abdomen

After decompressive laparotomy, there are numerous strategies for management of the subsequent open abdomen. Leaving the abdomen open, while critical to management of ACS, exposes patients to new risks. The risk of complications resulting from the open abdomen rises with duration of therapy, with a significant increase in patients left open for more than 8 days [43]. Exposure of the abdominal viscera to the environment may lead to formation of entero-atmospheric fistulae and also leads to significant fluid and heat losses. Frequent manipulation of the bowel also exposes patients to an up to 20% risk of entero-atmospheric fistula formation. Additionally, an open abdomen poses a significant nutritive risk to already-catabolic patients: roughly 2 g of protein are lost for every liter of fluid removed from the peritoneal cavity [44]. For these reasons, multiple methods for temporary abdominal closure or coverage of the viscera have been described. With temporary coverage, fluid and protein losses are decreased and more easily quantified, and septic complications are reduced [45, 46].

Even with temporary closure, patients with an open abdomen are at significant risk for loss of abdominal domain, wherein the abdominal musculature retracts the fascia laterally. With loss of domain, attempts at primary closure of the fascia or skin when ACS has resolved may fail, resulting in large ventral hernia defects in up to a third of patients. Finally, even though temporary closure can decrease risks associated with an open abdomen, it can nevertheless leave patients susceptible to increases in IAP and recurrence of ACS [47]. In these instances, the temporary closure device needs to be upsized to allow for further expansion of abdominal domain.

Numerous techniques exist for temporary closure of the open abdomen and will be discussed subsequently. These techniques can be broadly classified based on their use of a "silo," negative pressure device, or a patch closure, and some may be used in conjunction with others. Each technique carries unique drawbacks and benefits with regard to their cost and to their ability to manage and quantify fluid losses, minimize dressing changes, and minimize loss of domain.

The simplest temporary closure method is the silo, in which a sterile translucent plastic sheet or bag is sutured to the skin at the margins of the laparotomy. Commercial solutions, such as the Bogota Bag™, may be used, or, alternatively, bags for intravenous fluids or dialysate may be substituted as a cost-saving measure [48]. This method of closure is inexpensive, relatively simple, and allows for visual inspection of the viscera, but it hinders removal of fluid from the peritoneal cavity. Fluid buildup can lead to recurrent ACS or may result in deposition of fibrinous debris on the intestines, although the clinical ramifications of the latter are uncertain. Furthermore, these devices have to be sutured in place, thereby making their placement both time and labor intensive. Of the techniques described, the use of a silo is associated with the highest rate of failure for attempted primary fascial closure, with up to 70 % of attempts failing in one meta-analysis [49].

Patch-based techniques of closure are similar to silos, but involve suturing a synthetic material as an interposition between the fascial edges rather than the skin edges. While these techniques do decrease the lateral retraction of the fascia and minimize loss of abdominal domain, they are suboptimal for control of fluid losses. Two main, commercially available techniques exist for patch closure: the Wittmann Patch and the polytetrafluoroethylene (PTFE, Gore-Tex™) patch. In the Wittmann Patch, two sheets are sewn to the lateral edges of the fascial defect and connected at the midline with the use of a Velcro-like closure. This technique allows for expansion or contraction of the abdominal wall defect in response to changes in IAP. Furthermore, significantly higher rates of fascial closure are possible due to decreased fascial retraction supplemented by staged approximation of the abdominal wall [50]. Meta-analysis has shown the Wittmann Patch to be superior to all other methods of temporary closure in terms of rate of primary fascial closure with up to 90 % of patients successfully closed [49]. Similar to the Wittmann Patch, PTFE patches also allow for dynamic closure of the abdominal wall by serial plication of the midline of the patch to increase tension on the fascia. In one series, this technique allowed for similar primary closure rates to the Wittmann Patch, with 89 % of patients successfully closed [51]. Aside from their difficulty in management of fluid losses, both patch techniques share a common major drawback in their effects on the health of the fascial edges. Repeated fascial suturing from changing patches and the increased traction on the fascia can lead to necrosis of the edges of the fascia, which often necessitates debridement prior to final closure. This may make final fascial apposition challenging.

Negative pressure wound therapy (NPWT) systems, also known as vacuum-assisted closure (VAC) devices, are the most commonly used form of temporary closure device. Both commercially available sponge-based varieties (AbThera VAC therapy) and improvised towel-based lower-cost alternatives (Barker's VAC) have been described. In each system, an inert layer is inserted into the abdomen to protect the viscera and is then covered with a self-adhesive plastic sheet to which suction is applied. NWPT systems are superior in their ability to manage and quantify fluid/protein losses and may be used in conjunction with patch techniques. Additionally, the application of negative pressure to the wound opposes the lateral forces on the fascia without directly manipulating it, thereby improving primary closure rates without compromising the edges of the fascia.

Towel-based systems (Barker's VAC) are easy to apply and are lower cost than their commercially available alternatives. In these, a surgical towel is adhered to an inert polyethylene sheet, such as Ioban™, and is inserted between the viscera and the underside of the abdominal wall. Small slits are cut in the polyethylene sheet to allow drainage of fluids, and drain tubing is placed over the towel before placement of a self-adhesive elastic sheet over the abdominal wall defect. The drain tubing is then attached to a closed-suction system to provide negative pressure and drainage of excess fluid [52, 53]. Although this technique is simple, low cost, and allows for expansion of the abdominal wall under increased pressure, it does not provide effective suction to all portions of the abdominal cavity, allowing fluid to accumulate in the pelvis and paracolic gutters. Placement of additional drain tubing in dependent portions of the abdomen may mitigate these effects but increases the complexity of the system and has not been studied.

Commercial systems work by a similar mechanism to towel-based systems but use a perforated Silastic sheet inserted into the abdomen between the viscera and abdominal wall and are covered with a sterile sponge cut to fill the abdominal wall defect. The wound is then covered with a

self-adherent elastic sheet, and a proprietary closed-suction system is applied [54]. Because the perforated Silastic sheet can be inserted into dependent portions of the abdomen, this closure technique allows for application of more uniform suction to all parts of the abdomen, offering improved fluid management.

Meta-analysis has shown NWPT to be intermediate between patch- and silo-based systems in its ability to achieve primary fascial closure, with rates of 52 % for improvised towel-based systems and 60 % for sponge-based commercial systems [49]. A prospective, multicenter study of towel-based and sponge-based systems found similar rates of primary abdominal closure in patients requiring an open abdomen for more than 48 h, with a 51 % closure rate in towel-based and a 69 % closure rate in sponge-based systems. More importantly, the study was the first to show a difference in other outcomes between systems. All-cause 30-day mortality was significantly higher in the towel-based cohort than in the sponge-based cohort (30 versus 14 %, $p < 0.05$) despite their similar disease severity [55]. The authors speculate that this difference may be attributable to the systems' relative effectiveness in removing fluid rich in inflammatory cytokines from the abdomen. The use of additional dependent drains in towel-based systems, as described above, may mitigate some of this survival benefit, but further study is required.

Closure of the Open Abdomen

Regardless of the method chosen for management of the open abdomen, once therapeutic objectives have been achieved and an open abdomen is no longer necessary, definitive abdominal closure should be attempted as quickly as possible to minimize the deleterious effects of an open abdomen described above. Generally speaking, the length of time the abdomen is left open correlates with the incidence of complications, and a longer duration of open abdomen correlates with decreased rates of closure [43]. With every return to the operating room for washout or inspection of the abdomen, the patient should be assessed for potential closure. If repeated attempts at fascial closure are unsuccessful, functional closure using an inlay mesh or intentional creation of a ventral hernia with skin-only closure and planned future ventral herniorrhaphy may be attempted.

Primary fascial closure refers to the direct approximation of the fascial edges and is the ideal method for closing the abdomen given that it has the lowest incidence of complications following an open abdomen. Care must be taken when attempting primary fascial closure as it may precipitate return of abdominal compartment syndrome if the patient still requires large-volume fluid resuscitation or there is excessive tension on the abdominal wall [56]. Despite its superiority in properly selected patients, primary closure nevertheless has a high incidence of hernia formation, with up to 30 % of open abdomen patients developing a ventral hernia at some point after closure [57]. Because of this high incidence of hernia formation, primary fascial closure can be augmented with mesh reinforcement. Permanent, synthetic meshes are relatively contraindicated in patients with risk factors for mesh infection such as wound soilage, and many authors recommend the use of biologic mesh in these instances. More advanced techniques of fascial closure such as a separation of abdominal wall components laterally to allow for direct apposition of the fascia at the midline may be used, but a detailed discussion of these methods is beyond the scope of this chapter [58].

If primary fascial closure is not possible, an alternative is functional closure by approximating the superior and inferior aspects of the fascial defect as much as possible then placing a mesh inlay as a bridge between the edges of the remainder of the fascial defect. The biologic mesh inlay acts as scaffolding for ingrowth of native fascial tissue [59]. Once the mesh is placed, the skin is closed over the repair, and drains can be placed over the mesh to close the space and prevent seroma accumulation as needed. However, most studies find that the mesh will stretch over time resulting in a bulge and "neo-hernia" due to excessive abdominal wall laxity. If skin closure is not possible, functional closure should be avoided as exposed mesh will undergo accelerated degradation until a granulation tissue bed forms over the viscera. This process usually occurs over several weeks. The resultant granulation tissue will require skin grafting and will ultimately lead to a ventral hernia. While the late incidence of ventral hernia formation after functional closure is not well established, one study using acellular dermal matrix for repair of ventral hernias has shown an 80 % incidence of hernia formation over a mean follow-up of 21.4 months despite skin closure over the mesh [60].

Because of the dismal outcomes associated with functional closure of the abdominal wall, many surgeons prefer to create a ventral hernia with plans for subsequent definitive ventral herniorrhaphy (and possible component separation) once the patient has fully recovered and the volume of the abdominal contents has returned to normal. Skin-only closure is one option for tissue coverage of the abdominal viscera based on this strategy.

If the skin edges are similarly too retracted to allow for closure without undue tension or increased abdominal pressure, the abdomen can be left open until the viscera have become self-adherent and adherent to the abdominal wall, creating a "block" of tissue within the abdominal wall defect. This process is allowed to continue until a granulation tissue bed has grown over the viscera. An absorbable mesh (e.g., Vicryl™) can be sutured to the skin edges to cover the viscera and prevent evisceration until a granulation bed has

formed. After the defect is adequately covered with a granulation tissue bed, a split-thickness skin graft can be placed. Finally, these patients can return for elective ventral hernia repair after a 6–12-month interval. This interval allows maturation and ultimately dissolution of intra-abdominal adhesions and yields a lower incidence of enterotomy at the time of definitive hernia repair [61]. However, the granulation phase, prior to skin grafting, is associated with up to 20 % risk of developing an entero-atmospheric fistula formation. This risk is highest in patients with an exposed anastomosis [62].

Conclusion

Intra-abdominal hypertension and abdominal compartment syndrome are common following resuscitation in critically ill or injured patients. Failure to recognize the disorders in a timely fashion is associated with significant morbidity as well as mortality. Because physical exam does not offer a sensitive means to diagnose either disorder, patients at risk for IAH or ACS should routinely have their intra-abdominal pressure measured and undergo interventions to lower the IAP when significantly elevated pressures are noted.

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Nutrition in the Surgical ICU Patient

20

Beth E. Taylor and Craig M. Coopersmith

Introduction

Nutrition holds a pivotal role in the care of surgical and trauma patients admitted to the surgical intensive care unit (ICU). Critically ill surgical ICU patients are in a catabolic state driven by a systemic inflammatory response to insult or injury coupled with complications from infections, multiple organ dysfunction syndrome (MODS), and prolonged hospitalization [1–4]. Superimposed upon the host response to critical illness, the metabolic response to surgery or trauma also leads to an altered hormonal milieu that shifts from sparing of lean body mass to increased utilization as a gluconeogenic substrate and support of immune function and repair of tissue [5]. This use of lean body mass for energy combined with the physical unloading of muscle with bedrest, inactivity, and immobility leads to a progressive loss of skeletal mass [6]. A major goal of nutrition therapy is to help attenuate the metabolic response to stress, prevent oxidative cellular injury, favorably modulate immune responses, and slow the loss of lean body mass. Improvement in the clinical course of the surgical ICU patient may be achieved by early and adequate nutrition therapy (primarily by the enteral route), appropriate macro- and micronutrient delivery, and meticulous glycemic control. Unfortunately, early and consistent delivery of enteral nutrition (EN) is often challenging in this patient population.

Nutrition Assessment

Determination of which critically ill patients will benefit the most from nutritional intervention has been difficult to define. Recently, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics (Academy) have published definitions that take into account the deleterious impact of inflammation on nutritional status and distinguish between acute and chronic malnutrition (Table 20.1) [7, 8]. ASPEN and the Academy suggest those patients defined as "severely malnourished" will obtain the greatest benefit from early nutrition intervention. The key components of the current ASPEN/Academy definition of "severe malnutrition" include energy intake, degree of recent weight loss or gain, body fat, muscle mass, presence or absence of fluid accumulation, and grip strength [7, 8].

Nutritional risk is a combination of nutritional status and assessment of disease severity. The NRS 2002 and NUTRIC score have been used to define nutritional risk in randomized control trials (RCTs) in critically ill patients (Table 20.1) [9, 10]. The NUTRIC score has been validated with and without the use of interleukin-6 [10, 11]. Two RCTs in ICU patients show those at high nutritional risk are more likely to benefit from early EN (less infectious complications and mortality) than their low nutrition risk counterparts [10, 12]. For the surgical patient, current nutritional status, type of surgery, and potential anatomic alterations should all be considered when determining potential benefit from nutrition therapy.

In the ICU setting, traditional protein markers such as albumin, prealbumin, transferrin, and retinal-binding protein reflect the acute-phase response (increase in vascular permeability and decrease in hepatic synthesis) and do not represent nutrition status [13]. Neither should anthropometrics be used to determine the adequacy of nutrition therapy given fluctuations in fluid status and sequestration of fluid into extracellular spaces. Ultrasound (US), given its ease of use and availability, is emerging as a bedside tool to measure muscle mass and determine changes in muscle tissue over time [14, 15]. Computed tomography (CT) scans ordered for other reasons may also provide a quantification of skeletal muscle and adipose tissue depots if the lumbar region is available [5, 6]. However, validation and reliability studies regarding the use of US and CT in the surgical ICU are still pending.

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Table 20.1 Scoring systems to determine degree of malnutrition or nutrition risk

ASPEN severe malnutrition	NRS 2002 high nutrition risk	NUTRIC score high nutrition risk
Meet at least two of the following: Energy intake: ≤50 % of need for 5 days or more Weight loss: >2 % in 1 week, >5 % in 1 month, >7.5 % in 3 months Moderate fat loss, muscle wasting, and/or peripheral edema	*Total score* ≥5 = *high risk* Energy intake for 7 days 1 point: <50–75 % 2 points: <25–50 % 3 points: 0–25 % Weight loss 1 point: >5 % in 3 months 2 points: >5 % in 2 months BMI 18.5–20.5 3 points: >5 % in 1 month BMI <18.5 Diagnosis 1 point: chronic condition (e.g. COPD, CHF, CKD, DM) 2 points: severe PNA, major Abdominal surgery, CVA Malignant hematology 3 points: head injury, BMT, ICU pt (APACHE II >10)	*Total score* 5–9 = *high risk* Age (years) 0 point: <50 1 point: 50–74 2 points: ≥75 years APACHE II 0 point: <15 1 point: 15–19 2 points: 20–27 3 points: ≥28 SOFA 0 point: <6 1 point: 6–9 2 points: ≥10 # of comorbidities 0 point: 0–1 1 point: ≥2 Days from Hosp to ICU admit 0 point: 0–1 1 point: ≥1

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *CHF* congestive heart failure, *CKD* chronic kidney disease, *DM* diabetes mellitus, *PNA* pneumonia, *CVA* cerebral vascular accident, *BMT* bone marrow transplant, *ICU* intensive care unit, *APACHE* acute physiologic and chronic health evaluation, *SOFA* simplified organ failure assessment, *Hosp* hospital

Table 20.2 Calculation of nutrition requirements

Energy requirements		Protein requirements	
BMI	Energy (Kcal/kg/day)	Clinical condition	Protein needs[b] (grams/kg IBW/day)
<15	35–40	Normal (nonstressed)	0.75
15–19	30–35	Critical illness/injury	1.0–1.5
20–25	20–25	ARF (undialyzed)	0.8–1.0
26–29	15–17	ARF (dialyzed)	1.2–1.4
>29	15[a]	Peritoneal dialysis	1.3–1.5
		Burns/sepsis	1.5–2.0
		CVVHD	1.7–2.5

Adapted from [89], Chap. 5, Tables 5.5 and 5.15

BMI body mass index, *Kcal* kilocalories, *kg* kilograms, *IBW* ideal body weight, *ARF* acute renal failure, *CVVHD* continuous venovenous hemodialysis

[a]Do not exceed 2,000 kcal/day for obese patients – allowing for hypocaloric feeding

[b]Clinical conditions are not additive: to calculate needs, use highest value

Energy and Protein Requirements

Energy requirements may be determined using simplistic weight-based formulas (e.g., 25–30 kcal/kg/day), published predictive equations (e.g., Penn State, Mifflin St. Jeor) [16, 17], or use of indirect calorimetry (IC), which is considered the gold standard technique to assess energy requirements [18]. Unfortunately, IC may not be available, and, in addition, many variables in the ICU affect the timing and accuracy of IC measurements including presence of chest tubes, supplemental oxygen, continuous renal replacement therapy, anesthesia, and excessive movement. Over 200 predictive equations exist; however, none has more than approximately 70 % accuracy in ICU patients [19, 20]. Example recommendations using a simplistic weight-based approach are displayed in Table 20.2.

Lean body mass utilization for healing of wounds and supporting immune function is increased in the surgical ICU patient, thus making protein the most important macronutrient for this patient population. Often protein needs cannot be met with the use of an enteral formulation alone, and protein modulars are needed. A weight-based protein requirement example is presented in Table 20.2.

Preoperative Period

Patients anticipating major surgery generally undergo procedural planning and stratification of cardiopulmonary risk, but rarely is the optimization of nutrition management through the perioperative period addressed. Consideration for delay of surgery allowing for preop nutrition therapy would be beneficial in patients identified as severely malnourished or at high nutrition risk having elective procedures with no time constraints. Unfortunately, the appropriate duration and measures to determine sufficient nutrition therapy remain difficult to identify. Current expert opinion recommends 10–14 days of preoperative nutrition therapy [12, 24, 25].

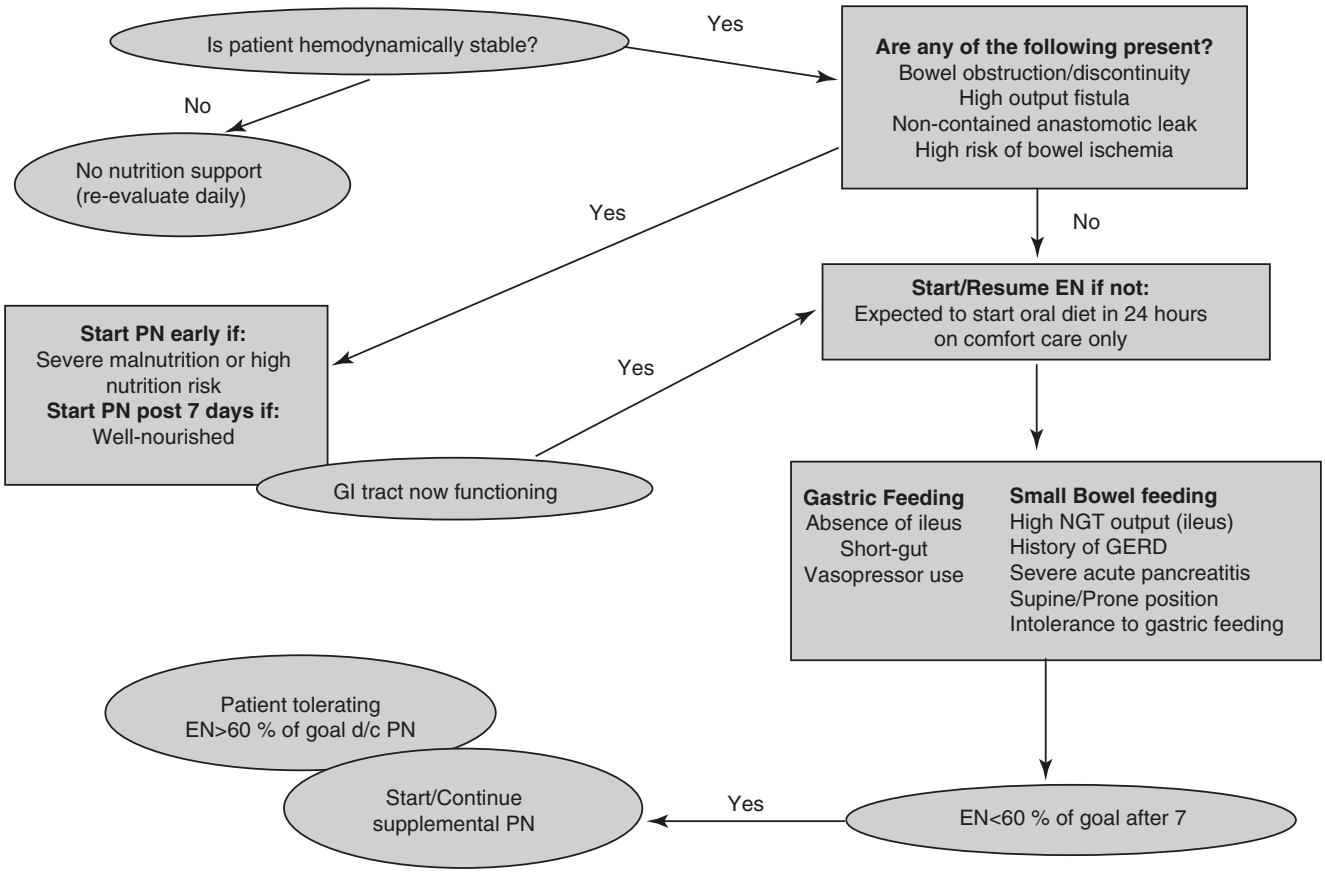

Fig. 20.1 Determining the route of nutrition support

Route of Nutrition

The benefit of EN in the ICU patient goes beyond the provision of macro- and micronutrients. Early EN (within 24–48 h of surgical ICU admission) supports both the functional and structural integrity of the gut. The use of EN decreases the risk of infection and late multi-organ failure by supporting the gut-associated lymphoid tissue and subsequently the mucosal-associated lymphoid tissue [26, 27]. Those patients at highest nutrition risk have increased gut permeability, and thus, EN is more likely to have a positive impact on infection, organ failure, and length of stay [28, 29].

In the past, there has been concern that the use of PN would further increase the risk of infection in those patients with a nonfunctioning GI tract. However, in the age of glycemic control and standard protocol medical management, the differences in infectious complications between the use of early EN or early PN are becoming narrower [30–32]. In a meta-analysis of ICU patients that included >60 % of surgical patients, early (with 48 h of admission) PN versus no nutrition or early EN showed no difference in infectious complications or 60-day mortality, suggesting safe provision of PN [32]. However, the long-term effect of early PN in postoperative patients has yet to be studied on a large scale. An algorithm outlining the decision process in determining the preferred route in surgical ICU patients is presented in Fig. 20.1.

Enteral Nutrition

In the surgical ICU population when feasible, early (24–48 h post admission to the surgical ICU) EN remains the first choice over parenteral nutrition (PN) and delayed feeding. In 2009, Lewis et al. performed a meta-analysis of early aggressive use of EN involving 13 trials and 1,173 patients that showed mortality was reduced from 6.8 % to 2.4 %, with use of early EN postoperatively versus STD (RR = 0.42, 95 % CI 0.18–0.96, $p = 0.030$) [29]. A subsequent meta-analysis by Osland included 15 studies and 1,238 postoperative patients and demonstrated complications were reduced in the group receiving early EN (RR 0.53, 95 % CI 0.33–0.86); however, mortality and LOS were not significantly different [33].

Based on these data, EN should be provided within 24–48 h of surgery. Clearly, in those patients with evidence of continued obstruction, bowel discontinuity, ongoing peritonitis, and high risk of bowel ischemia, early EN would be not be appropriate. A general approach to formulation

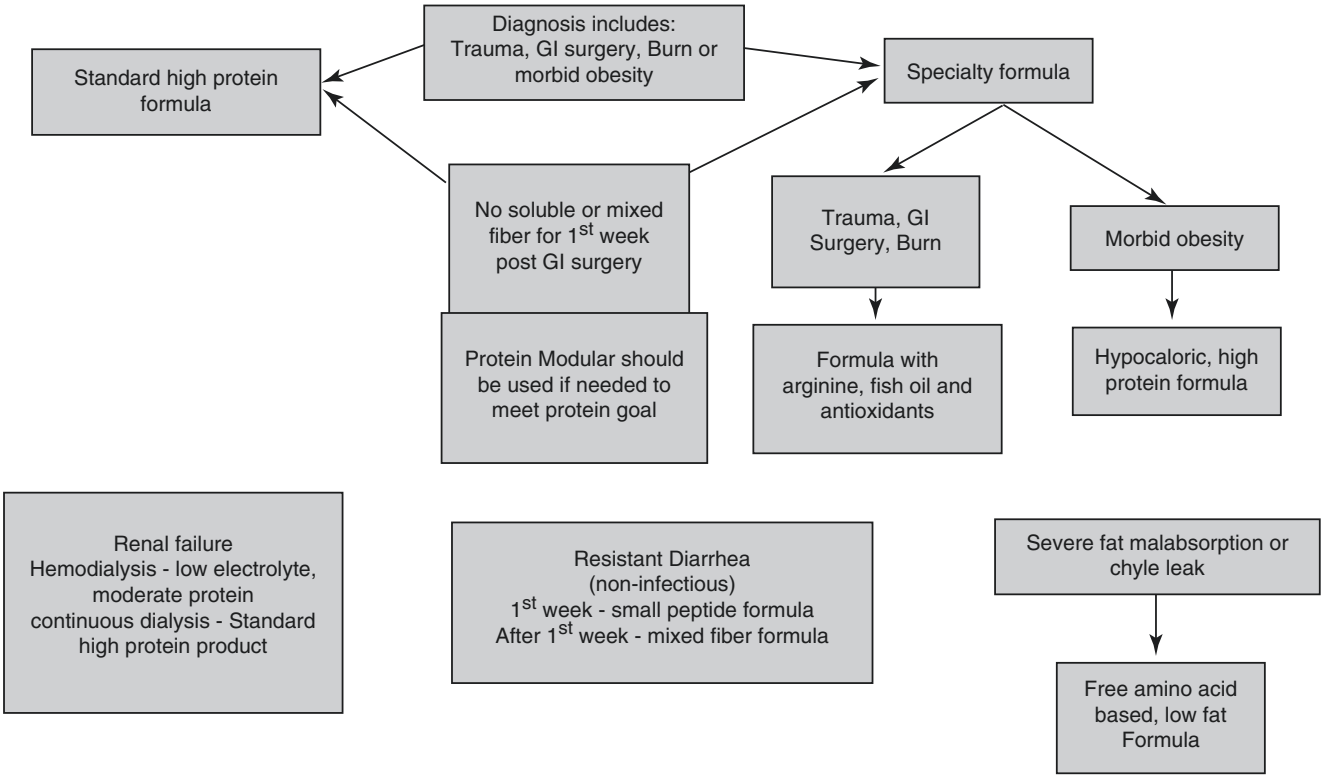

Fig. 20.2 Determining enteral nutrition (EN) formulation

selection in the surgical ICU patient is presented in Fig. 20.2. Noncomplicated well-nourished surgical and trauma patients requiring a short stay in the surgical ICU who can tolerate an oral diet should be allowed solid food as tolerated as opposed to starting with clear liquids. Even patients having undergone gastrointestinal (GI) surgery may tolerate solid foods. A RCT of over 400 patients post major GI surgery showed that giving solid food on the first postoperative day did not increase morbidity or mortality [34]. Another RCT demonstrated that postoperative nausea and complications occur with the same frequency whether patients are advanced first to a clear liquid or solid diet [35]. In fact, early start of solid foods may lessen risk of ileus as evidenced by passage of gas and stool [34]. Future use of clear liquids should be primarily based on patient preference with advancement to solid foods as soon as possible.

Immunonutrition

Immunonutrition (IMN) components, particularly arginine, omega-3 fatty acids, and antioxidants, have been shown to be beneficial in patients who have experienced trauma or major surgery. Studies to date suggest the benefit of IMN compared to standard enteral formulas (intact proteins with a general amino acid profile and omega-6 fatty acids) in surgical ICU patients is derived in part from the synergistic effect of fish oil and arginine. A meta-analysis of 35 RCTs showed that use of an arginine/fish oil-containing formula given postoperatively reduced infectious complications (RR = 0.78, 95 % CI 0.64–0.95, $p = 0.01$) but not mortality compared to a standard formula [36]. Similar findings were noted when the IMN and standard formulas were given perioperatively (both prior to and following surgery) in a meta-analysis of 21 RCTs representing 2,005 patients with significant reductions in infection (OR = 0.61, 95 % CI 047–0.79, $p < 0.01$) [37]. Another meta-analysis of 26 RCTs in 2,496 patients undergoing open gastrointestinal surgery resulted in decreased postoperative infections (RR = 0.64, 95 % CI 0.55, 0.74, no p-value provided) [38]. In these trials, use of the IMN product was generally restricted to 7–10 days.

Of the IMN components, arginine remains the most controversial and potentially the most beneficial to trauma and postoperative patients. The controversy lies within the use of arginine in septic patients. There is a theoretical concern that supplemental arginine will lead to upregulated nitric oxide synthase (NOS) enzyme activity in a postoperative septic patient [39]. However, this has not been proven in clinical trials [40]. Nitric oxide (NO) is a prominent compound necessary for proper cardiovascular function. NO production is driven by both arginine availability and NOS inhibitor asymmetric dimethylarginine (ADMA), a product of protein

methylation [41]. ADMA inhibits NO production by competing with arginine for NOS binding, and it is suggested that the net production of NO likely depends on the arginine:ADMA ratio [42].

A multicenter RCT of 176 septic patients compared the use of a standard enteral formula to another containing fish oil and arginine. A significant reduction in mortality (28 of 87 vs. 17 of 89; $p<0.05$), incidence of bacteremia (19 of 87 vs. 7 of 89; $p=0.01$), and nosocomial infection (17 of 87, 5 of 89; $p=0.01$) was noted [43]. However, APACHE II scores of 10–15 were associated with the group realizing benefit; therefore, it is unclear how these results would translate into patients with severe sepsis or septic shock. To date, no definitive answer exists for or against the use of arginine in sepsis, and therefore, arginine should be avoided in these patients.

The potential benefit of arginine is based on the theory that following major surgery or injury, specialized immune myeloid suppressor cells rapidly increase the levels of arginase 1, making the supply from endogenous arginine inadequate leading to a relative arginine deficiency making it a conditionally essential amino acid [44]. Arginine stimulates release of anabolic hormones such as growth hormone, prolactin, and insulin and initiates proliferation and activation of T-cells.

The benefit of IMN may be affected by timing, severity of malnutrition and nutrition risk, as well as diagnosis. A double-blinded RCT trial in 120 patients undergoing liver transplantation randomized to IMN or an isocaloric standard enteral formula given pre- and postoperatively demonstrated no significant differences in total body protein, muscle function, complications, or mortality [45]. Conversely, in another RCT of 305 malnourished (weight loss of at least 10 % body weight or BMI <18) patients undergoing resection for pancreatic or gastric cancer, differences were noted [46]. All patients received 2 weeks of PN preoperatively, given all patients were not candidates for EN. Then at 12 h postoperative, 152 patients were started on a small peptide IMN product, and 153 were started on an isocaloric small peptide product. Infectious complications were observed in 43 patients (28.3 %) in the IMN and 60 (39.2 %) in the SEN group ($p=0.04$). Significant differences were also noted in overall morbidity (33.5 % vs. 47.1 %, $p=0.01$) and mortality (1.3 % vs. 5.9 %, $p=0.03$) [46].

EN Access

The majority of surgical ICU patients can be fed via the gastric route. Historically, clinical concerns regarding ileus, aspiration, and increased risk of pneumonia with gastric feeds in postoperative patients often led to a delay in feeding until small bowel access could be obtained. However, a multicenter RCT found that small bowel feeding did not decrease rates of pneumonia [47]. Gastroparesis may occur in patients following GI surgery leading to a need for prolonged gastric decompression. In these patients, small bowel feeding should be considered. A team-based approach to small bowel tube placement has been shown to lessen time to placement and decrease risk of complications [48]. In surgical ICUs where timely bedside placement of small bowel tubes is not an option and patients display intolerance of gastric feeds, a trial of slow continuous infusion and use of prokinetics (metoclopramide or erythromycin) should be considered. Erythromycin and metoclopramide have been associated with undesirable effects including cardiac toxicity, tachyphylaxis, tardive dyskinesia, and QT prolongation and should be used cautiously with monitoring and continued trials of discontinuation. Placement of a gastrostomy, jejunostomy, or gastrojejunostomy should be considered at time of laparotomy in patients with major trauma or large GI resection in whom EN is expected to be needed for 4 weeks or greater.

Protocolized Management of EN

EN protocols addressing starting infusion rate, advancement, flushes, how to handle intolerances (gastric residual volumes, diarrhea, emesis, etc.), and circumstance under which EN should be adjusted or stopped have been shown to increase the overall percentage of EN provided [49–52]. In the surgical ICU, EN infusions are often interrupted for return trips to the operating room and diagnostic testing. Volume-based feeding protocols empower the nurses to increase feeding rates to "make up" for volume lost while EN is held [52]. An example of one such surgical ICU protocol was used in a pre- and post-study design and demonstrated a significant increase in percent of EN goal provided (63–89 %, $p<0.0001$) [53].

EN in Complex Situations

The optimal timing and use of different EN formulations in complex situations (new anastomosis, prolonged ileus, brain injury, open abdomen, vasopressor therapy) must be individualized. Baseline energy and protein requirements are determined as previously outlined. Although limited, increasing surgical experience and RCTs have demonstrated safety and efficacy using EN in complex surgical conditions.

New Anastomosis

A meta-analysis of early EN versus late EN showed no increase in anastomotic dehiscence (RR = 0.75; 95 % CI 0.39–1.4, $p=0.39$) with the direction favoring early EN sug-

gesting potential increased anastomotic strength with greater collagen and fibrin deposition and fibroblast infiltration [33]. A small RCT in 2014 designed to study reduction of postoperative ileus also commented on anastomotic leakage as a secondary outcome under the heading of "complications." Patients were divided into early enteral (study) or early parenteral (control) nutrition, with both groups being allowed liquids the day after surgery with progression to a normal diet as tolerated [54]. The ICU length of stay was not different between the groups. Of the reported surgical complications, there was significantly less anastomotic leakage noted in the EN group compared to the PN group (one patient vs. nine patients, $p=0.009$) suggesting EN across a new anastomosis may not increase the risk of anastomotic breakdown [54].

Postoperative Ileus

A postoperative ileus is associated with bowel manipulation leading to a localized, as well as a systemic, inflammatory response [55]. Experimentally, early feeding following surgery has been shown to reduce ileus by attenuating dysmotility and preventing bowel wall edema. In intention-to-treat analysis, a RCT of 123 patients undergoing major rectal surgery reported first time to defecation was significantly shorter ($p=0.04$) in patients randomized to early EN (study group) versus early PN (control group) [54]. Although several other studies have questioned the need for nasogastric decompression and delay of EN in bowel surgery patients, further research is needed in those requiring admission to the surgical ICU [56–59].

Vasopressor Support

Hemodynamic instability in critically ill patients may warrant the use of vasopressor support. Because splanchnic blood flow is highly dependent on cardiac output, redistribution during hypotension and sepsis decreases blood flow to the mucosal region that is highly vascularized due to the microvilli. The absorption of nutrients and oxygen exchange happen within the microvilli. In the absence of adequate blood flow, mucosal ischemia may result. Volume resuscitation in the postoperative patient does not immediately reverse blood flow to the gut. Delivery of EN increases mucosal oxygen requirements. If perfusion demand is higher than supply, nonocclusive bowel necrosis may result. Although this is a rare complication (<1 %), the mortality may be as high as 80 %; however, this is primarily based on case reports and retrospective data [60, 61]. Reported cases occur primarily in trauma and postoperative patients fed via a post-pyloric tube [62–67]. When the small bowel is hypoperfused and peristalsis is lessened, the stomach may act as a buffering chamber. Experts suggest surgical ICU patients receiving low, stable doses of vasopressors (a dose often based on clinical judgment and other signs of end-organ perfusion) may be started on a low or trophic rate of feeding into the stomach, with close monitoring of gastric tolerance or signs of worsening hemodynamic instability [60]. The feeding rate should be advanced slowly to goal with vigilant monitoring of abdominal exam every 4–6 h.

Traumatic Brain Injury

Initiation of EN should be within 24–48 h of injury, and similar to other critically ill patients, practitioners should have a low threshold for adding supplemental PN in patients with baseline malnutrition or with EN intolerance lasting greater than 7 days. These patients are often very catabolic with energy expenditure ranging from 100 % to 200 % of resting energy expenditure with the presence of other injuries. Protein requirements are in the range of 1.5–2.5 g/kg/day [68, 69].

Temporary Abdominal Closure

The temporary abdominal closure technique is commonly used following damage control laparotomy post resuscitation to avoid abdominal compartment syndrome. Although the goal is timely fascial closure, patients may have an open abdomen for days to weeks. A multicenter retrospective review of 597 patients with a temporary abdominal closure reported 39 % of the patients were provided EN prior to closure [70]. In a subgroup analysis of the 307 patients with no bowel injury, use of EN was associated with significant reductions in time to abdominal fascial closure, pneumonia, intra-abdominal complications, and mortality as compared to those patients receiving no EN (all differences, $p<0.02$) [70]. Another retrospective review compared early EN (≤4 days) with late EN (>4 days) and found earlier fascial closure ($p<0.02$) and less fistula formation ($p<0.05$) in the early EN group [71]. These studies suggest if no known contraindication (bowel discontinuity, high-output fistula, etc), patients with a temporary abdominal closure can be safely fed with EN. Energy requirements are similar as for other surgical ICU patients. However, patients with an open abdomen have the equivalency of a large open wound that produces a high-protein exudate. A range of 15–30 g of protein/L of exudate has been reported and should be replaced with use of high-protein EN formulas or protein supplements [21–23].

Parenteral Nutrition

Laparotomy with bowel manipulation combined with an inflammatory response leads to gut dysfunction (decreased mucosal blood flow, ileus, etc.) that may be compounded by ICU interventions (fluid resuscitation, vasopressor use, etc.) [72]. Continued gut disuse with PN may worsen gut dysfunction and allow the gut to become a reservoir for bacteria and

toxins. It has been theorized these toxic products can be aspirated or translocated late in the hospital course causing late complications of nosocomial infections and multisystem organ failure [72]. For these reasons, use of PN should be reserved only in those patients with a nonfunctioning GI tract. Once PN is started, continued efforts should be made to initiate EN as soon as the patient's medical status allows, continuing "supplemental" PN until the patient is able to tolerate 60 % of their goal EN rate [73].

Regardless of the ability to use the GI tract, initiating PN in a patient who is well nourished (low nutritional risk) and continuing PN for less than 7 days provided no further benefit over no nutrition [74]. In contrast, patients who are severely malnourished (high nutritional risk) appear to benefit from early PN (within 48 h of admission) without increased infectious complications when EN is not feasible [75–77].

One caveat is the high nutrition-risk patient in the early or acute phase of sepsis, in which PN should be avoided. There is a lack of data specifically addressing the use of PN in septic patients, and insights must be drawn from subset analysis of larger populations. In a mixed ICU study by Casaer et al., early supplemental PN added to hypocaloric EN resulted in increased infectious complications and longer length of ICU stay in the subset of patients with a diagnosis of sepsis [78]. A prospective single-day point-prevalence trial in 415 patients with a diagnosis of severe sepsis or septic shock showed that hospital mortality was significantly higher in patients receiving PN alone (62.3 %) or EN with supplemental PN (57.1 %) compared to those receiving EN alone (38.9 %) ($p = 0.005$) [79]. However, both the mean APACHE II and SOFA scores were significantly higher in the PN alone group. A secondary analysis of a RCT multicenter trial analyzed 353 patients with severe sepsis or septic shock who received EN, PN, or EN + PN and found patients with EN alone had lower mortality than those given EN and supplemental PN [80]. At present, only hypothesis-generating results are available for early PN in patients with severe sepsis or septic shock. Confirmation is needed with a RCT.

Oral Diet

The concept of advancing a postoperative patient first to a clear liquid diet has no physiologic basis. Although clear liquids may leave the stomach more rapidly than solid foods, they are also the texture easiest to aspirate [35]. In 241 patients who had undergone an abdominal operation, a RCT demonstrated no difference in dietary intolerance between those receiving a clear liquid diet (N-135) or regular diet ($N = 106$) [81]. In a RCT of over 400 patients who underwent major GI surgery and were successfully extubated within 24 h of surgery, solid foods on postoperative day 1 did not increase morbidity or mortality [34]. Early advancement to solid foods appeared to decrease risk of ileus as evidenced by early passage of gas and stool [34]. Potentially, a clear liquid diet should only be used in the surgical ICU based on patient preference or when the surgeon has a high level of concern regarding the integrity of the anastomosis.

Probiotics

Over the past decade, there has been increased understanding that the intestinal microbiome influences the immune function, physiology, nutritional status, and overall health of the host [82, 83]. In trauma and surgical patients, within hours of injury or insult, the microbiome is substantially altered due in part to changes in intravascular volume, blood flow to the GI tract, and widespread use of antibiotics and artificial nutrition support [82, 84, 85]. Initial efforts to use probiotics to maintain the "normal" microbiome in critically ill patients have had varying success [86]. Although a systematic review of both medical and surgical ICU patients demonstrated an association between probiotic use and decreased infectious complications and ventilator-associated pneumonia, there is difficulty in extrapolating the results of different probiotic species provided among the studies [86]. Therefore, use of probiotics should be restricted to select surgical ICU patient populations where RCTs have documented safety and outcome benefit.

A double-blind RCT was done in patients undergoing a pylorus-preserving Whipple procedure [87]. The use of a commercial probiotic product Synbiotic 2000 (Medipharm, Des Moines, IA) (consisting of 10^{10} CFU of each of *Pediococcus pentosaceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1, *L. paracasei* ssp *paracasei* 19 and *L. plantarum* 2362, as well as 2.5 g inulin, oat bran, pectin, and resistant starch) led to a significant reduction in infection when the probiotic preparation was started 1 h postoperatively compared to controls receiving placebo (12.5 % vs. 40.0 %, $p < 0.05$) [87]. In a pre- and post study of 67 liver transplant patients, 34 received fiber, and 33 received fiber plus mixed probiotics. Ten patients in the fiber-only group developed bacterial infections, compared to three in the group receiving fiber plus mixed probiotics ($p < 0.005$) [88]. Until more data are available using a single strain or commercially prepared readily available probiotic, general recommendations regarding the use in surgical ICU patients cannot be made.

Conclusion

Timely nutrition intervention leads to positive clinical outcomes in critically ill patients who have experienced insult or injury and are at high nutritional risk or unable to resume adequate oral intake within 7 days. Current data

and expert consensus support the following recommendations for nutrition in the surgical ICU:

1. Use EN in preference to PN in the presence of a functioning GI tract.
2. Start EN (containing arginine, fish oils, and antioxidants) within 24–48 h of trauma or surgery in nonseptic patients, and continue for 7–10 days.
3. Adopt volume-based EN protocols.
4. Hold small bowel EN in patients with increasing vasopressor requirements and consider trophic (10–20 ml/h) gastric feeds if not contraindicated for other reasons.
5. Begin PN in severely malnourished or high nutrition-risk patients early in those with nonfunctioning GI tracts or within 5–7 days if not tolerating at least 60 % of goal of EN prescribed.

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Antibiotic Strategy and Stewardship

21

Sarah M. Kolnik and Heather L. Evans

Antibiotic stewardship is the optimization of antibiotic regimens to ensure the best treatment selection for individual patients with minimization of side effects and cost, while attempting to limit the development of resistance [1, 2]. Comprehensive antibiotic management strategies may use a variety of methods to limit antibiotic use in volume, duration, and spectrum. These strategies should also include multidisciplinary efforts to monitor compliance with clinical practice guidelines, policies, and protocols. Formulary restriction, antibiotic cycling, selective reporting of culture susceptibilities, and decision support tools to aid in drug selection are among the means by which antimicrobial use can be directed. Equally important in the critical care setting is the prevention and treatment of nosocomial infections common to critically ill patients.

Preventing Resistance

Antibiotic resistance has been as a public health concern for decades. In 2014, the World Health Organization (WHO) published a global surveillance report finding very high rates of bacterial resistance in each of the WHO geographic regions [3]. The report concluded that a "post-antibiotic era," where simple infections once again contribute to significant mortality, is a possibility within the next century. With the acknowledgment that a significant contributing factor to antibiotic resistance is the overuse and misuse of antibiotics, the Centers for Disease Control and Prevention (CDC) has highlighted improving antibiotic usage in health-care settings as one of four key strategies to slowing the development of resistance [4]. First and foremost, the CDC recommends that health-care facilities that develop multidisciplinary antibiotic stewardship programs and core elements should include a leadership commitment, institutional accountability, drug expertise, action plan, infection tracking, reporting, and provider education. A recent meta-analysis found that antibiotic stewardship programs, either prescription restrictive or prescriber persuasive, were effective in decreasing antibiotic resistance and hospital-acquired infections [5]. A community-based antibiotic stewardship program demonstrated a 50% reduction in the number of *Clostridium difficile* infections within its first year of intervention [6]. The implementation of antibiotic stewardship programs is often multifaceted, and despite encouraging results from individual studies and demonstrated effectiveness in meta-analyses, it is difficult to identify the components of the programs that are the most beneficial. Carling and colleagues [7] reported that the ultimate success of their stewardship effort depended on a high degree of provider acceptance, attributed to having noninfectious disease personnel involved in the effort. Successful stewardship requires multidisciplinary cooperation, systems-based change, and support from hospital leadership [8].

Antibiotic Formulary Restriction

Antibiotic restriction is an external control over clinician prescribing instituted to address antimicrobial resistance in the face of provider noncompliance with clinical practice guidelines. Restrictions may be applied at various levels, from limiting drugs available on formulary, to requiring prior approval from infectious disease experts, to other predefined dispensing criteria. In the setting of increasing Gram-negative resistance to aminoglycosides in the 1980s, the association between a change in antibiotic usage and alteration of antibiotic sensitivities was recognized in the initial reports of antibiotic restriction in the intensive care unit (ICU) [9]. Early studies that restricted antibiotics by requiring infectious disease or pharmacy consultant preapproval found decreased resistance and cost savings through the imposed use of less expensive unrestricted antibiotics [10]. Over the following

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decades, the majority of studies evaluating antibiotic restriction have demonstrated a reduction in the targeted antibiotic with associated improvements in resistance rates. However, most also report that one consequence of restriction is significantly increased prescribing of alternative agents. For example, a 6-month restriction of fluoroquinolones in the intensive care unit (ICU) setting was associated with a decrease in resistant *Pseudomonas aeruginosa* from 71.3 to 52.4 % that was maintained for up to 12 months following restriction [11]. This study also showed a twofold increase in aminoglycoside use and a fivefold increase in macrolide use. In addition to improved resistance rates, some antibiotic stewardship programs have demonstrated improved clinical outcomes. May and colleagues found a reduction in vancomycin-resistant *Enterococcus* spp. and *Clostridium difficile* infections following restriction of cephalosporin use [12].

In contrast to the initial reports of reduction in resistant organism isolation, subsequent studies have shown the converse. "Squeezing the balloon" [13] describes the phenomenon where resistance to the alternatively chosen replacement antibiotic classes develops in the time period of their use [14]. A nationally representative survey of hospitals in the United States found that restricted formularies were associated with an overall higher rate of antibiotic resistance [15]. Implementation of antibiotic restriction through a variety of mechanisms has been shown to decrease rates of use of intended drugs and lower resistance prevalence, though these practices are also associated with increased use of alternative classes and variable effects on overall rates of resistance.

Antibiotic Cycling

An alternative to restricting specific antibiotic use is the scheduled periodic withdrawal and reintroduction of different antibiotic classes within a clinical environment. This practice is known as "antibiotic rotation" or "cycling." Empiric antibiotic regimens are designed to address selective antibiotic pressure, preventing the preferential selection of resistant microbes through single-class antibiotic overuse. Resistant bacterial strains are assumed to have a growth disadvantage when homogenous antibiotic pressure is withdrawn, and exposure to the new class of antibiotics should eliminate resistance selected during the previous cycle. In an early analysis on cycling from the 1990s, Gerding and colleagues [16] observed that gradual increase of gentamicin use after formulary restriction was not associated with increase in resistance to any of the aminoglycosides in use. After encouraging results in decreasing resistance patterns with cycling antibiotics over months–years [17], more intricate cycling schedules were developed and evaluated. Using predominant resistance patterns as the basis for the drug choices, Gruson and colleagues [18] detailed a comprehensive effort to control rising quinolone and cephalosporin resistance in a medical ICU through a combined cycling and antibiotic restriction schedule devised each month, based on the previous month's antibiotic use and microbial resistance pattern. Although the drugs chosen for the rotation schedule were again targeted against Gram-negative organisms, the incidence of MRSA pneumonia decreased during the study period. This report also found improved drug sensitivities for several commonly resistant Gram-negative organisms responsible for ventilator-associated pneumonia (VAP) following the initiation of cycling.

Despite the encouraging results from these early studies of single antibiotic class cycling, mathematical models suggest that the temporal cycling of antibiotics is inferior to mixing, a strategy whereby multiple antibiotic classes are used simultaneously in the environment to increase antibiotic heterogeneity [19]. Raymond and colleagues [20] designed a study that combined antibiotic mixing and rotation, with two antibiotic classes used in the environment simultaneously for the empiric treatment of suspected intra-abdominal infection, pneumonia, or sepsis of unknown origin. They found a decrease in the incidence of all infections, infections caused by resistant Gram-negative organisms, and in-hospital mortality during the rotation period. At the same time, there was a reduction in hospital-acquired and resistant hospital-acquired infection rates on the non-ICU wards, suggesting that the influence of antibiotic rotation on resistance patterns in one unit may be sustained after the patients are transferred to a new location [21].

It is important to note that whether one employs cycling or mixing, the degree of variation in prescribed antibiotics is always greater than what one would achieve with formulary restriction alone; formulary restriction of necessity constraints provides choices to those available for use instead of allowing selection from an unconstrained menu of therapeutic agents. This variation has been denoted using a concept called the antibiotic heterogeneity index with complete heterogeneity equal to 1. A target of an AHI of 0.85 has been suggested as a means of reducing selection pressure for multiple drug resistance bacterial growth [22].

Preventing Infection

Critically ill patients are at increased risk for health-care-associated infections due to their underlying pathology, poor nutritional status, indwelling devices, and frequent contact with health-care providers caring for other infectious patients. An antibiotic stewardship program for the critically ill must also include best practices for the prevention, diagnosis, and appropriate treatment of common health-care-associated infections. The common infections in the ICU setting include ventilator-associated pneumonia (more recently termed ventilator-associated infection), central line-

associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and *Clostridium difficile* colitis.

General Control Measures

Handwashing and Barrier Precautions

Hand hygiene is one of the most important infection control practices that providers can utilize to prevent horizontal transmission or contamination between patients. Handwashing programs have been shown to decrease infection rates in critical care settings and are cost effective [23]. The greatest barrier to practice is long-term provider compliance [24]. Studies have evaluated the currently available antiseptic solutions, both alcohol-based and chlorhexidine products, and while both solutions have been found to be more effective than soap and water alone, neither has been found to be more effective than the other [25]. Alcohol solutions cause less skin irritation and are more cost effective. Barrier precautions, gloves and gowning for patients that are known to have drug-resistant infections, have been found to be effective as decreasing infection rates [26, 27].

Decolonization

The use of antibacterial solutions, such as 2% chlorhexidine wipes, for daily washing has been an accepted practice in many ICUs. Recent well-designed studies have shown conflicting results regarding universal decolonization strategies in ICUs. One multicenter, cluster-randomized study demonstrated a reduction in patient acquisition of multidrug-resistant organisms and fewer hospital-acquired bloodstream infections with universal decolonization [28]. A subsequent single-institution, multiple-ICU randomized study found no reduction in overall health-care-associated infections and suggested the findings did not support universal daily bathing [29]. Although data is conflicting, limited cost and few adverse effects make universal decolonization a reasonable infection control strategy, and it continues to be a component of expert panel recommendations [30].

Health-Care-Associated Infections

Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

Critically ill patients are at high risk for hospital-acquired pneumonia (HAP), with an incidence of up to 27% of intubated patients [31]. HAP is a clinical definition used to alert providers to the fact that a hospitalized patient will have a different microbial exposure profile that should be taken into consideration with treatment. A significant majority of cases of HAP are associated with mechanical ventilation, and ventilator-associated pneumonia (VAP) is that which occurs >48 h after intubation. Trauma patients have injury-specific risk factors for developing pneumonia including intubation in the field, chest trauma, and potential history of aspiration [32]. Critically ill patients who subsequently develop pneumonia have an attributable mortality of up to 50% when matched to patients with similar illness severity [31]. Limiting the number of ventilator days by preventing the first intubation, facilitating early extubation, and preventing re-intubation is the best way to prevent VAP. Standardized endotracheal protocols, including elevation of the head of bed and the use of closed suction systems, have been shown to decrease VAP rates in critical care units. Chlorhexidine oral rinses used in the perioperative period have been shown to reduce nosocomial infection rates, and systemic review has found that oral hygiene with chlorhexidine significantly reduces respiratory infections in ventilated patients [33, 34]. Antibiotic administration should not be delayed in the septic patient, though when possible, culture diagnosis through bronchoscopy or bronchial-alveolar lavage should be obtained to guide antibiotic selection and duration. For empiric treatment prior to culture results, a distinction is made between early onset (usually within 4–5 days of admission) and late onset (>5 days of hospitalization). For those patients with early-onset HAP, the important bacteria to cover include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and Gram-negative enteric organisms in intubated patients. Patients with late-onset HAP, *Pseudomonas*, *Acinetobacter*, and drug-resistant organisms, including methicillin-resistant *Staphylococcus aureus*, should have coverage. Local antibiograms are important to monitor, as specific resistance patterns may be unique to individual institutions or vary between units or even within a single unit of mixed patient types within individual facilities.

Central Line-Associated Bloodstream Infection

Patients admitted to the ICU are at increased risk for bloodstream infections (BSIs) due to the frequent use of central and peripheral intravascular catheters, either for monitoring or therapeutic purposes. Central line-associated bloodstream infections (CLABSIs) are primary BSIs, or those not associated with an infection from a different source, in patients who have an indwelling central line within 48 h of the onset of infection. CLABSIs have an estimated incidence of 80,000 per year in ICU patients and increased morbidity in this population [35]. Different insertion sites have been associ-

ated with varying risk of infection. Subclavian central lines have a lower incidence than those at the internal jugular site, and femoral lines have the highest infectious rates. The most common source of infection is a patient's skin flora, and preventative measures at the time of insertion include sterile prep with 2 % chlorhexidine solution and full barrier precautions with sterile technique followed with gloves, gown, mask, and hat. Standardized insertion techniques with ongoing provider education have been shown to decrease infection rates [36]. Diagnosis of CLABSI requires one of two criteria to be met, (1) the patient has a recognized pathogen (not a common skin contaminant) cultured from one or more blood cultures and the organism cultured from the blood is not related to an infection at another site; (2) the patient has at least one of the following signs or symptoms: temperature over 38.0 °C (100.4 °F), chills, or hypotension. Signs and symptoms and positive laboratory results are not related to an infection at another site, and common skin contaminant is cultured from two or more blood cultures drawn on separate occasions [37]. For a local infection at the catheter site, treatment can consist of removal of the catheter without antibiotic administration. If the patient clinically improves and has normalization of their white count, then no further antibiotic would be warranted. If a patient appears clinically unwell or has signs or symptoms of sepsis, empiric treatment may be initiated prior to culture or sensitivity results. Antibiotics that cover for skin flora, including methicillin-resistant *Staph aureus*, should be used. Once culture and sensitivity data have returned, antibiotic treatment can be guided to the specific organisms. Treatment should be started with the removal of the likely culprit catheter.

CAUTI

Urinary tract infections (UTIs) are the most common health-care-associated infection in the intensive care unit (ICU), accounting for up to 40 % of all health-care-associated infections in critically ill patients [38]. The majority of UTIs are associated with urinary catheter use, and a significant number of patients in the ICU will have a urinary catheter for a portion of their hospitalization [39]. A UTI may progress to urosepsis and will typically first begin with the development of simple bacteriuria that occurs from either seeding of the urinary bladder with initial catheter insertion or the development of biofilms along the catheter surface. For patients with a short-term catheter in place, the common causative organisms are *Escherichia coli*, although *Pseudomonas aeruginosa*, *Enterococcus*, and yeast infections can also occur in critically ill patients. Patients who have had a catheter for greater than 30 days are likely to have a polymicrobial infection due to Gram-negative organisms, Gram-positive organisms, and yeast, with most patients having three to five organisms isolated [40]. The definition of a UTI is the presence of the signs and symptoms of UTI, including dysuria, urinary frequency, flank pain, or hematuria, without another identified source of infection. For critically ill patients with urinary catheters in place, many of these symptoms will be masked, and a urinalysis and urine culture are the gold standard tests for diagnosis. The presence of $>10^5$ colony-forming units on culture, or the presence of 10^3–10^5 colony-forming units, and a positive urine culture are required for the diagnosis of UTI. A catheter-associated urinary tract infection (CAUTI) is diagnosed in a patient who meets the prior clinical criteria with a current indwelling catheter or has had a urinary catheter removed within the prior 48 h.

For patients with asymptomatic bacteriuria, antibiotic administration is not recommended, as treatment has not been shown to alter rates of eventual progression to symptomatic UTI or improve outcomes [41]. Empiric antibiotics should be initiated in patients with severe symptoms or signs of urosepsis. Selection of antibiotic should include consideration of the amount of urinary excretion to obtain adequate urinary concentration and the local resistance patterns. For patients with mild symptoms or when the diagnosis of UTI is questionable, antibiotic administration should be delayed until the return of culture results. The recommended duration of antibiotics from the Infectious Diseases Society of America is currently 7 days of treatment for patients who have a quick response to antibiotics and 10–14 days for patients with severe symptoms or a delayed response. A 5-day course can be considered in patients with mild disease, as some studies are demonstrating no difference with a shortened duration of antibiotics.

Difficile-Associated Disease

The 1970s saw the emergence of antibiotic-associated colitis, and it was at the end of the decade that *Clostridium difficile* was identified as the causative agent. "*C. diff*" colitis is most frequently observed following treatment with clindamycin, cephalosporins, and fluoroquinolones, and the risk of infection is increased with either the use of multiple antibiotics or longer duration including "extended prophylaxis" regimens [42]. A recent analysis found that annually in the United States, there are greater than 400,000 cases of *C. diff* colitis with an associated case mortality of 10 % and that the incidence continues to increase despite declines in the rates of other health-care-associated infections [43]. In the critically ill patient, *C. diff* colitis should be suspected with the occurrence of watery diarrhea, and a stool sample should be sent for testing. Screening in asymptomatic patients is not recommended due to the possibility of identifying carriers in whom treatment is not recommended. Following diagnosis,

treatment recommendations differ based on the severity of disease. Mild disease is the presence of diarrhea without other symptoms, while moderate disease includes the presence of mild symptoms. A severe case of *C. diff* includes the prior criteria plus two of the following: hypoalbuminemia, WBC >15,000, and/or abdominal tenderness. And complicated *C. diff* includes the previous plus other signs/symptoms of ongoing infection. Treatment includes ensuring that any unnecessary antibiotics are discontinued, and for mild/moderate disease, the first-line agent is PO metronidazole, while for severe disease, PO vancomycin (PR in the case of ileus) or IV metronidazole. Treatment duration for initial infections is 10–14 days. For patients who fail initial treatment, all further episodes should be treated as complicated infections.

Surgical source control can be obtained for patients who fail to respond to medical therapy or for those who progress to hemodynamic compromise despite appropriate antibiotic treatment [44]. Surgical source control regimens span the "Pittsburgh" approach of laparoscopic loop ileostomy coupled with warm colonic lavage and a trans-ileocecal valve access catheter for antibiotic delivery in an antegrade fashion to the time-honored approach of total abdominal colectomy and end ileostomy. Procedure selection depends on the degree of critical illness with those who are unstable being appropriate only for the latter approach. With more mild disease, colon preservation rates of up to 92 % may be achieved [45].

De-escalation

While antibiotic stewardship is most commonly linked with restricting certain antimicrobial, antiviral, or antifungal agents, an oft overlooked but essential feature is de-escalation [46]. This aspect of stewardship helps ensure that tailoring of empiric therapy occurs in a timely and appropriate fashion to help reduce the driving force for selection of resistant organisms. Furthermore, de-escalation therapy is also linked with IV to oral conversion approaches for agents whose bioavailability is therapeutically equivalent regardless of route of administration [47]. Failing to follow through with tailoring and then stopping therapy leads to unnecessary therapy, resistance promotion, financial waste, and complication induction spanning *C. difficile*-associated disease and, more rarely, organ dysfunction (renal, bone marrow, etc.).

Conclusion

Based on the plethora of surveillance, consultation, and communication function, it is increasingly clear that institutional antibiotic stewardship benefits from a team-based approach including infectious disease, a Pharm. D, often an advanced practice provider with a close relationship with the intensivist. Regardless of which strategy is employed, stewardship sows benefits that improve outcomes, reduce resistant pathogen promotion, reduce infection occurrence and transmission, and reduce overall cost.

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Sepsis, Severe Sepsis, and Septic Shock

22

Andrew C. Gaugler and Nicholas Namias

Introduction

Sepsis, the deleterious inflammatory response of the body to infection, has been a thorn in the side of the physician since the earliest days of Western civilization. The word "sepsis" comes from the Greek *sipsi*, which means "to make rotten." The physicians and surgeons of antiquity noted the appearance of putrefication of wounds along with the presence of fever, which often accompanied injury and surgery. However, it has taken nearly two millennia for these phenomena, infection and its inflammatory host response, to reach a point of rudimentary understanding.

For hundreds of years, the purulence of an infected wound was thought to be essential for wound healing. The nineteenth century brought groundbreaking progress with the introduction of surgical handwashing by Semmelweis, Pasteur's discovery of microbial causes of infection, and Lister's development of antiseptic techniques. In the pre-antibiotic era of the early twentieth century, the syndrome of sepsis was thought to wholly arise from bacteria in the bloodstream [1].

Following the Second World War, antibiotic use became widespread, and mortality from infection and sepsis began to dramatically decrease. However, it was not until David Ashbaugh first described the acute respiratory distress syndrome (ARDS) in adults in 1967 that the first correlations between infection, trauma, and end-organ dysfunction due to systemic inflammation were made [2].

Throughout the 1980s, it became more evident that many other organ systems were affected by the systemic inflammation caused by infection and injury. The work of physicians and researchers of the last two centuries has brought us to our modern definition of sepsis: the inflammatory host response to infection [3].

Epidemiology

Sepsis accounts for over 20 % of all ICU admissions nationwide, is the most common cause of mortality in the noncardiac intensive care unit, and is the tenth leading cause of all deaths in the United States [4, 5]. Infection and multi-organ failure account for the majority of late death following both blunt and penetrating trauma [6, 7]. In a recent review of sepsis in the surgical patient, postoperative sepsis was ten times more common than perioperative myocardial infarction and pulmonary thromboembolism [8].

In the general medical population, pneumonia, urinary tract, and intra-abdominal infections account for greater than 65 % of all cases of sepsis [4]. When the surgical ICU patient is separated out from the general medical population, infections within the peritoneal cavity are by far the most common cause of sepsis, with the majority requiring either operative or image-guided intervention for source control [8].

Risk Factors

The possibility of infectious complications leading to sepsis syndrome and subsequent organ dysfunction and shock is inherent in both major operations and severe injury. Several factors however seem to increase the likelihood that these complications will occur and are associated with poor outcomes. Any underlying organ system pathology seems to increase the incidence of septic complications in a stepwise fashion. However, even for otherwise healthy individuals, longer than expected times in the operating room, the need for emergency surgery, and significant delays in operating

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for emergent pathology all contribute significantly to the patient's risk of sepsis [8–11].

Sepsis Syndromes

Sepsis syndrome encompasses the wide spectrum of the injurious host response to infection. The presence of two or more signs of the systemic inflammatory response syndrome (see Table 22.1) with an infectious cause defines sepsis [3, 12]. Surgical sepsis can be further defined as sepsis within 14 days of a major surgical procedure (general anesthesia time greater than 1 h) or sepsis requiring surgical intervention for source control [8]. The development of hypotension, hypoperfusion, or evidence of end-organ dysfunction, as a result of the host response to infection, defines severe sepsis. Refractory hypotension after adequate resuscitation with intravenous fluids is termed septic shock [3, 12].

Quantifying Organ Dysfunction in Severe Sepsis and Septic Shock

The deleterious systemic inflammatory response of the human body to an infectious insult can have detrimental effects on all organ systems. The evaluation and management of the septic patient is complicated by the wide array of clinical manifestations, sites and etiologies of infections, and patient comorbidities. Recent efforts have been aimed at development of statistically validated biomarkers and mathematical models of severity scores that could aid in risk stratification and prognostication.

Historically, one of the most widely used scores has been the APACHE II (Acute Physiology and Chronic Health Evaluation II) model, which was used to classify severity of disease within 24 h of ICU admission based on age and 12 discreet variables. Higher scores correspond to more severe disease and higher risk of death [13]. The APACHE score has been extensively used in research; however, its applicability to the bedside is limited. Recently, more focused scales directed at the septic patient in particular have been developed, chiefly the Predisposition, Infection, Response, and Organ Failure (PIRO) and Sequential Organ Failure Assessment (SOFA) scores. Currently, these scores are being validated for the prognostic staging of sepsis and objectively quantifying severity of organ dysfunction in the ICU (Table 22.2). However, recent studies have validated PIRO as effective in risk-stratifying septic patients admitted from the emergency department [14–16].

Biomarkers in Sepsis

In certain patient populations, especially critically ill polytrauma patients and those undergoing major surgical procedures, sepsis can be especially difficult to diagnose due to the preexisting inflammatory response due to their primary disease process. Several biomarkers have been proposed as tools to aid the clinician in differentiating between sepsis and other causes for the SIRS response. Procalcitonin, C-reactive protein, interleukin 10, interleukin 6, TNF-alpha, and numerous other markers have been investigated. At this time, no single biomarker has been identified that can reliably predict sepsis. However, procalcitonin has been shown to be useful in the identification of early posttraumatic sepsis [17].

Markers of Tissue Hypoperfusion

One of the chief contributing factors for the development of end-organ dysfunction and failure in severe sepsis and septic shock is tissue hypoperfusion. Hypotension alone is often insufficient to diagnose shock or regional tissue hypoperfusion. Based on data from the Surviving Sepsis Campaign, blood lactate levels greater than 4 mmol/dL were associated with an increased risk of in-hospital mortality both with and without hypotension [18]. Additionally, lactate clearance, the percent change in lactate level over time, has been shown to be an effective marker in predicting response to treatment and risk of death. Lactate clearance within the first 6 h of

Table 22.1 Diagnostic criteria for sepsis syndromes

SIRS	Sepsis	Surgical sepsis	Severe sepsis	Septic shock	MODS
Two or more of the following criteria:	SIRS with documented infection	Sepsis within 14 days of a major surgical procedure or sepsis requiring surgical procedure for source control	Sepsis with organ dysfunction hypotension or hypoperfusion	Sepsis with persistent hypotension despite adequate fluid resuscitation	Failure of two or more organ systems requiring support
T>38 °C or <36 °C					
HR>90/min					
RR>20/min or PaCO2<32					
WBC>12,000 or <4,000					
or >10 % bands					

Table 22.2 Sequential organ failure scoring criteria

Respiratory			Nervous		
	PaO2	SOFA		GCS	SOFA
	<400	1		13–14	1
	<300	2		10–12	2
	<200[a]	3		6–9	3
	<100[a]	4		<6	4
Cardiovascular			Hepatic		
	Variable	SOFA		Total bilirubin	SOFA
	MAP <70	1		1.2–1.9	1
	Dob or Dop<5	2		2.0–5.9	2
	Dop>5 or NE≤0.1[b]	3		6.0–11.9	3
	Dop>15 or NE>0.1	4		>12.0	4
Coagulation			Renal		
	Platelets	SOFA		Cr	SOFA
	<150	1		1.2–1.9	1
	<100	2		2.0–3.4	2
	<50	3		3.5–4.9	3
	<20	4		>5.0	4

[a]With mechanical ventilation
[b]*Dop* dopamine, *Dob* dobutamine, *NE* norepinephrine dose in mcg/kg/min

admission from the emergency department is especially useful in determining response to treatment [19]. Other markers of tissue hypoperfusion, including invasive and noninvasive monitoring devices for regional oxygenation index directly at the tissue level, are currently under investigation for future use [20].

Treatment of Severe Sepsis, Septic Shock, and Organ Dysfunction

Immediate recognition, fluid and vasopressor resuscitation, early broad-spectrum antibiotic therapy, source control of surgical sepsis, and support of dysfunctional or failed organ systems are the foundations of care for the septic patient. There have been multiple road maps of protocol-driven care for sepsis and septic shock released in recent years. The Surviving Sepsis Campaign Guideline 2012 update contains an evidence-based approach for care of severe sepsis and septic shock that is outside the scope of this chapter, but which the individual physician should be familiar. The protocol-driven approach to sepsis is heavily influenced by the "early goal-directed therapy" (EGDT) approach articulated by Rivers in 2001 [4, 21].

Early Goal-Directed Therapy

Early goal-directed therapy (EGDT) is a concept of targeting therapy in the early hours of septic shock to reach certain physiologic end points for resuscitation. In his single-center trial reported in 2001, Rivers randomized patients to a protocol aimed at using fluids, vasopressors, invasive hemodynamic monitoring, and transfusion to resuscitate to CVP of 8–12 mmHg, MAP>65 mmHg, superior vena cava oxygen saturation >70 %, and a urine output of greater than 0.5 ml/kg/h and demonstrated a 16 % reduction in mortality when compared with usual care [21]. The findings of this study caused a dramatic shift in the critical care management of septic shock and heavily drove many of the recommendations found within the Surviving Sepsis Campaign Guidelines. However, Rivers' study was not without criticism. EGDT mandates invasive hemodynamic monitoring with oximetric central venous catheters or intermittent superior vena cava blood gases and advocates for resuscitation to supraphysiologic end points. What is also unclear is which elements of EGDT were responsible for the dramatic improvement in outcomes.

Two recent studies have aimed at comparing EGDT and/or protocol-based resuscitation with usual care at the discretion of the attending critical care physician in patients with severe sepsis and septic shock. The ProCESS study was a multicenter, randomized, controlled trial with 1,341 patients with septic shock, randomized to protocol-based care (that did not require invasive hemodynamic monitoring, inotropes, or transfusions), EGDT, and usual care. The study showed essentially no difference in mortality across all groups at 60 days, 90 days, and 1 year [22].

ARISE 2014 was a similar multicenter international randomized controlled trial that compared EGDT to usual care in over 1,600 patients with severe sepsis or septic shock. Like the ProCESS trial, the ARISE investigators were unable

to show any difference in early or late mortality between the two groups [23].

These two studies have shed new light on numerous aspects of the care of patients with severe sepsis and septic shock. First, invasive hemodynamic monitoring for resuscitation in the septic patient does not appear to improve outcomes. Second, transfusion of packed red blood cells should be used judiciously and only in the setting of symptomatic anemia. Most importantly, the individual judgment of the seasoned critical care physician cannot be replaced by a standardized protocol. Though Rivers' controversial concept of EGDT may not hold up in the modern care of the septic patient, what cannot be overlooked is the impact his landmark study had on the recognition and early, aggressive treatment of severe sepsis and septic shock.

Fluid Resuscitation in Sepsis

Intravenous fluid resuscitation is the first-line therapy for improving hypotension and end-organ dysfunction in severe sepsis and septic shock. During the resuscitative phase, ensuring adequate intravascular volume and end-organ perfusion are a top priority. A minimum volume of 30 mL/kg challenge of intravenous crystalloid bolus should be used for initial resuscitation, and intravenous fluid administration should continue as long as there is evidence of physiologic improvement in hemodynamic parameters [12]. Numerous studies have been conducted to evaluate the safety and efficacy of the various crystalloid and colloid fluids for resuscitating the septic patient. Crystalloids are the preferred fluid in sepsis, as there has been no clear benefit in administering colloid solutions over crystalloids and colloid use is associated with increased cost. It has been proposed that large volumes of crystalloid administration are associated with an increased risk of ARDS. However, recent trials have shown resuscitation volumes in the first 24 h of care have little effect on the incidence of ARDS [24]. Albumin can be safely used to supplement crystalloid resuscitation in patients already receiving large volumes of crystalloids, but there has been no demonstrated survival benefit. Hydroxyethyl starches should be avoided in severe sepsis and septic shock due to lack of benefit and potentiation of acute kidney injury [12, 25].

Invasive Hemodynamic Monitoring

Fluid balance monitoring is a heavily debated topic in severe sepsis and septic shock. The use of pulmonary artery catheters and central venous catheters for pressure monitoring is controversial due to lack of clear efficacy and risk of harm. Newer-generation monitors based on arterial line pulse pressure variation can be useful for following trends during resuscitation but should be interpreted with caution due to lack of widespread validation and lack of accuracy in spontaneously breathing, lightly sedated patients and those with cardiac arrhythmias.

Antimicrobial Therapy

Following the establishment of adequate intravenous access and starting aggressive intravenous fluid therapy, the next priority in resuscitation should be the administration of effective broad-spectrum intravenous antibiotics. Antimicrobial therapy should be instituted as soon as clinically feasible after recognition of sepsis. Multiple agents should be directed at the most likely infectious cause of the patient's individual presentation. In the surgical patient, since the majority of presentations are related to an intra-abdominal source, agents active against enteric bacteria and anaerobes should be added, and in appropriate patients, agents active against drug-resistant organisms and antifungal agents should be added. In the immunosuppressed surgical population, antiviral agents should also be considered. Antibiotic therapy should be de-escalated to culture-directed therapy, usually by the third day after presentation [12]. Duration of antibiotic therapy remains a topic of debate. For patients with intra-abdominal infections having undergone adequate source control, a recent trial comparing a fixed 4-day regimen versus administering the regimen until 2 days after normalization of fever, leukocytosis, and ileus showed no benefit to a prolonged regimen [26].

Source Control

Immediately following volume resuscitation and initiation of antimicrobial therapy, a focused search for an infectious source amenable to source control must be urgently sought. Drainage of an intra-abdominal, cutaneous, or perianal abscess, debridement of necrotic tissue, or even the removal of an infected device or line are all potentially lifesaving measures in the septic patient [12]. Source control can be obtained by either surgical or nonsurgical means. Often intra-abdominal abscesses, empyema, and other foci such as the biliary tract can be drained via percutaneous, image-guided techniques. Other causes, such as necrotizing fasciitis, hollow viscus perforation, and perianal infection, require urgent operation. While the need for definitive source control may seem intuitive in the surgical population, it is of utmost importance that the critical care physician search out any potential source of undrained infection and that the adequacy of source control be continuously reassessed.

In a recent study of patients with septic shock from GI perforation, shorter times from hospital admission to the ini-

tiation of surgery reduced mortality, provided they received adequate early hemodynamic resuscitation. For patients in that study who had a significant delay from admission to surgical intervention greater than 6 h, there were no survivors to 60-day follow-up. Surgical intervention for patients with severe sepsis or septic shock with an amenable source should undergo emergency operation as soon as possible, even if ongoing resuscitative measures need to be continued in the operating room [11].

Damage Control in Intra-abdominal Sepsis

Damage control surgery and resuscitation is a concept in trauma surgery aimed at staving off the lethal triad of acidosis, hypothermia, and coagulopathy. It is a combined resuscitative and surgical effort aimed at halting ongoing blood loss and controlling contamination with an abbreviated laparotomy, while restoring adequate circulating volume and providing continued physiologic support in the ICU. Definitive surgical management is then performed in a staged fashion after reversal of initial physiologic derangement [27].

After its introduction in 1993, the damage control approach was widely adopted by the trauma community and is widely used in patients undergoing laparotomy for septic shock. This type of rapid source control with delayed definitive operation has become a lifesaving tactic in selected patients [28, 29]. In the setting of damage control laparotomy for abdominal catastrophe, there is evidence in both human and animal models that intraperitoneal fluid resuscitation may decrease time to abdominal closure, increase fascial closure rates, and decrease postoperative infectious complications; however, larger studies are needed to confirm these findings [30, 31].

Cardiovascular Support

Institution of vasopressor therapy is vital to sustain life in the septic patient who does not adequately respond to intravascular volume loading. Below a certain MAP threshold level, which depends on the physiologic state of the individual patient, autoregulation in the tissue bed can be lost, and organ perfusion becomes linearly dependent on pressure. In the initial resuscitative phase, volume administration must be the first priority. Adding vasoactive agents prior to restoring circulating volume is associated with increased mortality [32]. An arterial cannula should be placed when feasible following initiation of vasopressor therapy to guide accurate dose titration and monitor response. For most patients, a MAP of 65 mmHg will maintain tissue perfusion and is the goal pressure recommended in the Surviving Sepsis Guidelines [12]. Trials of using higher MAP for all patients have been completed and have failed to show any difference in outcomes [33]. However, the optimal MAP for the patient should be individualized. A higher MAP may be required in patients with underlying atherosclerosis or preexisting hypertension. Likewise, younger patients with lower baseline blood pressures will tolerate lower MAP with sustained tissue perfusion. Blood pressures should not be a blind target and should be supplemented with other evidence of adequate end-organ perfusion such as mental status, skin perfusion, and urine output.

Norepinephrine remains the first-line vasopressor of choice in septic shock. Improving blood pressure results mainly from its vasoconstrictive effects and has some effect on heart rate and stroke volume. Dopamine may be useful in patients with decreased systolic function; however, its use is associated with more tachycardia and arrhythmias than norepinephrine, and its routine use should be avoided. Epinephrine has been recommended by some groups to augment or replace norepinephrine when a second agent is needed to maintain perfusion. Epinephrine may stimulate lactate production from skeletal muscle and decrease the utility of lactate clearance. Concerns for detrimental effects on splanchnic circulation are not unfounded, but there has been no evidence to date that shows an increased risk of death for using epinephrine over norepinephrine [12, 34, 35].

Vasopressin can be added to norepinephrine to aid in raising MAP, but doses higher than 0.04 U/min are only recommended for salvage therapy. In early septic shock, vasopressin levels are elevated and decrease to normal in most patients after the first 24 h. In the face of continued hypotension, vasopressin levels should be elevated, and this state is thought to represent a relative vasopressin deficiency. The clinical significance of relative vasopressin deficiency remains unknown [12].

Inotropic support may be needed in patients with adequate intravascular volume/adequate left ventricular filling pressures and adequate MAP with evidence of low cardiac output. Although both norepinephrine and epinephrine have some inotropic effect, dobutamine is the drug of choice in septic patients with decreased cardiac output, once euvolemia has been achieved.

Approximately 30 % of septic patients will have a transient elevation of cardiac enzymes during the course of septic shock. A recent investigation into the role of vasopressors and cardiac ischemia showed no difference in outcomes between patients receiving norepinephrine or vasopressin. Interestingly, transient troponin elevation had no effect on mortality [36].

Another recent investigation has focused on the role of beta-adrenergic blockade in septic shock. Though beta-blockers have been used in cardiovascular disease to reduce myocardial demand due to increased heart rate, they can have serious deleterious effects. The beta-adrenergic stimu-

lation and resultant tachycardia can also have deleterious effects in the septic patient, especially when compounded by tachycardia associated with vasopressors. There were no adverse events in the 77 patients with septic shock requiring norepinephrine to maintain a MAP>65 and treated with esmolol for HR>95. There was an additional trend toward decreased 28-day mortality as well [37]. Further study is needed before a generalized statement about the use of beta blockade in sepsis can be made.

Corticosteroids

Corticosteroids have been recommended as an adjunct to vasopressor-resistant septic shock. ACTH stimulation testing is no longer recommended prior to initiating glucocorticoid therapy, in the septic patient [12]. This change is based on the findings of the CORTICUS trial in 2008, which demonstrated no survival benefit to hydrocortisone therapy and failed to predict steroid responsiveness based on ACTH stimulation [38]. Doses of 200 mg of hydrocortisone per day are recommended (in divided doses) and should be tapered after vasopressors are no longer needed. Corticosteroids may reduce vasopressor dosages and duration; however, the mechanisms by which this occurs are still unknown. Definitive evidence to endorse or condemn steroids for septic shock is lacking, and large randomized controlled trials are needed to guide therapy in the future [12, 39, 40].

Transfusions

The transfusion of blood products is a common adjunctive therapy in patients with septic shock. Clearly, patients with ongoing hemorrhage in the setting of septic shock usually require transfusion, but other patients are transfused for anemia without the presence of hemorrhage as well. In the past, patients were routinely transfused to a hematocrit of 30 %, with the belief that increased red cell mass would improve tissue oxygenation and decrease myocardial ischemia. In Rivers' EGDT study, transfusions were used to target goal ScvO2, regardless of hematocrit. As early as 1999, the Transfusion Requirements in Critical Care (TRICC) study showed no benefit in transfusing the critically ill patient until hemoglobin fell below 7 g per deciliter [41]. These findings were corroborated by the Transfusion Requirements in Septic Shock (TRISS) study, which found that in patients admitted to the ICU with septic shock, there was no benefit in transfusing above hemoglobin of 7 g per deciliter [42]. With the increased recognition of adverse events related to blood transfusion, such as ABO mismatch, increased risk for infection, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO), the risk/benefit ratio must be thoroughly assessed by the treating physician prior to initiating transfusion.

Coagulation Disorders in Septic Shock

Sepsis causes systemic inflammation, endothelial injury, and microvascular thrombosis contributing to organ failure in animal and human models. However, evidence for a clinical hypercoagulable state in sepsis and septic shock is lacking. Recent prospective studies have shown that on admission to the ICU, most patients in septic shock present with a hypocoagulable state. Failure of the coagulopathy to resolve has been associated with increased risk of mortality [43]. Routine chemical prophylaxis for venous thromboembolism has been shown to be safe and effective and should be used in the absence of an absolute contraindication. Use of heparin in patients with septic shock or demonstrated DIC due to infection may also decrease mortality [44].

Activated Protein C

After promising results of a 6 % reduction in mortality for severe sepsis, activated protein C was approved for use in 2001. Its use was quickly advocated for in previous versions of the Surviving Sepsis Campaign Guidelines. In a recent, randomized, double-blinded placebo-controlled trial of nearly 1,700 patients, there was no evidence for a significant reduction in 28-day or 90-day mortality. The drug was subsequently removed from the market and its use is no longer recommended [12, 45].

Acute Kidney Injury and Septic Shock

Defined as an abrupt decline in renal function over the course of hours to days, acute kidney injury (AKI) is a serious, but potentially reversible, complication of septic shock. Over 50 % of all ICU admissions will be complicated by at least some degree of renal dysfunction. AKI clinically presents as a decrease in urine output, rise in serum creatinine, or buildup of nitrogen waste products. More accurately, acute kidney injury can be defined and categorized by the RIFLE criteria, set forth in 2002 by the Acute Dialysis Quality Initiative (see Table 22.3) [46].

Sepsis in the surgical patient presents a unique challenge to the surgical intensivist. Surgical procedures, trauma, general anesthesia, and emergent operations for source control all add to the underlying risk of AKI associated with sepsis and critical illness. AKI occurs in almost 70 % of all patients with surgical sepsis, and the risk approaches 90 % for patients with septic shock. Nearly all patients who develop AKI in

Table 22.3 RIFLE criteria for renal failure

	Creatinine criteria	Urine output criteria
Risk	Increased Cr × 1.5	UOP<0.5 mL/kg × 6 h
Injury	Increased Cr × 2	UOP<0.5 mL/kg × 12 h
Failure	Increased Cr × 3 or Cr ≥4 mg/dL	UOP<0.3 mL/kg/h × 24 h or Anuria × 12 h
Loss	Persistent ARF = complete loss of renal function >4 weeks	
ESRD	End-stage renal disease	

the setting of sepsis will do so in the first 7 days of the ICU course. Hypotension at the time of diagnosis is strongly associated with subsequent AKI and likely reflects the end result of hypoperfusion of the renal tissues. When acute kidney injury complicates sepsis, the risk of hospital mortality increases to 25 %. Additionally, patients with surgical sepsis complicated by AKI are more prone to other infections, multi-organ failure, increased ICU days, and decreased likelihood of discharge to home [47].

Treatment of AKI is supportive. Judicious fluid and electrolyte management, cautious use of diuretics for volume overload, and continued management of sepsis are necessary until the acute phase resolves. Consultation with the nephrologist should occur early in the course of acute kidney injury, and dialysis should be initiated if indicated. Fluid and electrolyte clearance are equivalent in both continuous and intermittent renal replacement therapy. However, due to decreased fluid shift and the ability to manage fluid removal on an ongoing basis, continuous renal replacement therapy is more appropriate in the patient with unstable hemodynamics due to septic shock [12].

ARDS and Sepsis

Acute respiratory distress syndrome, first defined by Ashbaugh in 1967, is broadly defined as acute hypoxemic respiratory insufficiency with bilateral pulmonary infiltrates on chest radiograph, not explained by left atrial hypertension. Multiple definitions and classifications have evolved since its description. The most recent iteration, the Berlin Definition, classifies ARDS on partial pressure of arterial oxygen to fractional concentration of inspired oxygen (P:F ratio) as mild (200<P:F≤300), moderate (100<P:F≤200), and severe (P:F≤100) [48]. Severe sepsis is the most common risk factor for ARDS in all patients and carries a mortality rate of nearly 40 %. Although a full iteration of the management of ARDS is outside the scope of this chapter, the general principles of ventilator management include lung-protective ventilation strategies (VT = 6 ml/kg IBW and Pplat ≤30 cm H20), liberal use of PEEP to assist oxygenation, and recruitment maneuvers and prone positioning for severe refractory hypoxemia [12]. Although concerns have been raised for intravenous fluid volumes causing or worsening ARDS, end-organ perfusion of the patient in septic shock should remain the top priority in resuscitation [24].

Neurologic Dysfunction in Severe Sepsis

Like all organ systems affected by the deleterious, systemic response to infection, the central nervous system may also be affected. The patterns of brain dysfunction in severe sepsis range from acute delirium to coma. Less commonly, severe sepsis or septic shock may cause focal neurologic deficits or seizures. These patterns of central nervous system dysfunction may be seen in up to 60 % of patients who develop severe sepsis or septic shock during their hospital course [49].

The neurological manifestations of severe sepsis and septic shock are thought to arise secondary to disseminated intravascular coagulation, and imaging findings are often similar to those in microvascular ischemic events. Although the initial workup for many of these patients will include a CT scan, MRI has been recommended as the test of choice due to its ability to reveal diffuse white matter lesions and increased sensitivity for ischemic stroke. These findings are associated with increased risk of inpatient mortality and decreased likelihood of discharge to home [50].

Multi-organ Dysfunction Syndrome

Like sepsis, severe sepsis, and septic shock, the damaging immune response associated with an infectious insult affects the organ systems along a continuum of severity. Multiple organ dysfunction syndrome (MODS) exists when organ function is compromised to an extent in the acutely ill patient that homeostasis cannot be maintained without intervention. The majority of deaths in the ICU due to septic shock are the end result of multiple failed organ systems. As discussed earlier in this chapter, the Sequential Organ Failure Assessment or SOFA score can be used to objectively quantify the degree of dysfunction in the cardiovascular, pulmonary, hepatic, renal, coagulation, and neurologic systems. This score can be easily recalculated daily based on the above parameters and provides an additional metric that accounts for the amount of global dysfunction of the patient with complicated sepsis. SOFA scores of greater than 15 points are associated with 90 % mortality.

Persistent Inflammation/ Immunosuppression Catabolic Syndrome

The successful management of severe sepsis and septic shock has allowed more patients with more severe degrees of organ dysfunction to survive much longer than in previous

decades. Often, these patients remain in the ICU for weeks to months with ongoing need for ventilator and renal support, low to moderate doses of vasopressors, and smoldering organ dysfunction. They develop secondary infections and receive multiple courses of antibiotics, drainage procedures, and numerous lines and catheters. This prolonged critical illness leads to progressive protein catabolism, muscle wasting, and failure to regain strength. We redefine success in these patients as discharge to a long-term acute-care facility, rather than return to meaningful functional status.

This syndrome of persistent inflammation, immunosuppression, and catabolism has been termed PIICS by Moore and colleagues. Their criteria include a prolonged hospital course greater than 14 days, laboratory evidence of persistent inflammation as a C-reactive protein>150 mcg/dL, immunosuppression with total lymphocytes <800/mm3, and catabolism with weight loss>10 % over hospital stay, marked by albumin<3 mg/dL, prealbumin<10 mg/dL, or retinol-binding protein<10 mcg/dL. Correcting the trajectory for these patients is difficult and their potential for rehabilitation, at this time, is dismal. As the therapeutic management of severe sepsis and septic shock continues to advance, caring for these patients will provide new challenges for rehabilitation and surgical nutritional support [51].

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23 Source Control and Supporting Therapeutics: Integrating Bacterial Invasion, Host Defense, and Clinical Interventions with Source Control Procedures

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Introduction

Surgeons are integrally involved in addressing devitalized, perforated, or infected organs and tissue. The integrated moniker appended to this practice regardless of complexity is "source control" [1, 2]. Nonetheless, such undertakings have not occurred in a vacuum and have relied on and benefitted from the synergistic effects of fluid resuscitation and adjunctive antimicrobials agents to improve patient outcome. Advances in technology, particularly in catheter-based and imaging technology, have changed the landscape of source control by eliminating or delaying operative therapy for certain conditions that would have been previously managed primarily by an operative procedure. Prime examples include the postoperative abscess or diverticular perforation and/or abscess where drainage by interventional radiology instead of early operation may be performed.

Such practices, while designed to limit patient morbidity and hailed as routinely benefiting patients by reducing operative risk, may engender other practices that may not be as beneficial. Repeated imaging with ionizing radiation, prolonged periods of partially controlled infection with persistent activation of pro- and anti-inflammatory cascades, extended courses of antimicrobial agents with subsequent induction of multidrug-resistant organisms (MDRO), and the multiple readmissions for catheter malposition or dislodgement are all potentially anticipated but undesired consequences of less invasive approaches that consume resources and may engender poor outcomes [3, 4]. Prolonged antibiotic therapy in particular is associated with untoward outcomes characterized by increased infection-related morbidity and mortality, especially if prior therapeutic administration is not considered when prescribing empiric therapy [5, 6].

The ability to effectively clear incompletely drained or débrided foci of pathogens is altered by the presence of biofilm, specific organism virulence factors, neutrophil delivery and function, and the ability (or inability) to adequately deliver antibiotics to the site of infection [7]. Advances in human genome typing and the integration of genomics and proteomics with clinical circumstances have improved our understanding of how individual pheno- and genotypes respond to self and nonself bacterial challenges. As an example, individuals who are at higher risk for persistent postoperative hyperalgesia following thoracotomy can now be identified by preoperatively examining their DNA profile. Armed with that data, the anesthesiologist may craft an appropriate anesthetic and analgesic technique to mitigate that risk. This conceptual approach has been identified as the "perioptome" [8]. The Research Outcomes Consortium is delineating the host response to injury and inflammation at the genome level; no similar analysis is underway related to infection [9]. Since genome manipulation to improve outcome after infection is not realistic at present, the clinician must rely on standard approaches to infection management. Accordingly, this manuscript will review existing source control practices and integrate them with factors that may influence the host response to infection including metabolic derangements, plasma volume expansion, organ failure, biofilm, immunonutrition, immunomodulators, evolving organism virulence factors, and epigenetics.

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Source Control

In 2001, John Marshall popularized the term "source control" to encompass all of the physical interventions (surgical and other) that are used to treat infection, including those to eliminate the infection source, control ongoing contamination when present, and restore premorbid anatomy and function [10]. He described a standard approach to surgical infection that embraced (a) fluid resuscitation to ensure adequate delivery of neutrophils, oxygen, and antibiotics to the site of infection; (b) adjunctive antibiotics to support host defenses and control bacterial tissue invasion; and (c) the key element – control of the source of infection [11]. This approach has been used successfully for decades and is well applied to the debridement of devitalized tissue as in a necrotizing soft tissue infection, resection of a perforated or ischemic intestinal segment, or drainage of a localized peritoneal abscess.

Application of the source control conceptual framework is less clear in some circumstances that complicate surgical critical care. These problematic circumstances include but are not limited to central vein catheter-related infection with an intravascular biofilm sheath, tertiary peritonitis, entero-atmospheric fistula in a patient with an open abdomen, and MDRO pneumonia in a patient with persistent respiratory failure. Other circumstances that may provide similar challenges include peri-prosthetic spinal hardware infection with osteomyelitis where hardware removal would create an unstable spine, a percutaneously drained abscess with a persistently positive drain culture, as well as sinusitis in an orally intubated patient in the ICU. Infection resolution failure may reflect the inability to resect the infected structure, an inability to respond to therapy due to immunoincompetence, or the inability to deliver antibiotics to the intended site.

Changes in Source Control Procedures

Despite the importance of adequate source control in the management of surgical infections, particularly intra-abdominal infections, there is a trend toward nonoperative methods of source control. Percutaneous image-guided drainage procedures are now the standard for the initial, and perhaps final, management of most isolated and even multiple intra-abdominal abscesses [12–17]. Similarly, a minimally invasive step-up approach (percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy), as compared with open necrosectomy in patients with necrotizing pancreatitis and infected necrotic tissue, reduced the rate of the composite endpoint of major complications or death [13]. However, the appropriate selection of patients for this approach is complex, and current studies frequently do not include severely critically ill patients or those with multiple complex collections. In poorly selected patients, such approaches may not achieve an ideal outcome.

Recent data has improved our understanding of patients that may respond to antibiotics without complete drainage. In a meta-analysis of the nonsurgical management of patients with perforated appendicitis with either localized appendiceal abscess or phlegmon, more than 80 % were treated without any source control procedure. In these patients, the lack of source control was related to either the presence of a phlegmon without abscess, small abscess size, or the lack of an access route for abscess drainage. Interestingly, in these patients, nonsurgical treatment failed in only 7.2 % of patients, and the risk of recurrence was 7.4 % [14]. Another meta-analysis comparing nonoperative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon) with 1,572 patients found a decreased complication and reoperation rate with conservative management [15]. These data support the practice of nonsurgical treatment without interval appendectomy in patients with appendiceal abscess or phlegmon in patients similar to those who met the inclusion/exclusion criteria of these studies.

In contrast, a meta-analysis of randomized controlled trials (RCTs) comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis reported that nonoperative management with antibiotics was associated with significantly fewer complications, better pain control, shorter sick leave, but overall had inferior efficacy because of a high rate of recurrence in comparison with appendectomy [16]. Other systematic reviews have confirmed these findings [17, 18]. Additionally, the dramatic increase in the use of computerized tomography to diagnose appendicitis complicates the interpretation of recent studies versus older studies due to the increase in identification of appendiceal inflammation. Since only a small number of RCTs of poor methodological quality are available, additional well-designed RCTs are required.

We have clearly entered a new era in which less invasive strategies for source control are increasingly utilized. The adequacy of source control must be considered in the conduct of clinical trials in surgical infections for the future to appropriately interpret results of therapeutic interventions and strategies.

Source Control and Clinical Trials

Inadequate source control has been identified as a significant risk factor for adverse outcome in surgical trials. The importance of source control in the management of intra-abdominal infections is evident, and the failure or inability to achieve adequate source control is associated with worse clinical out-

Table 23.1 Adequacy of initial source control in the PROWESS trial

	Drotrecogin-alfa	Placebo	Total
	$N=177$	$N=182$	$N=359$
	n (%)	*n* (%)	*n* (%)
Adequate	90 (50.8)	86 (47.3)	176 (49)
Inadequate	38 (21.5)	51 (28)	89 (24.8)
Indeterminate	49 (27.7)	45 (24.7)	94 (26.2)

Data from Barie et al. [22]

come in terms of increased rates of treatment failure and increased mortality [19, 20]. In this context, inadequate source control represents the composite of several situations including the inability or the unsuccessful attempt to drain or remove all infected material, recurrence of infection despite early control, and the failure to heal suture lines and anastomoses. A recent study of 224 patients with septic shock and candidemia reported that hospital mortality for patients having adequate source control and antifungal therapy administered within 24 h of shock onset was 52.8 % ($n=142$) compared to 97.6 % ($n=82$) in patients with inadequate therapy ($p<0.001$) [21].

Inadequate source control may also explain a large portion of clinical failures in trials of antimicrobials and other agents studied for sepsis treatment. A surgical evaluation committee adjudicated the adequacy of source control of surgical patients in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial and determined that the initial source control procedure was adequate in only 50.8 % of drotrecogin-alfa (activated) and 47.3 % of placebo patients (Table 23.1). During the 28-day study period, source control was definitively adjudicated as adequate in only 57.1 % and 56.6 % (103 of 182) of the drotrecogin-alfa (activated) and placebo patients, respectively [22]. Despite these important findings, not all clinical trials of infections that require source control have adopted the approach to include objective evaluation of adequacy of source control in the clinical trial design and conduct.

Source Control Issues Related to Pathogens

Bacterial Invasion and Multidrug-Resistant Organisms (MDRO)

A brief review of bacterial resistance is in order as MDRO pathogens are relatively new but occur in the context of conserved microbial constituents such as LPS or lipoteichoic acid that trigger the repertoire of the human immune system's response to bacterial invasion. A host of bacterial characteristics enable invasion despite the panoply of human host defense mechanisms. Bacterial virulence factors that enable either evasion of host defense agents (immune effector cells, complement, immunoglobulins) cause the dysregulation of host defenses (T helper cell activation by superantigens such as streptococcal spe-A, spe-B, and spe-C), enable resistance to administered antimicrobials agents, and enhance tissue invasion are protean. Additionally, toxin production from noninvasive organisms also may create severe disease without bacterial invasion. The prime example is *Clostridium difficile*, in which *C. difficile*-associated colitis may cause severe illness without tissue invasion, the incidence of which and number of related hospital admissions have increased significantly over the last decade [23–27]. Over the past several decades, patient acuity has steadily risen and is associated with a decrement in immune competence that may significantly compromise how an individual patient responds to a bacterial challenge. Increasing patient acuity is also accompanied by the rise of multidrug resistance in both Gram-positive and Gram-negative organisms and directly impacts resource utilization, care cost, as well as outcome [28]. An abundance of data demonstrates that all areas of patient care (home, outpatient office, nursing home, skilled nursing facility, rehabilitation facility, outpatient procedure center, and acute care inpatient hospital) are beleaguered by MDROs [29].

Both infection control practices and antibiotic stewardship programs have been employed as measures to reduce the prevalence of MDRO and the antibiotic selection pressure that drives the genesis of resistant pathogens [30, 31]. While few data conclusively support preemptive isolation of all patients admitted to an acute care facility until proven to be free of MDRO colonization or infection, isolation is a common practice [32]. Variations include weekly swabs for MDRO detection, isolation of those from chronic care facilities, isolation of all ICU patients, or isolation of those who have previously been proven to have been colonized or infected with MDRO (typically MRSA, VRE, or extended spectrum beta-lactamase (ESBL)-producing Gram-negative rods). For example, a major infection control intervention is hand hygiene using alcohol-based cleansing agents that is ubiquitous in acute care facilities, shopping malls, coffee bistros, and grocery stores and is the subject of regular review by hospitals organizations as well as patients and visitors [33, 34]. Nonetheless, infection control practices do not alter MDRO genesis, instead only altering transmission but may impact the empiric antimicrobial agents that are selected to accompany source control procedures.

Antimicrobial prescriptive practice control may assume many forms with varying degrees of success in reducing resistance pressure and control of MDRO genesis. Formulary control to limit the ability to prescribe certain antimicrobial agents alone or in combination has been a time- and finance-honored practice in many institutions and is part of a practice known as antimicrobial stewardship [35–37]. Generally, such control rests with an infectious disease specialist as

well as with pharmacy. Such practices have demonstrated some efficacy in institutions with a low prevalence of MDRO but may be less effective in those with high prevalence rates. Instead, formulary control may lead to the relatively homogeneous use of an only limited array of antimicrobial agents. Instead, current data supports antibiotic heterogeneity as a means of reducing selection pressure by presenting microbes with an array of antimicrobial agents [38, 39]. Either no restriction or a preplanned sequencing of antibiotics (undertaken with a wide variety of methods) can achieve antibiotic heterogeneity. The degree of heterogeneity may be calculated as an antibiotic heterogeneity index (AHI), with a target index exceeding 0.85, where an index of 1.0 indicates complete heterogeneity. Investigations into the deliberate management of antibiotic heterogeneity note reduced MDRO genesis with such programs [40]. As such, antibiotic heterogeneity may provide one arm of an overarching source control program by deliberately influencing the spectrum of microbes that may need to be addressed in hospitalized or long-term care facility patients who require source control [29].

Organism Virulence Factors

There are a host of traditionally identified virulence factors that span the elaboration of biofilm, endotoxin, exotoxins, M proteins, and superantigens. However, as genomic and proteomics analysis advances, our understanding of the molecular underpinnings of bacterial-host interactions is further illuminated. Some examples include worsened acute lung injury during pulmonary infection with *P. aeruginosa* related to deletion of host aquaporin 5 from type I alveolar epithelial cells, an aquaporin that appears related to mucin production as well as dendritic cell antigen presentation – key actions in host airway defense [41].

Relatedly, different strains of *P. aeruginosa* isolated from critically ill patients were assessed for their relative virulence impact using a murine model. In this model, the type 3 secretion system (exotoxin release) and quorum sensing regulated elastase appeared to confer the greatest virulence and may be suitable targets for specific intervention [42]. Similarly, adhesin barrier-disruption activity (another quorum sensing regulated gene product) has been tied to the ability of small bowel luminal *Pseudomonas aeruginosa* to translocate and confer near uniform lethality in a murine model of intestinal ischemia and reperfusion injury [43]. Understanding such mechanisms may help devise strategies that target specific virulence factors to help manage the bacteria that remain behind in tissue or gain access to the bloodstream during source control procedures.

Acinetobacter has emerged as a major nosocomial MDRO, facilitated by tolerance to desiccation and multidrug resistance. Recent studies document that *Acinetobacter* produce autoinducers, hormonelike molecules, as signals to sense cell density and activate adaptations by quorum sensing (QS). Quorum sensing by autoinducer-receptor mechanisms plays a role in biofilm formation in *Acinetobacter* infections [44]. Strategies that either inhibit QS or cause the premature expression of QS-regulated genes (quorum quenching) could provide broad-spectrum control of particular bacterial diseases such as *Acinetobacter* infections (Fig. 23.1). Inhibition of quorum sensing signals, which further regulates biofilm production and possibly other virulence genes, has been targeted for development of novel therapeutics [45].

While there are a host of organism virulence factors, the key feature is that as we augment our understanding of those factors, we may derive specific interventions that inactivate key virulence factors (including biofilm) or enhance host defense against those factors. Such interventions are not currently available but form the horizon of forward-looking undertakings that potentially enable source control *prior* to host invasion.

Biofilm

Biofilm is an extracellular exopolysaccharide matrix that is elaborated by a wide variety of organisms that provides a supportive matrix of nutrient sequestration enhancing bacterial proliferation, as well as a physical, chemical, and electrostatic barrier to antibiotic ingress. As such, biofilms allow a community of disparate bacteria to function together to channel water pathways for enhanced growth success (even if at a reduced rate of division) and sharing of genetic material between promiscuous strains [46, 47].

Biofilms have been noted to be a cause of persistent infection even after presumed appropriate therapeutic antimicrobial administration [48]. Biofilm composition includes polysaccharides, extracellular DNA, proteins, autolysins, and adhesins that also facilitate bacterial communication using quorum sensing molecules [49]. As such, biofilm reduces the efficacy of administered antibiotics even when the target bacteria are judged susceptible both in vitro and in vivo.

Mechanical methods of biofilm disruption in open body cavities such as the peritoneal space or the pleural space maybe partially effective, but such methods are not suitable for the intravascular space. Perhaps most prominently, biofilm is identified coating the inner aspect of indwelling endotracheal tubes of all varieties where it reduces the available inner diameter for gas flow and may result in increased airway pressures and reduced CO_2 clearance and may precipitate unplanned tube changes – a potentially dangerous event in certain patient populations. Biofilm-related diseases involving the respiratory system include cystic fibrosis, diffuse panbronchiolitis, and bronchiectasis, all of which are

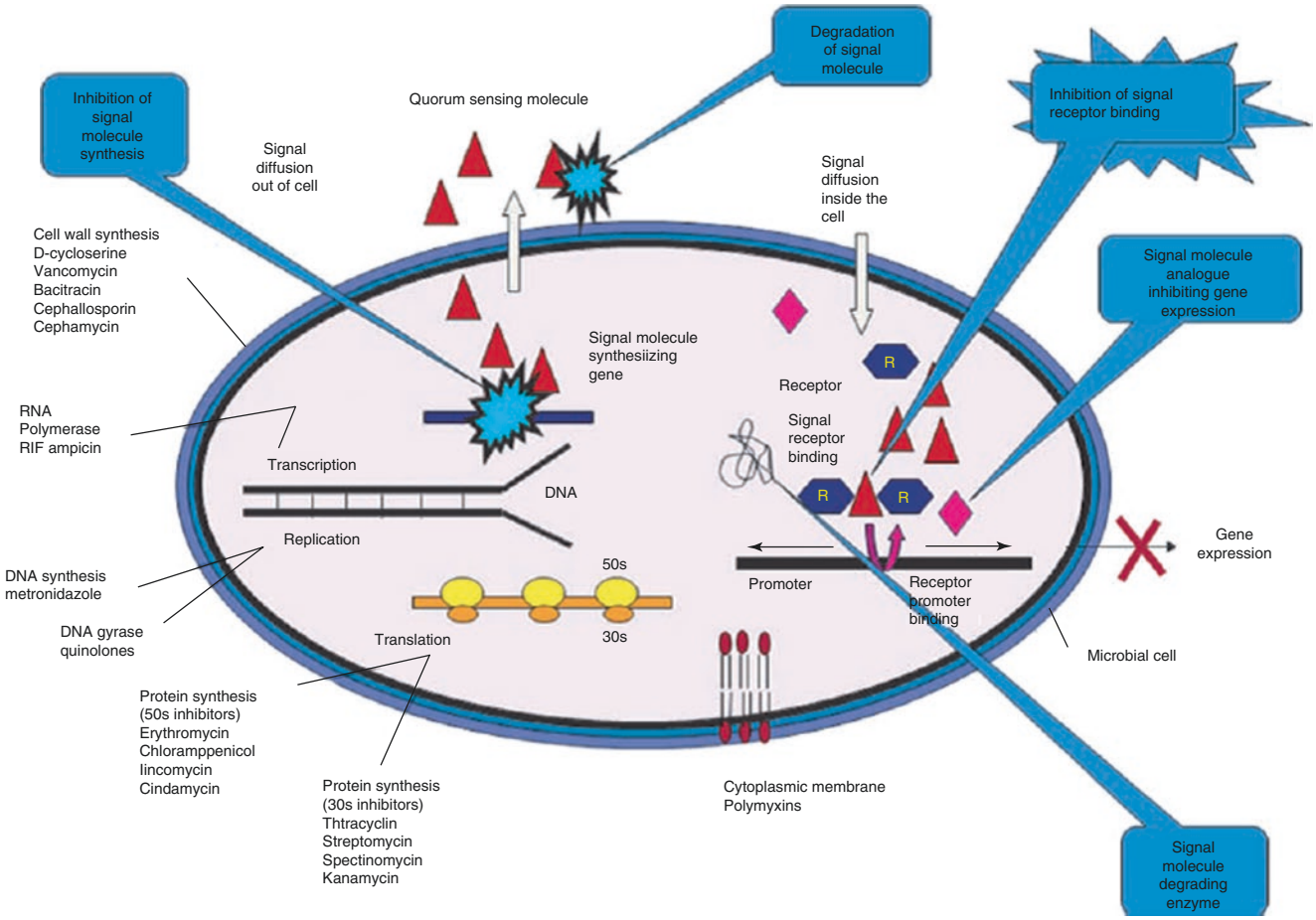

Fig. 23.1 Modes of action of both antimicrobial agents and quorum quenchers in *Acinetobacter* (From Bhargava et al. [44] reprinted by permission of Taylor & Francis Ltd, http://www.tandfonline.com)

difficult to fully eradicate [50]. Biofilms are also key in implant-associated infections, particularly in orthopedic and vascular surgery, and source control in implant-related infections commonly requires implant removal.

Organisms that are well known to elaborate biofilm include methicillin-resistant *Staphylococcus aureus*, coagulase-negative *Staphylococcus* spp., *Pseudomonas* spp., *Klebsiella* spp., *E coli*, *Proteus* spp., *Morganella* spp., *Acinetobacter* spp., and *Streptococcus* spp.; others have been reported although less frequently than those above including *Salmonella* spp. and *Pasteurella* spp. Note that many of the reported organisms are members of the ESKAPE ensemble of pathogens noted for ESBL production or inducibility [51].

More importantly, novel delivery methods to penetrate biofilm to enhance antibiotic efficacy are essential. Recently the nonpathogenic bacterium *B. subtilis* has been found to produce a quartite of D-amino acids that has efficacy in disruption biofilms and offers a potential method of biofilm management in clinical care [52]. In fact, time-honored methods of managing difficult bacterial infections such as honey have been noted to impede biofilm formation [53].

Biofilm-associated bacterial growth plays a key role in bacterial adaptability and antibiotic resistance. Drugs that could slow growth in biofilm-associated infections could have significant efficacy in these infections. A recent study used a systems biology approach to identify drug targets in biofilm-associated *Pseudomonas* infection using metabolic modeling to study the effect of gene deletion on bacterial growth and served as a powerful tool to identify novel candidate antibiotic targets [54]. Promising strategies for biofilm-associated infections may include the use of compounds that can dissolve the biofilm matrix and quorum sensing inhibitors, which increases biofilm susceptibility to antibiotics and phagocytosis [55].

Source Control Issues Related to the Host

Metabolic Derangements

Perhaps the most common serious metabolic derangement that drives therapeutic decisions is metabolic acidosis. On hospital entry, metabolic acidosis is most commonly related

to hypoperfusion in the absence of underlying renal or hepatic failure. In sharp contradistinction, patients who have undergone fluid resuscitation may have their acidosis establish by induced hyperchloremia instead of stemming from lactic acid derived from anaerobic metabolism [56, 57]. Importantly, there is an increased mortality associated with hyperchloremic metabolic acidosis in patients admitted to the ICU regardless of admission diagnosis [58].

However, all acidoses are not alike with regard to host response. In cultured RAW cells made acidotic with lactic acid as opposed to chloride from hydrochloric acid, equivalent pHs were established, but very different nuclear and intracellular signaling responses were identified [59]. In particular, cells rendered acidotic with chloride demonstrated differential activation of NF-kB as well as upregulation of nuclear domains that are associated with inflammation. Lactic acid, the downstream effect of hypoperfusion, demonstrated the opposite pattern consistent with an anti-inflammatory response despite an identical pH. Unchecked inflammation is thought to be maladaptive and related to multiple organ failure following infection or injury. Therefore, while these cell data are devoid of a readily translatable clinical correlate, modulation of the host immune response with avoidance of hyperchloremia is a readily achievable and logically supported therapeutic goal that may help with managing untoward host responses (inflammation) to infection.

On the other hand, there is clinical data with regard to ICU relevant outcomes. Such a strategy is associated with a shorter time to pH normalization, reduced total fluid resuscitation, and importantly, reduced minute ventilation needs [60]. Unfortunately, this study did not measure plasma or bronchoalveolar lavage or aspirate fluid levels of commonly inflammatory mediators such as TNF-α, IL-6, or IL-8. Reduced minute ventilation may support reduced pulmonary inflammation by decreasing the opening and closing of incompletely recruited alveolar segments, a process that leads to inflammation from shear stress along the common wall and is known as intratidal shear [61, 62]. Decreasing the frequency of intratidal shear in lungs that may have direct or indirect lung injury, capillary leak, and increased extravascular lung water may be one important way to modulate overall inflammation in those requiring mechanical ventilation. While intuitively attractive, the above hypothesis remains unproved but a reasonable avenue of future research.

Plasma Volume Expansion

This topic is linked to metabolic derangements through electrolyte-induced abnormalities of acid-base balance, specifically hyperchloremic metabolic acidosis (HCMA). Normal saline solution (0.9 % NSS), the most ubiquitous resuscitation fluid utilized in the USA and the world, is associated with the induction of HCMA through the delivery of fluids with a chloride concentration above that of plasma [63]. Thus, avoiding inducing HCMA may be an appropriate therapeutic target to achieve. Several studies have identified successful strategies to avoid or reduce HCMA including the use of colloids (less chloride delivery), custom crafted fluids (lower chloride content than standard crystalloids), as well as damage control resuscitation (DCR) since biologically active colloids have a lower chloride content than crystalloids and are used in preference to crystalloids [64]. The association of reduced HCMA as it impacts DCR has yet to be explored.

The Saline versus Albumin Fluid Evaluation (SAFE) trial randomized nearly 7,000 critically ill patients to albumin vs. normal saline and demonstrated no difference in mortality. However, in a subgroup analysis of 1,218 patients with severe sepsis, albumin resuscitation was associated with a trend toward reduced mortality (RR of death 0.87, 95 % CI 0.74–1.02) despite using a hyperchloremic diluent for the albumin [65]. It is likely that any signal from hyperchloremia would have been masked by the trial design that included only hyperchloremic fluids. Nonetheless, a recent systematic review and meta-analysis regarding albumin as a resuscitation fluid for patients with sepsis reported a significant mortality benefit (RR 0.82, 95 % CI 0.67–1.00) – an observation that may be related in part to albumin's pharmacologic and toxic oxygen metabolite-scavenging properties [66].

There are currently at least two important randomized clinical trials, including the Volume Replacement with Albumin in Severe Sepsis trial (ALBIOS, $n = 1{,}818$, 4 % albumin to achieve serum albumin 3 g/dL vs. saline) and the Fluid Resuscitation in Early Septic Shock trial (PRECISE, NCT00819416, phase II clinical trial, 5 % albumin vs. saline for first 7 days of ICU care). The pilot PRECISE trial met the prespecified feasibility targets for patient recruitment, and the PRECISE team is planning the larger trial [67, 68]. The ALBIOS trial found no improvement in the rate of survival regardless of resuscitation fluid selection, but both fluid arms had significant chloride loading since albumin is mixed in saline. An additional study in France (Early Albumin Resuscitation during Septic Shock, NCT00327704) completed enrollment in March 2010 (794 patients) and compared 20 % albumin (Vialebex) 100 ml every 8 h versus saline 100 ml every 8 h during the first 3 ICU days, but has found no outcome benefit.

Avoiding HCMA may have other benefits related to the delivery of neutrophils, oxygen for oxidative burst-based bacterial destruction, as well as antibiotic agents through preserving an open microcirculation. Recall that RBC deformability is essential for passage through capillary beds. Such passage is upended by tissue edema and is impeded by rouleaux formation, a key element in the "no reflow" phenomenon identified in reperfused beds [69]. An elegant study

evaluating how acidosis interacts with RBC volume and shear stress at low and high flow rates noted that acidosis increased RBC volume by 7% [70]. Importantly, this increase in size is reversible in the laboratory with NaOH, with $NaHCO_3$ being the clinical correlate. This increase in volume and the effects of acidosis on protein structure and function may be sufficient to uncouple the spectrin linkage system that is critical for microtubular array anchorage and membrane deformation to enable RBC passage through small capillary channels [71, 72].

Interestingly, impeded RBC deformability is also noted when RBC are superfused with lymph derived from the mesenteric system of rodents with peritonitis in a cecal ligation and puncture model [73]. While the pH and chloride content of the lymph was not assessed, the similar impact on RBC deformability is compelling. Thus, avoiding HCMA may be appropriate to explore as one means of supporting innate host defense in the context of a source control procedure by enabling delivery of host defense agents as well as exogenous therapeutics. It is important to note that virtually no study of surgical infection, innate immunity, or source control is parsed on the basis of acid-base status sorted by the presence or absence of HCMA and perhaps therefore merits investigation.

Adequacy of resuscitation in infection and sepsis is a primary goal and is a major component of adequate source control [74]. Recent studies, however, have identified that overresuscitation may be harmful. A post hoc analysis of the Vasopressin in Septic Shock Trial (VASST) study concluded that a more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 h [75].

Excessive fluid resuscitation increases the risk of abdominal compartment syndrome in critically ill surgical/trauma, burn, and medical patients [76–78]. Similarly, in a multicenter study of burn patients, administration of excessive fluids (>25% of predicted) increased the odds of ARDS (odds ratio [OR] 1.7), pneumonia (OR 5.7), multiple organ failure (OR 1.6), bloodstream infections (OR 2.9), and death (OR 5.3) [79].

It is now widely recognized that resuscitation fluids are not innocuous and may potentiate the cellular injury caused by hemorrhagic shock [80]. This concept of "resuscitation injury" has steadily gained attention since a report by the Institute of Medicine (1999) described in detail the wide spectrum of adverse consequences that can follow resuscitative efforts [81]. An ever-increasing basic science literature supports the new paradigm that cellular injury is influenced not only by shock but also by our resuscitation strategies. Commonly used resuscitation fluids can exaggerate immune activation. Therefore, in addition to the immediate side effects, delayed complications of fluid resuscitation such as systemic inflammatory response, fluid overload (leading to compartment syndromes, pulmonary edema), dilutional anemia and thrombocytopenia, electrolyte and acid-base abnormalities, as well as cardiac and pulmonary complications must be considered [82, 83].

Organ Failure

The influence of organ failure has been well described with regard to its impact on infection, with hepatic failure and pulmonary failure incurring the greatest risk for infection-related morbidity and mortality [84, 85]. However, there is comparatively less data on how organ failure management hinders or enables host defense. Since mechanical ventilation carries with it a well-characterized risk of ventilator-associated pneumonia (now ventilator-associated conditions and events), study in this organ system may be less ideal. Instead, those requiring renal support techniques would seem to be an ideal population in which to evaluate the impact of organ failure mitigation or management on host defense. Unlike mechanical ventilation, renal support may be started or stopped in a preplanned fashion to test specific hypotheses.

The majority of relevant data in renal failure derives from those with continuous renal support technologies. In this subset of individuals with acute kidney injury (AKI), continuous technologies allow one to collect, measure, and evaluate the effluent. Such analyses have identified high concentrations of both inflammatory and anti-inflammatory mediators in the effluent [86]. Patients who have severe sepsis or septic shock and undergo continuous renal support may derive a significant improvement in hemodynamics and outcome. Specifically, improvements in immune competence, antigen presentation ability, leukocyte trafficking, neutrophil oxidative capacity, and responsiveness may be identified in septic patients undergoing continuous renal support [87]. Patient selection for this intervention remains unclear and is complicated by different indications for renal support, different therapeutic targets, different dialysis doses, changes in filter bioincompatibility, and different durations of therapy. Furthermore, unlike virtually all other ICU therapies that are titrated off, continuous renal support is most commonly abruptly terminated without well-defined criteria or a weaning period. Nonetheless, since current renal support technology can manage fluids, electrolytes, pH, and a host of toxins, those with AKI both with and without infection remain an ideal target population for study of organ failure mitigation and infection.

Immunonutrition and Immunomodulation

While severe protein-calorie malnutrition is recognized to impede host bacterial defense by reducing the efficacy of neutrophils in particular, the ability to enhance host defenses

remains inadequately clarified and appreciated. Few interventions, other than addressing relative or absolute deficiencies in vitamins (in particular Vitamins C and D) and trace elements, have been documented to support outcomes, with most of the benefits identified in wound healing rather than enhanced cellular or humoral defense mechanisms; some benefits have been identified after injury [88]. Specific formulae of amino acids as well as lipids (omega-3 and omega-6 fatty acids) may influence inflammation management through Toll-like receptor (TLR) and protein-associated molecular pattern interactions in septic patients [89]. Nonetheless, no specific immune-enhancing formula appears suitable for all infection-related conditions, and benefit has not been universally realized. The RCT comparing twice-daily enteral supplementation of omega-3 fatty acids, gamma-linolenic acid, and antioxidants compared with an isocaloric control in adult patients with acute lung injury was stopped early for futility after 272 patients were enrolled and reported no difference in clinical outcomes [90].

While not traditionally thought of as immunonutrition, enteral nutritional support as opposed to parenteral nutrition also enhances immune competence. Luminal nutrition enhances gut mucosal barrier function, reduces translocation, and may reduce infection-related complications, although not mortality [91]. Interestingly, the results of the EDEN study, a RCT of adult ICU patients ($n=1{,}000$) with acute lung injury requiring mechanical ventilation conducted through the ARDS Clinical Trials Network, documented that a strategy of initial trophic enteral nutrition, compared with full enteral feeding for the first 6 days, did not improve ventilator-free days, 60-day mortality, or infectious complications but was associated with less gastrointestinal intolerance [92]. Therefore, we now recognize that the early provision of enteral nutrition, even at low-caloric volume, is adequate in critically ill patients to support infection-related outcomes.

The Society of Critical Care Medicine/American Society of Parenteral and Enteral Nutrition (SCCM/ASPEN) Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient recommend that enteral nutrition (EN) is the preferred route of feeding over parenteral nutrition (PN) for the critically ill patient who requires nutrition support therapy (Grade B) [93]. Furthermore, if early EN is not feasible or available over the first 7 days following ICU admission, no nutrition support therapy should be provided (Grade C). In the patient who was previously healthy before critical illness with no evidence of protein-calorie malnutrition, the use of PN should be reserved and initiated only after the first 7 days of hospitalization (when EN is not available). If there is evidence of protein-calorie malnutrition at admission and EN is not feasible, it is appropriate to initiate PN as soon as possible following adequate resuscitation (Grade C).

Controversy exists regarding the timing of initiating parenteral nutrition in critically ill adults in whom caloric goals are not met by enteral nutrition alone. A multicenter observational study ($n=2{,}920$) found that although the supplemental use of parenteral nutrition improved provision of calories and protein, it was devoid of clinical benefit [94]. A large RCT in adult ICU patients compared early initiation of parenteral nutrition 48 h after ICU admission ($n=2{,}312$) vs. late initiation, defined as not before day 8 ($n=2{,}328$) [95]. A protocol for early initiation of enteral nutrition was applied to both groups, and insulin was infused to achieve normoglycemia. Late initiation of parenteral nutrition was associated with faster recovery (reduced mechanical ventilation and renal support therapy) and significantly fewer ICU infections (22.8 % vs. 26.2 %, $p=0.008$) when compared with early initiation of parenteral nutrition. These studies confirm the potential adverse effects of parenteral nutrition in critically ill patients, particularly related to risk of hospital-acquired infections. While these studies did not perform a direct comparison of EN and PN, the high rate of infectious complications should steer one away from PN except under proscribed circumstances.

Since gut-associated lymph appears inflammatory and may be related to the induction of multiple organ failure, specific formulation of luminal nutrition offers the potential to impact the human genomic response to bacterial challenge by mitigating against small bowel lymph-directed inflammation; such interventions may minimize bacteria or bacteria-product translocation [96]. To wit, one recent study using molecular fingerprinting documented that gut-derived bacteria may be recovered from remote sites following small intestinal manipulation offering the therapeutic target of enabling gut mucosal barrier integrity and function to reduce the incidence of bacteremia and remote infection [97].

Epigenetic Phenomena and Receptor-Ligand Interactions

Observations from septic patients are relevant to understanding the outcomes of patients who have undergone source control procedures in that septic patients have reduced long-term survival in comparison to age-matched healthy controls [98]. A durable feature of sepsis survivors is the significant occurrence of recrudescent as well as secondary infections during their index and subsequent hospitalizations [99]. Certain phenomena related to postinfection phenotypic modifications may be instructive in understanding the molecular underpinning of host adaptive or maladaptive responses, including the aforementioned increased susceptibility to subsequent infection, and perhaps increased mortality.

The study of such genomic alterations without altering an organism's genomic content is known as epigenetics. While

the breadth of epigenetics and receptor-ligand interactions is well beyond the scope of this manuscript, certain features merit review, in particular: (1) support of persistent inflammation driven by the interactions of microbial pathogen-associated molecular patterns (PAMPs) that activate innate immunocytes through pattern recognition receptors and damage-associated molecular patterns (DAMPs) and (2) histone tail methylation with activation or suppression of particular gene sequences [100].

PAMPs such as Toll-like receptor 2 (TLR-2; Gram-positive infection) and TLR-4 (Gram-negative infection) incite broadly based inflammation via the well-characterized cytokine response and in particular increase IL-12, a key molecule in bacterial defense [101]. However, in post-septic immunosuppression, the cytokine response to subsequent nonself protein challenge is reduced [102]. By way of example, dendritic cells are depleted following sepsis, and when peripheral repopulation is allowed to occur, the newly resident dendritic cells demonstrate reduced responsiveness as evaluated by IL-12 production to fungal challenge [103]. The finding provides a mechanistic explanation for host defense failure observed in tertiary peritonitis patients and may allow one to understand how patients succumb to pathogens that are sensitive to the prescribed antimicrobial agents. Recall that antibiotics remain an adjunct to endogenous defense mechanisms. Understanding how host defense failure occurs may offer future therapeutic target for intervention designed to enhance endogenous mechanisms.

As a result of bacterial invasion or host inflammation – in particular following ischemia-reperfusion injury – injured cells release or elaborate DAMPs such as hypoxia-inducible factor, high mobility group box protein-1, and extracellular DNA. A recent human study in major trauma patients documented that injury releases mitochondrial DAMPs into the circulation which activate neutrophils through formyl peptide receptor-1 and TLR-9, leading to neutrophil migration and degranulation, resulting in SIRS and a sepsis-like state which can elicit neutrophil-mediated organ injury [104]. Thus, infection that requires resuscitation can lead to remote organ injury that are causally related to inflammatory mechanisms instead of being directly related to invasive pathogen products.

Extracellular DNA when accompanied by histones is termed a nucleosome [105]. Of key importance is that histones are toxic to bacteria when present in high concentration and, based on their structural relationship to the DNA helix, have protruding tails [106]. It is these tail regions that may be methylated and result in significant functional alterations in gene activation or suppression [107, 108]. Histone deacetylases (HDACs) play a key role in homeostasis of protein acetylation in histone and non-histone proteins and in regulating fundamental cellular activities including cell survival, repair, healing, autophagy, and anti-inflammation. HDAC inhibitors have been shown to exert anti-inflammatory activities via the suppression of inflammatory cytokines and nitric oxide and have pro-survival and anti-inflammatory properties, resulting in improved survival in septic shock models [109, 110].

It is likely that despite substantially reducing the bacterial burden present in a necrotizing soft tissue infection by radical excisional debridement, an abscess by percutaneous drainage, or a pneumonia via therapeutic bronchoscopy, epigenetic modification of host immunity drives the success or failure of therapeutic efforts. Current evidence supports that cytokine-induced gene silencing via the JAK-STAT pathway leads to increased methyltransferase activity and subsequent di- or trimethylation of different regions of the histone tails and offers a useful paradigm with which to frame further inquiry [111]. In fact, such a process may also explain the recent observation that the outcome of critical illness-associated infection does not depend on the identified pathogen – a previously well-embraced tenet [112]. Relatedly, recent evidence supports a more uniform host genome response to blunt injury and nosocomial infection and organ failure (Fig. 23.2) [113].

Early sepsis is characterized by excessive inflammation and the "cytokine storm." As sepsis persists, patients often have reactivation of endogenous viruses and risk for development of nosocomial infections, suggesting an immunosuppressive state later in sepsis. A recent comprehensive immune analysis of adult patients who died in the ICU following sepsis compared with patients who died of non-sepsis etiologies confirmed biochemical, flow cytometric, and immunohistochemical findings consistent with immunosuppression and raise the hope that immune-enhancing therapy may be a valid approach in selected patients with sepsis [114]. These data suggest that future immune modulation in sepsis, as a component of source control, must include specific diagnostic studies to evaluate the individual patient immune response since there is extensive diversity in the pathways of inflammation and immune response during sepsis. Such an analysis is clearly more sophisticated that those currently brought to the bedside and will rely on technological advances to enable real-time genome-based clinical decision-making.

Conclusion

Source control may be conceived as more than draining purulence and debriding devitalized tissue. Elements of care that impact the host response to bacterial invasion should be specifically addressed and optimized. While many of these such as plasma volume expansion and metabolic management are under the clinician's direct control, others such as genomically targeted therapies designed to inactivate bacterial virulence factors remain a future potential. On the near horizon are interventions designed

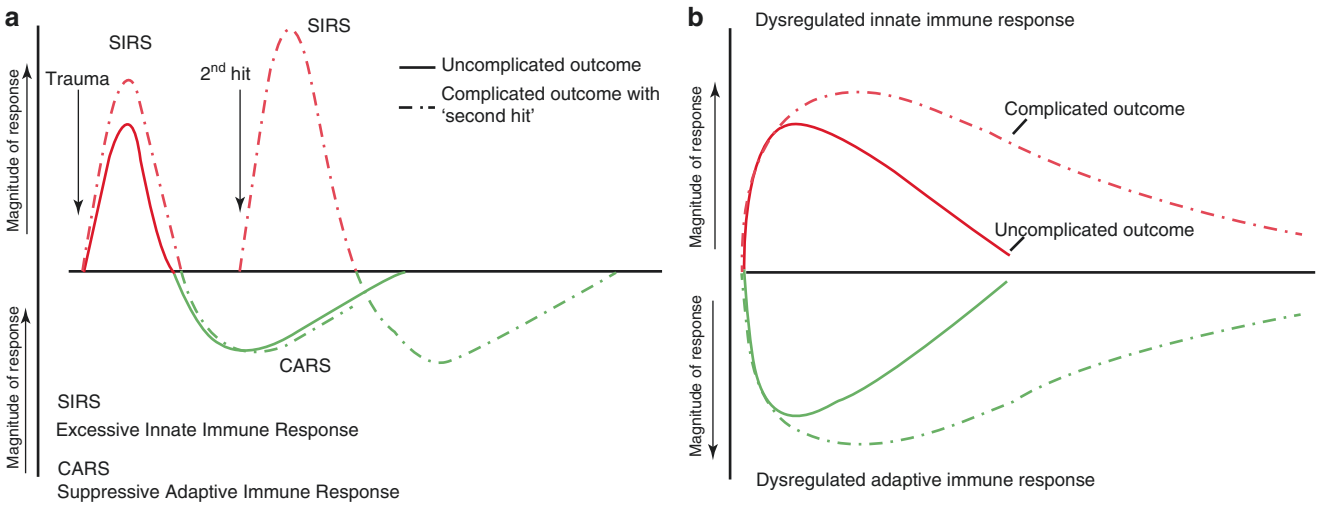

Fig. 23.2 A genomic storm: refining the immune, inflammatory paradigm in trauma. (**a**) The current paradigm explains complications of severe injury as a result of excessive proinflammatory responses (SIRS) followed temporally by compensatory anti-inflammatory responses (CARS) and suppression of adaptive immunity. A second-hit phenomenon results from sequential insults, which leads to more severe, recurrent SIRS and organ dysfunction. (**b**) The proposed new paradigm involves simultaneous and rapid induction of innate (both pro- and anti-inflammatory genes) and suppression of adaptive immunity genes. Complicated recoveries are delayed, resulting in a prolonged, dysregulated immune-inflammatory state (Reproduced with permission from: Xiao et al. [113])

to target biofilm formation and perhaps modification of bacterial virulence factors. Future research efforts should focus on understanding and improving host defense before, during, as well as after, host invasion, and how to best enable the success of native (host-based) and exogenous (intervention-based) source control measures.

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Soft Tissue Infections

24

Addison K. May

Introduction

Skin and soft tissue infections encompass a broad array of pathological conditions ranging from simple superficial abscesses to severe necrotizing infections involving the skin, subcutaneous tissue, muscle fascia, and musculature. They are a common cause of hospitalization, disability, and antibiotic therapy. Less severe skin and soft tissue infections are typically managed without the need for surgical intervention or the involvement of surgeons. However, more severe necrotizing infections place patients at risk of soft tissue loss, limb amputation, and death. For severe necrotizing infections, rapid and aggressive surgical debridement, appropriate antibiotic therapy, and supportive critical care management are required to optimize outcomes. Timely recognition of the extent, depth, and severity of the skin and soft tissue infection is paramount if appropriate and timely therapeutic intervention is to be achieved. In the chapter to follow, infections of the greatest clinical importance to surgeons and intensivists will be discussed in greater detail including (1) non-necrotizing infections (cellulitis, bite wounds, and complex abscesses), (2) necrotizing infections (necrotizing cellulitis, fasciitis, myositis, and myonecrosis), and (3) surgical site infections.

Terminology and Classification

A variety of terms describing infections of the skin and underlying soft tissue structures are used, including terms used by the Food and Drug Administration (FDA) and others used more commonly in clinical practice. For the purpose of therapeutic clinical trials (predominately antibiotic therapy), the FDA uses the term *skin and skin structure infections (SSIs)* [1]. However, until very recently, the FDA trials have excluded *necrotizing infections*, thus excluding infections involving the fascial planes and muscle as well as those infections with the greatest likelihood of adverse outcome. In clinical trials, the FDA classifies skin and skin structure infections as either "uncomplicated" or "complicated." *Uncomplicated SSSIs* are defined as those that respond to either a simple course of antibiotics alone or simple drainage alone and include superficial cellulitis, folliculitis, furunculosis, simple abscesses, and minor wound infections [1–4]. *Complicated SSSIs* are defined as those that involve the invasion of deeper tissues or require significant surgical intervention or occur in the presence of a significant underlying disease state that complicates the response to therapy. These infections include complicated abscesses, infected burn wounds, infected ulcers, infections in diabetics, and deep space wound infections [1]. The FDA terminology, designed for clinical trials, varies from that used in clinical settings.

For clinical application in the ICU and surgical setting, the author prefers the more inclusive term *skin and soft tissue infection* (frequently abbreviated SSTI) to include both non-necrotizing and necrotizing infections that may involve the skin, subcutaneous tissues, fascia, and/or muscle [5–7]. Within clinical practice, SSTIs may be classified as [8]:

1. Non-necrotizing SSTIs including:
   (a) Superficial infections (impetigo, erysipelas, and cellulitis)
   (b) Simple abscesses, furuncles, and carbuncles
   (c) Complex abscesses
2. Necrotizing SSTIs (NSSTIs):
   (a) Necrotizing cellulitis
   (b) Necrotizing fasciitis
   (c) Necrotizing myositis and myonecrosis
3. Incisional surgical site infections:
   (a) Superficial
   (b) Deep

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Terms and Classification Specific to NSSTIs

Several terms and classifications have been specifically applied to NSSTIs. The term necrotizing fasciitis is commonly and incorrectly used in lieu of necrotizing soft tissue infection, ignoring the potential involvement of the dermis and subcutaneous fat or muscle tissues and confounding an in-depth understanding of the pathophysiology of these infections. NSSTIs should be appropriately described by the tissue layer actually involved including necrotizing cellulitis, necrotizing fasciitis, necrotizing myositis, or myonecrosis [3, 8]. The individual tissues may be involved in isolation or in conjunction with each other. Fournier gangrene is a term used to describe NSSTIs predominately involving the perineum, vulva, or scrotum that occurs most frequently in diabetic patients, morbidly obese patients, and those who are otherwise immunocompromised [3, 8]. NSSTIs may also be classified by the bacterial pathogenesis of the infection as [8, 9]:

Type 1: polymicrobial – gram-positive and gram-negative, aerobic, and anaerobic bacteria
Type 2: monomicrobial – due to virulent, gram-positive aerobic cocci
Type 3: monomicrobial – due to virulent, gram-positive or gram-negative bacilli

The distinction between the three types is clinically relevant, determining the most appropriate antibiotic therapy, the speed at which operative intervention is required, and prognosis. Type 1 infections are the most common, are typically necrotizing fasciitis, and frequently arise from indolent infections that subsequently enter the fascial plane. Types 2 and 3 are more rapidly progressive due to the virulent nature of the pathogens involved.

Pathogenesis of SSTI

The likelihood, severity, and progression of infectious processes are determined by the balance of two factors: host tissue susceptibility and bacterial pathogenicity [10, 11]. The individual components that make up the skin and soft tissues (dermis, subcutaneous fat, fascia, and muscle) vary significantly in their ability to resist and limit the germination and spread of infection. Healthy, well-perfused dermis and muscle are both able to limit the invasion and spread of most bacterial species much more successfully than the deep fascial layers. Experimental models demonstrate an injection of 10^5 colony-forming units (CFU) of *Staphylococcus aureus* (*S. aureus*) into a normal well-vascularized dermis to form an abscess [10, 11]. Open skin wounds with adequate neovascularity can be closed with 10^5 CFU without a significant incidence of infection. Although hair follicles, skin pores, and sebaceous glands can become occluded and abscesses develop such as in folliculitis and furunculosis, these infections typically remain well localized. Well-perfused, healthy muscle also maintains good resistance to most bacterial species, limiting the involvement to settings where specific toxin production creates settings favorable to bacterial growth. However, limitations in tissue perfusion, immunocompromised states, tissue trauma, and foreign bodies can all significantly alter skin and soft tissue resistance to infection. In the experimental models mentioned above, the introduction of a foreign body reduces the number of bacterial colony-forming units required to establish an infection significantly, to 10^2 CFU [10–12].

The deep fascia is much more susceptible to infection than either the dermal or muscular tissues and is thus more frequently involved in necrotizing infectious processes. The deep fascia has tenuous blood supply, and its attachments to adjacent tissues are easily disrupted, creating an avascular compartment that allows the collection of fluid and the relatively uninhibited spread of infection along the fascial plain. The tenuous nature of fascia explains its susceptibility to necrotizing infection and why fasciitis is more common than necrotizing cellulitis and myositis, accounting for greater than 70 % of necrotizing infections.

Bacterial species also vary significantly in their pathogenicity in soft tissue infections, with virulence determined by both toxin production and reproduction rate. Toxin production may alter the integrity of the healthy, normally resistant tissue, limit perfusion, and alter the host inflammatory/immune response to infection. For instance, group A streptococcus (GAS) produces a variety of toxins that enable it to invade and spread through healthy dermis and muscle, requiring the introduction of only 10^2 CFU to establish infection versus 10^6 CFU of *S. aureus*. These characteristics enable GAS to cause severe infections in normal tissues including erysipelas, cellulitis, necrotizing cellulitis, and necrotizing myositis, GAS thus being described as "flesh-eating" bacteria [12]. Currently, the most common pathogen isolated from SSTIs is community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), and its pathogenicity is strongly associated with its toxin production [13–15]. The best characterized toxin produced by CA-MRSA is the virulence factor Panton-Valentine leukocidin (PVL) [16]. This dermonecrotic cytotoxin may be carried by either methicillin-sensitive or methicillin-resistant strains of *S. aureus*, but it is more commonly produced by certain clonal strains of CA-MRSA, particularly the USA300 clone [17, 18]. Enterotoxins and superantigens such as toxic shock toxin-1 (TSST-1) may also be produced by CA-MRSA and contribute to its virulence. Toxin production by CA-MRSA allows it to colonize, invade, and initiate SSTI in previously healthy, intact skin in otherwise healthy adults.

Bacterial reproduction rate is also a significant determinate of the patients clinical course and presentation. Bacterial reproduction determines the rate at which the number of bacteria will increase within the host tissue. Thus, species that rapidly reproduce and have significant toxin production that enhances virulence can invade normally resistant tissues and initiate a rapidly progressive infection, either as a single pathogen or in concert with other pathogens. GAS, community-associated methicillin-resistant *S. aureus* (CA-MRSA), and clostridial species are the commonly encountered pathogens that may produce rapidly progressive soft tissue infections, although a variety of other pathogens may do so including *Vibrio*, *Aeromonas*, *Eikenella*, *Pasteurella*, and *Bacillus* species [5, 6].

Non-necrotizing SSTI

The majority of SSTIs are generally mild to moderate in severity and are non-necrotizing in nature. Non-necrotizing SSTIs include (a) superficial infections (impetigo, erysipelas, and cellulitis), (b) simple abscesses (furuncles, carbuncles, folliculitis, and minor trauma-related wound infections), and (c) complex abscesses [2, 3]. A large portion of these infections are uncomplicated and respond to either a short course of antibiotics or to simple drainage. However, many of these infections, if left untreated or inadequately treated, may evolve into more severe necrotizing infections. In the management of non-necrotizing soft tissue infections, surgeons and intensivists may be involved in the diagnosis and treatment of complex abscesses and surgical site infections and may have to determine whether the inflammatory changes manifested in the dermis represent simple, non-necrotizing cellulitis or a more severe, underlying necrotizing infection. Differentiation of necrotizing versus non-necrotizing soft tissue infections will be discussed in greater detail later in the chapter.

Epidemiology

While a wide variety of bacteria may be isolated from skin and soft tissue infections, *Staphylococcus aureus* is the most common pathogen, isolated in nearly one half of all infections [2, 13, 14, 19]. However, the frequency of streptococcal infections determined by culture surveillance significantly underestimates its incidence due to this organism's predilection to cause erysipelas and cellulitis, infections that rarely provide positive culture data. The incidence of all SSTI appears to have increased over the past two decades, paralleling the increase in community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections [20].

The dramatic rise in the incidence of CA-MRSA-related SSTI over the past several decades justifies expanded discussion. In the early 1980s, community outbreaks of MRSA SSTI infections began to be reported in patients without standard risk factors for MRSA [16]. These pathogens were noted to have antibiotic sensitivities that were not typical of hospital-associated MRSA, and thus the term community-associated was applied to the organisms. Outbreaks were reported in otherwise healthy Alaskan natives, children, inmates in correctional facilities, institutionalized adults with developmental disabilities, nursing homes, and athletes [6]. Over the subsequent decades, the incidence of CA-MRSA has increased, and in most locations it is the most common skin and soft tissue infection pathogen [14–16, 21–23].

Treatment of Non-necrotizing SSTI

Discussion will focus on those infections that are pertinent to decisions in surgical or critical care settings including non-necrotizing cellulitis, bite wounds, and complex abscesses.

Non-necrotizing Cellulitis

The term non-necrotizing cellulitis incorporates two clinical entities, erysipelas and cellulitis, that are diffusely spreading skin infections not associated with underlying suppurative foci. The term "cellulitis" is frequently interchangeable with the term "erysipelas," and the latter term is frequently preferred in Europe. However, a fine distinction exists between erysipelas and cellulitis. Erysipelas has two classic features of this skin infection that include: (1) a clear line of demarcation between involved and uninvolved tissue and (2) lesions raised above the surrounding normal skin [3, 24]. Cellulitis involves deeper layers of the dermis and subcutaneous tissue and has less distinctive features than erysipelas, but both involve rapidly spreading areas of edema, erythema, and heat and may be accompanied by lymphangitis [25]. These non-necrotizing infections are most commonly caused by β (beta)-hemolytic streptococci (usually group A) but may also be caused by other streptococcal species [25–27]. In specific clinical situations, other bacterial species may cause a spreading, non-necrotizing cellulitis such as *Haemophilus influenzae* in children and pneumococcal cellulitis in the limbs of patients with altered immunity. Rarely, *S. aureus* may be involved but these infections usually are more suppurative and less diffuse. Superficial, non-necrotizing infections caused by certain strains of group A streptococci may also be associated with streptococcal toxic shock syndrome characterized by the rapid progression of septic shock and organ failure [28–30].

These infections generally arise when organisms enter through breaches in the skin. A number of predisposing factors for these infections broadly include conditions

involving alterations in integrity of the skin (i.e., dermatoses, fungal infections ulcerations), alterations in lymphatic and venous drainage (i.e., saphenous vein harvest, lymph node dissections), alterations in vascularity of the skin, and alteration of host defenses (e.g., diabetes mellitus) [31–35]. Antibiotic therapy is most commonly based on empiric diagnosis established by clinical findings as cultures are most frequently negative. Blood cultures are positive in less than 5 % of cases, and positive results from either needle aspiration or punch biopsy range from ≤5 to 40 % [36–40].

Antibiotic treatment options for erysipelas and cellulitis have not been established through randomized, prospective studies, but significant clinical practice has established standards of therapy. For cases of erysipelas and cellulitis due to streptococci, penicillin given parentally (for severe infection) is the agent of choice [3]. Other regimens include antistaphylococcal penicillins, cefazolin, and ceftriaxone [25, 41, 42]. However, treatment failures with beta-lactam antibiotics do occur despite in vitro microbial sensitivity to the agents used [43–46]. The mechanism of failure is believed to involve the failure of bacterial killing by cell wall-inhibiting agents when high numbers of bacteria in the static phase lead to decreased expression of penicillin-binding proteins [46–48]. Protein synthesis inhibitory agents such as macrolide and lincosamide antibiotics may be as effective and potentially superior in certain settings [45, 46, 49]. Clindamycin either alone or in combination with a cell wall-inhibiting agent was found to be more effective than cell wall-inhibiting agents alone in a retrospective analysis of pediatric group A streptococcal infection [46, 49]. Roxithromycin proved to be equivalent to penicillin for the treatment of erysipelas in a randomized, multicenter trial [50]. However, increasing macrolide resistance among streptococci introduces concern for these agents, and local sensitivity patterns should be considered when using these agents alone for the treatment of complicated group A streptococcal infections [46, 51, 52]. Additionally, since clindamycin has been demonstrated to reduce exotoxin and superantigen production by pathogenic strains of group A streptococci, the drug is frequently used as an adjunct in the treatment of streptococcal toxic shock syndrome [45, 48, 53]. However, the most effective antibiotic regimen in this setting has not been established in prospective studies. If methicillin-sensitive *S. aureus* is suspected, the treatment of choice is a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin for non-methicillin-resistant staphylococcal infections [3, 25]. However, as previously discussed, the recent dramatic increase in community-associated MRSA makes the empiric treatment of staphylococcal infections with beta-lactam antibiotics problematic, and other agents should be considered unless the risk of resistant staphylococcus is low (see discussion below) [22, 54].

Bite Wounds

Since bite wounds are relatively common and involve pathogens not generally encountered in other settings, special consideration is provided. The majority of bite wounds are mammalian in origin, produced predominately by humans, dogs, and cats [55, 56]. Infection rates vary widely depending on the severity of the bite wound, the location of the bite wound, and the animal source. Nonhuman bites that are low risk and not involving the hand have infection rates that appear to be less than 2 %; human bites involving the hand with significant penetration have infection rates of greater than 50 %. Unfortunately very limited data exists to guide the principle management of bite wounds including (1) irrigation, debridement, or decontamination of the wound, (2) primary wound closure, (3) prophylactic antibiotics, and (4) therapeutic antibiotics. Thus, most recommendations are based on consensus opinion and not randomized data.

The main principles of treatment for bites wounds are the recognition of risk of complication, wound care, and appropriate antibiotic therapy. Wounds at high risk of infection include those with deep puncture, crushing injury, devitalized tissue, and heavy contamination [56]. Bites involving the hand appear to have a higher infection risk, and infectious complications portend greater risk of long-term dysfunction. Human bites appear to have higher infection risk in general than do dog or cat bites [56]. Irrigation, debridement, or decontamination of wounds is considered standard of care although no randomized studies or large cohort studies exist examining such management techniques. Primary wound closure is believed to be advantageous for most bite wounds, assuming adequate debridement and irrigation have been achieved [56]. However, limited data exist to support this practice as only one small randomized study has been performed regarding primary closure. Tetanus immunization is considered standard of care though no studies have been performed for bite wounds [56].

The use of prophylactic antibiotics in the setting of bite wounds is controversial, and the benefit of antibiotics likely varies depending on the risk of infection, animal type, location, and timing of antibiotics after the injury. A Cochrane Review found no significant difference in the overall infection rate of mammalian bites with prophylactic antibiotics, with significant heterogeneity between trails [56]. When results were analyzed by wound site, antibiotic prophylaxis decreased infection rates for hand wounds only, though the total number of patients in all groups were small and positive results from a single study of human, hand bite wounds with 48 total patients [57]. Only human bite wounds appeared to show benefit from prophylaxis; however, these findings are driven by one study of human, hand bite wounds [56, 57]. A randomized trial of low-risk human bite wounds less than 24-h-old that did not involve the hand demonstrated no benefit to prophylactic antibiotics (total $n = 127$) [55]. Penicillins

(with and without beta-lactamase inhibitors) and cephalosporins have been included in studies without significant differences in infection rates, though studies are inadequately powered.

For the treatment of established infections from bite wounds, no study examined antibiotics versus placebo. However, antibiotics are considered standard. Inadequate studies exist to guide any recommendation for antibiotic selection, though antibiotics that cover the mouth flora of the biting animal or human are considered standard.

Complicated Abscesses

Complicated abscesses may involve a variety of pathogens and are frequently polymicrobial in origin [13, 58]. The majority of infections occur in individuals who have some underlying alteration in host defenses such as diabetes, vascular insufficiency, or traumatic injury. Common sites of origin include: perineal or perianal infection in diabetic patients, perirectal abscesses, diabetic foot or lower extremity ulcerations, traumatic injuries, chronic cutaneous cysts, intravenous drug injection sites, surgical site infections, gastrointestinal pathology with perforation, genitourinary pathology, animal bites, and pressure ulcers [58–60]. Initiating pathogens often vary depending on the originating site of the infection. Gram-positive aerobic pathogens are isolated in over 50 % of all complicated abscesses and necrotizing infections, and depending on the source of origin, anaerobes, *Pseudomonas* spp., gram-negative *Enterobacteriaceae*, and clostridial species may commonly be present. An accurate clinical history and examination should suggest the underlying etiology and direct empiric therapy.

Complicated skin and subcutaneous abscesses are typically well circumscribed or walled off and respond to adequate incision and drainage with adjuvant antibiotic therapy. Inadequate resolution should prompt consideration of further drainage, resistant pathogens, host immune failure, and evaluation to rule out progression to a necrotizing infection. During incision and drainage, appropriate examination must be undertaken to ensure that all loculations have been identified and that occult involvement of fascia or deeper tissue spaces are not involved. Certain areas, such as the perineum and perirectal space, may have deep space involvement that is very difficult to identify, and computed tomographic imaging should be considered preoperatively to rule out occult, deep soft tissue involvement. CA-MRSA SSTI frequently involves previously healthy skin in an otherwise healthy adult. Patients frequently believe that they have been bitten by a spider due to the character of the local wound involvement – a small central dark area surrounded by a firm indurated abscess and a variable degree of cellulitis. The depth and area of involvement is often under appreciated by clinicians leading to inadequate incision and drainage. For CA-MRSA, the abscess cavity and necrotic tissue usually extend to the margin of the area of induration, with loculations extending widely into the subcutaneous fatty tissue.

Empiric antibiotic therapy should be directed toward the likely pathogens involved [3–8]. For polymicrobial infections, several classes of agents or combinations of agents provide adequate antibiotic coverage. Broad-spectrum agents with coverage of gram-positive, gram-negative, and anaerobic pathogens may be required depending on clinical setting. In nosocomial settings, coverage of resistant pathogens encountered locally should also be considered. The high frequency of CA-MRSA SSTI supports the empiric cover of this pathogen in the majority of settings unless specific data indicate otherwise. Infections of great enough severity to require hospitalization generally require intravenous administration of antibiotics with appropriate spectra. De-escalation therapy should be considered and based upon culture results.

MRSA species isolated from SSTI may have variable sensitivity to trimethoprim-sulfamethoxazole, tetracycline agents, and clindamycin, supporting the empiric use of agents with more consistent coverage. While vancomycin has been the gold standard, several randomized trials support linezolid as a first-line alternative in SSTI [61–66]. One randomized study demonstrated superiority of linezolid in the treatment of complicated SSTI (88.6 % vs. 66.9 % cured for linezolid vs. vancomycin, $p<0.001$) [64]. Additionally, linezolid has been shown to inhibit toxin production in vitro providing theoretical advantage [67]. Other newer agents with activity against MRSA tested in randomized trials of complicated skin and skin structure infections include quinupristin/dalfopristin, daptomycin, and tigecycline [16, 68]. Although each is approved for the treatment of complicated SSSI, the randomized studies to evaluate the efficacy of these agents contained too few MRSA to draw conclusions for recommendations.

Necrotizing SSTI

Necrotizing skin and soft tissue infections (NSSTIs) are discussed separately due to the increased severity and mortality, the variation of pathogens, and the importance of early diagnosis and early, aggressive surgical debridement on outcome relative to non-necrotizing SSTIs. NSSTIs are serious infections, producing progressive tissue destruction with significant potential for soft tissue and limb loss and mortality.

Epidemiology, Bacteriology, and Outcome of NSSTI

Although data are sparse, the incidence of NSSTI appears to be increasing somewhat in parallel to all SSTI [69, 70]. Analyzing the National Inpatient Sample for the period

between 1998 and 2010, Psoinos et al. demonstrated an increasing number of cases per year (from 3,800 to 5,800) of NSSTI, as well as a significant increase in comorbid disease and obesity among patients [69]. While the outcome from NSSTI appears to be improving over that past several decades, mortality remains significant [5, 6, 69]. Analysis of 6,181 cases in 80 publications between the years 1980 and 2014 reveals an overall mortality of 20 % (Table 24.1). However, outcome by decade in these publications has declined; published mortality in the 1980s is 32 %, declining to 16 % published after 2010 (Table 24.2).

The pathogens involved in NSSTIs differ somewhat from those isolated from non-necrotizing infections, particularly those NSSTIs that are rapidly progressive (types 2 and 3). In an analysis of 198 consecutive patients with necrotizing skin and soft tissue infections, Elliot et al. documented a significant increase in the frequency of rapidly growing, virulent pathogens, particularly *Streptococcus*

Table 24.1 Selected necrotizing soft tissue infection publications between 1980 and 2014

Author	Year	Number of cases	Number of deaths	Percent mortality	Author	Year	Number of cases	Number of deaths	Percent mortality
Casali	1980	12	4	33 %	Catena	2004	11	7	64 %
Kaiser	1981	20	8	40 %	Wilkinson	2004	44	6	14 %
Freeman	1981	14	4	29 %	Escobar	2005	42	5	12 %
Oh	1982	28	10	36 %	Kao	2005	59	7	12 %
Rouse	1982	27	20	73 %	Legbo	2005	24	4	17 %
Majeski	1983	30	10	33 %	Cheng	2005	17	11	65 %
Walker	1983	8	3	38 %	Taviloglu	2005	98	34	35 %
Miller	1983	15	4	27 %	Endorf	2005	65	11	17 %
Adinolfi	1983	11	3	27 %	Tiu	2005	48	14	29 %
Spirnak	1984	20	9	45 %	Anaya	2005	166	28	17 %
Stamenkovic	1984	19	8	42 %	Bakleh	2005	81	16	20 %
Barzilai	1985	11	4	36 %	Liu YM	2005	87	29	33 %
Pessa	1985	33	11	33 %	Kwan	2006	36	13	36 %
Freishlag	1985	21	7	35 %	Ozalay	2006	22	3	14 %
Gozal	1986	16	2	12 %	Ogilvie	2006	150	14	9 %
Sudarsky	1987	33	2	6 %	Yilmaziar	2007	67	33	49 %
Clayton	1990	57	10	18 %	Lee	2007	74	11	15 %
Asfar	1991	10	3	30 %	Yaghoubian	2007	124	21	17 %
Ward	1991	14	6	43 %	Peer	2007	38	8	21 %
Wang	1992	18	6	33 %	Golger	2007	99	20	20 %
Francis	1993	25	6	24 %	Tsai	2007	32	10	31 %
Chow	1993	12	3	25 %	Hefny	2007	11	2	18 %
Brown	1994	54	19	35 %	Miller, AT	2008	11	4	36 %
McHenry	1995	65	19	29 %	Lui BM	2008	118	26	22 %
Bosshardt	1996	45	12	27 %	Frazee	2008	122	20	16 %
Elliot	1996	198	50	25 %	Hsiao	2008	128	24	19 %
Bilton	1998	68	14	21 %	Gunter	2008	52	5	10 %
Adant	1998	7	1	14 %	Chan	2008	21	5	24 %
Hsiao	1998	34	9	27 %	Anaya	2009	350	62	18 %
Haywood	1999	20	4	20 %	Chen	2011	323	52	16 %
Brandt	2000	37	9	24 %	Cheng	2011	18	6	33 %
Wall	2000	21	6	29 %	Huang	2011	472	57	12 %
Theis	2002	13	4	31 %	Kao	2011	296	50	17 %
Singh	2002	75	20	27 %	Bernal	2012	393	30	8 %
Gallup	2002	23	3	13 %	Chao	2012	72	15	21 %
Fustes-Morales	2002	39	7	18 %	Das	2012	247	58	24 %
Childers	2002	163	46	28 %	Sugihara	2012	379	65	17 %
Wong	2003	89	19	21 %	Keung	2013	201	48	24 %
Tilou	2004	46	8	17 %	Okoye	2013	64	9	14 %
Qazi	2004	25	6	24 %	Bulger	2014	43	4	9 %
Publication years:				**Total publications:**			**# cases**	**# deaths**	**Mortality**
1980–2014				**80**			**6,181**	**1,245**	**20 %**

Table 24.2 Mortality trends in published series of necrotizing soft tissue infections

Publication date:	Number of studies	Number of cases	Number of deaths	Percent mortality
Total 1980–2014	80	6,181	1,245	20.1 %
1980–1990	17	375	119	31.7 %
1991–2000	15	628	167	26.6 %
2001–2010	37	2,670	565	21.2 %
2011–2014	11	2,508	394	15.7 %

spp. and clostridial species [19]. In contrast to non-necrotizing, complicated SSTI, streptococcal species were the most commonly isolated organisms, occurring in greater than 50 % of those patients in whom only one pathogen was isolated in this study. Streptococcal species were also the most frequent pathogens isolated from 707 patients included in six separate studies on NSSTI, being isolated in 39.2 % of patients, followed by *S. aureus*, which was isolated from 30.1 % of patients [19, 71–75]. Most patients with necrotizing infections have polymicrobial infections with an average of 4.4 organisms isolated per infection in the study by Elliot et al. [19].

Therapeutic Considerations in NSSTI

While necrotizing soft tissue infections are life-threatening infections, the clinical presentation, severity of systemic manifestations, and the speed of progression vary widely, these features determined by the pathogenesis of the NSSTI. In general, this variability is predominately determined by whether highly virulent and rapidly dividing gram-positive cocci (type 2 NSSTI) or gram-positive or gram-negative bacilli (type 3 NSSTI) are the inciting pathogens in the infection [9]. The pathogenicity of these pathogens, enabled significantly by the production of a combination of toxins, allows these bacterial species to invade and spread in tissues normally resistant to infection. Thus, infections involving previously healthy skin or muscle usually involve virulent, toxin-producing agents that allow the invasion of these fairly resistant tissues.

Type 2 NSSTI

Pathogens producing type 2 NSSTIs include *Streptococcus pyogenes* (group A beta-hemolytic streptococcus, GAS), group B streptococcus, and CA-MRSA. Of these species, GAS is associated most frequently with severe, rapidly progressive NSSTIs [7, 11]. The presentation may range from relatively minor cellulitis to severe, rapidly progressive NSSTI with pronounced systemic symptoms and a high mortality rate [29, 30]. Pathogenic strains produce a variety of virulence factors and exotoxins that contribute to pathogenicity and the clinical presentation, including antiphagocytic M proteins, hemolysins, streptolysins O and S, leukocidins, and streptococcal pyrogenic exotoxins which are associated with streptococcal toxic shock syndrome [28, 29, 76–79]. Toxin production by GAS allows it to invade, divide, and spread through healthy dermis and, less frequently, healthy muscle. As an obligate aerobic bacterium, only carbon dioxide (CO_2) is produced as a byproduct of metabolism. As CO_2 diffuses readily through tissues, the collection of gas in tissues is not characteristic, despite the organism's rapid growth.

Type 3 NSSTI

The most common pathogens producing type 3 NSSTI are clostridial species, particularly the species *Clostridium perfringens*. However, other species of bacilli may also produce a variety of toxins and can cause rapidly progressive type 3 NSSTI. These agents are usually associated with specific environmental exposures that include *Pasteurella multocida* (animal bites), *Eikenella corrodens* (human bites), *Vibrio* spp. (shell fish or saltwater exposure), *Aeromonas hydrophila* (contaminated freshwater exposures), and *Bacillus cereus* (soil and water) [80].

NSSTIs caused by *Clostridium* spp. are among the most aggressive and can rapidly be fatal. Although clostridia are obligate anaerobes, *Clostridium* spp. are among the only pathogens that are able to invade and destroy healthy muscle rapidly. Under ideal conditions, growth is rapid, with a germination time for *C. perfringens* of approximately 8 min [77]. The clinical manifestations are related to the elaboration of potent extracellular toxins. The major virulence factors of *C. perfringens* are a toxin (phospholipase C) and y toxin (perfringolysin) [81]. In addition to direct tissue injury, these toxins impede the migration of polymorphonuclear leukocytes and destroy neutrophils at the site of infection, allowing the infection to worsen [82]. These toxins also lead to hemolysis, microvascular thrombosis, and myonecrosis. The resulting reduction in oxygen tension encourages rapid multiplication of the bacteria in muscle. Rapid growth under anaerobic conditions produces large amounts of poorly diffusible gas, resulting in crepitus to palpation. Alpha toxin directly inhibits myocardial contractility and indirectly induces systemic cytokine expression, both of which may contribute to the rapid circulatory collapse observed in these patients [81].

Clostridium perfringens is the most common pathogen, accounting for 70–80 % of all such infections, but several other species have been reported [81]. Classically, clostridial infections have been associated with traumatic wounds, but recent studies have demonstrated an increasing incidence of these infections associated with the injection of illicit drugs [71, 83, 84]. Clostridial species may be isolated from the human gastrointestinal tract and perineum and are common in soil contaminated with animal excreta. Infections that

occur without a history of trauma or injection should precipitate a workup for an initiating source. *Clostridium septicum* has been associated with leukemia or gastrointestinal neoplasms [85].

Type 1 NSSTI

These infections are polymicrobial by definition and account for the majority of cases of necrotizing fasciitis. A variety of pathogens may be isolated, and frequently four or more species are isolated, typically involving gram-positive and gram-negative bacteria as well as a mixture of aerobic and anaerobic pathogens. These infections typically arise from a more indolent infectious process that subsequently reaches the fascial plane and then spreads along the fascial plane, enabled by the tenuous blood supply and attachment to surrounding tissue. Common inciting processes include perirectal and perineal abscesses; chronic diabetic ulcerations; retroperitoneal infections from colon pathology; surgical site infections; inoculation and infection related to intravenous drug abuse; inadequately treated, chronic dermal abscesses; and dermal lacerations [4]. An accurate clinical history and exam should be undertaken to identify the likely source and to identify the polymicrobial nature of these infections. While these polymicrobial infections can spread widely and become both limb and life threatening, they tend to spread less rapidly than type 2 and type 3 infections, caused by highly virulent pathogens.

Diagnosis of NSSTI

Early diagnosis of the presence of a necrotizing soft tissue infection is critical if optimal outcomes are to be achieved. However, distinguishing a NSSTI which necessitates surgical debridement from a non-necrotizing cellulitis which responds solely to antibiotic therapy can be difficult. For patients with NSSTI, the admitting diagnosis is incorrectly made as either cellulitis or abscess in 65–80 % of cases [73, 75, 86]. Unfortunately, any delay in diagnosis is potentially catastrophic, since the concomitant delay in appropriate surgical therapy has been shown to increase mortality [19, 58, 59, 87, 88].

Pain, erythema, warmth, and swelling are present in the majority of cases but are not specific to necrotizing infections and may not be universally present [73, 75]. Clinical features independently associated with the diagnosis of NSSTI include (1) pain that is disproportionate to findings on physical exam, (2) tense edema, (3) presence of bullae, (4) skin ecchymosis/necrosis, (5) cutaneous anesthesia, (6) systemic toxicity, and (7) progression despite antibiotic therapy [6, 7]. The presence of gas within the soft tissues on radiographic imaging is also strongly associated with the diagnosis of NSSTI. These clinical and radiographic findings should prompt immediate surgical exploration in any patient in whom infection is within the differential diagnosis without the presence of clear alternative causes. However, while these signs are fairly specific to NSSTI, they typically occur late in the course of disease and are present in the minority of cases (7–44 %) [75, 88–90].

Radiographic evaluation by either plain radiograph or computed tomography (CT) scanning is considerably more sensitive for detecting gas in tissues than is the finding of crepitus by physical exam. However, gas is not universally present in NSSTI, particularly in those caused by strictly aerobic pathogens such as group A streptococcus. CT scanning and magnetic resonance imaging (MRI) may detect other findings that assist in diagnosing a NSSTI including the presence of fluid along fascial planes and edema within tissues. Notably, neither fluid nor edema is specific for the presence of necrotizing infection, and the sensitivity and specificity of these modalities have not been established.

Laboratory values may be useful to aid in the early diagnosis of NSSTI [89]. Those laboratory parameters shown to correlate with the presence of a NSSTI by multivariate analysis include (1) admission white blood cell count of $>14\times10^9$/L, (2) serum sodium of <135 mmol/L, (3) blood urea nitrogen of >15 mg/dL, and (4) CRP ≥150 mg/L. However, the sensitivity and specificity of these parameters are insufficient without the presence of other clinical parameters, and their absence should not be used to rule out NSSTI in the presence of hard clinical signs [91]. Wong et al. evaluated the predictive capability of various laboratory parameters in a population of patients (89 patients with NSTI, 225 with cellulitis or abscess) by multivariate analysis and created the "Laboratory Risk Indicator for Necrotizing Fasciitis" (LRINEC) score [86]. The LRINEC score classifies patients as low, intermediate, and high risk for NSSTI (Tables 24.3 and 24.4). While the LRINEC score may aid in establishing the diagnosis in patients without "hard" signs of necrotizing infection, it has not been prospectively validated in large cohorts and poor predictive power in numerous reports in specific settings (see slide 34 of NSTI-SCCM extended). The use of full-thickness biopsy and frozen section has been advocated, but neither have been adequately evaluated or widely adopted [93]. If the presence of a necrotizing infection cannot be excluded, surgical exploration is indicated.

Therapeutic Approach for NSSTI

Aggressive and timely resuscitation, prompt administration of appropriate antibiotic therapy, and timely surgical debridement are all required for optimal outcome. Among these therapies, surgical intervention is the mainstay. Unfortunately, no randomized studies of surgical therapy for NSSTI have

Table 24.3 Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score

Value	LRINEC score, points
C-reactive protein, mg/L	
<150	0
>150	4
WBC count, cells/mm^3	
<15	0
15–25	1
>25	2
Hemoglobin level, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium level, mmol/L	
≥135	0
<135	2
Creatinine level, mg/dL	
≤1.6	0
>1.6	2
Glucose level, mg/dL	
≤180	0
>180	1

Adapted from Wong et al. [86]

Table 24.4 Probability of necrotizing soft tissue infection (NSTI) based upon Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score categories

Risk category	Points by LRINEC score	Probability of NSTI (%)
Low	≤5	<50
Intermediate	6–7	50–75
High	≥8	>75

Adapted from Wong et al. [86], Anaya and Dellinger [92]

been published. Numerous retrospective studies demonstrate that (1) time to first debridement, (2) adequacy of first debridement, and (3) extent of tissue involvement at first debridement are important and alterable predictors of survival [19, 59, 72, 74, 87, 88, 94–98]. However, definitions of delayed or inadequate initial therapy have not clearly described by the authors. In most studies, a delay in surgical debridement of greater than 24 h after admission is associated with a significant increase in mortality. However, surgical drainage and debridement at the earliest possible time almost certainly improves outcome.

Surgical Therapy for NSSTI

As noted above, surgical drainage and debridement of involved tissues is the mainstay of therapy in necrotizing soft tissue infections. However, no randomized studies or significant case series are available to direct the actual surgical approach. While retrospective reviews identify adequate and early surgical debridement as predictors of survival, they do not report quantifiable methods of defining adequate debridement [19, 59, 72, 74, 87, 88, 94–98]. Several issues should be considered: (1) determining the extent of resection, (2) full thickness versus fascial excision for necrotizing fasciitis, (3) serial wound examination and debridements, and (4) diverting colostomy versus other methods of control of the fecal stream for perineal and scrotal infectious processes. The determination of extent of resection is most commonly based on clinical judgment and the gross appearance of tissues involved. Dermis, subcutaneous fat, deep fascia, and muscle may each be involved in the infectious process; their involvement varying depending on the clinical setting, bacteriology, and inciting insult.

The most common NSSTI is a polymicrobial (type 1) necrotizing fasciitis. As noted above, the infection in this entity spreads widely along fascial planes, frequently with little involvement of surrounding muscle, subcutaneous, or dermal tissues. Excisional debridement of the involved fascia, drainage of purulent fluid, and prevention of recurrent fluid collections is required. Involved, nonviable adjacent tissues should be excised, but if the muscle, subcutaneous tissue, and dermis are viable and well perfused, excision is not required. A "step ladder" approach, with parallel incisions in healthy dermis and subcutaneous tissue to the underlying involved deep fascia, may allow adequate excision and drainage while preserving overlaying tissue [77]. The ability to separate fascia easily from the normally adherent surrounding tissue strongly suggests involvement with infection [88, 97, 99]. However, in elderly and critically ill patients with extensive edema, the ease of separation can be difficult to distinguish from noninfected fascia, and the previous of necrotizing infection still requires considerable clinical judgment. For dermis, subcutaneous tissue, and muscle involvement, the lack of inflammation or purulence and the presence of normal bleeding at the line of incision are commonly used to determine involvement and the adequacy of debridement. Viable muscle also maintains contractility, which can be assessed with the electrocautery unit. Nonviable muscle, subcutaneous tissue, and dermis should be excised. As many cases of necrotizing fasciitis are initiated from a more indolent, remote infection, an evaluation for the initiating process should be performed.

NSSTI types 2 and 3 (monomicrobial infections caused by virulent pathogens) may invoke a necrotizing cellulitis involving previously healthy dermis and subcutaneous tissue or a necrotizing myositis/myonecrosis involving previously healthy muscle. Involvement of these tissue layers may occur in isolation or in conjunction with other layers. The speed at which these infections spread makes early aggressive debridement paramount.

Necrotizing infections have the potential for rapid and continued progression despite surgical debridement. Thus, frequent reevaluation of the wound should be undertaken. Many authors recommend return to the operating room

within 24 h to ensure adequacy of debridement and lack of progression, and the average number of operative procedures is typically three to four per patient [87, 88, 99]. While little data are available to support any particular re-debridement schedule, return to the OR in less than 48 h was associated with reduced mortality and reduced acute kidney injury and patients returning after 48 h [100]. Prevention of heavy and recurrent contamination of dressings may be problematic in patients with perineal, perianal, or scrotal involvement. When fecal soilage of dressings is problematic, diverting colostomy is recommended by many, although the use of specifically designed rectal system to control the fecal stream has been used successfully to avoid diverting colostomy [101, 102].

Antibiotic Therapy for NSSTI

Recommendations for antibiotic therapy are extrapolated from studies of complicated SSTI and other clinical settings of similar severity, animal data, and sensitivity patterns of common pathogens as very limited prospective data exists to guide antibiotic therapy for NSSTI. As indicated earlier, FDA guidelines for the study of soft tissue infections exclude patients with these more severe infections from prospective trials [1]. The majority of randomized studies evaluating complicated skin and skin structure infections report clinical success rates of ranging from 75 to 90 % or greater, depending on the study population and analysis group. Typically, mortality for the populations included in these studies is well less than 1 %.

The majority of NSSTIs are type 1, polymicrobial infections that may involve gram-positive and gram-negative, aerobic, and anaerobic bacteria. Thus, empiric broad-spectrum coverage is indicated. For the majority of complicated and necrotizing soft tissue infections, a number of single-agent or combination regimens that provide anaerobic, gram-positive, and enteric gram-negative coverage may be effective. Several single-agent regimens have been evaluated in prospective, randomized trials of complicated skin and skin structure infections including: imipenem-cilastatin, meropenem, ertapenem, piperacillin-tazobactam, ticarcillin-clavulanate, levofloxacin, and tigecycline. Ampicillin-sulbactam has been shown to be effective in complicated skin and skin structure infections; however, recent increases in resistance among gram-negative rods introduce concern about selecting this as a single agent. Numerous combination regimens are recommended by different sources, but have not been studied rigorously. These combinations typically include penicillins or cephalosporins with either an aminoglycoside or fluoroquinolone and anaerobic agent such as clindamycin or metronidazole. There are inadequate data comparing regimens to support the use of any one antimicrobial regimen over another for the treatment of these severe infections. Thus, for non-rapidly progressive soft tissue infections, the use of one of the single agents or combination regimens noted above, along with an anti-MRSA drug if suspicion of this pathogen is present, is the general recommendation. The clinical presentation and physical findings, along with the rapidity with which the pathological process evolves, should alert the practitioner to the potential presence of specific, highly virulent pathogens such as group A streptococci, *Clostridium* spp., and *Vibrio* spp., as discussed below. If such pathogens are suspected, then antibiotic therapy should be altered appropriately.

Recommendations for antibiotic therapy for type 2 and type 3 NSSTIs include the addition of antiribosomal agents to the therapeutic regimen due to the contribution of toxin production to the pathogenesis. While no prospective studies examine antibiotic efficacy in these settings, animal and retrospective human data support the use of protein synthesis-inhibiting antibiotics in combination with cell wall active agents, particularly if toxin production is important pathogenically or if a high inoculum is present. The choice of protein synthesis-inhibiting agent should be based on the known or predicted sensitivity of the organism(s) to the agents considered, predominately based on whether the agent is gram-positive or gram-negative. Recommended agents include clindamycin (if resistance is not of concern) or linezolid for gram-positive infections (*Streptococcu*s, CA-MRSA, and *Clostridium* spp.) and members of the tetracycline class for the gram-negative pathogens such as *Vibrio* spp. and *Aeromonas* spp.

Incisional Surgical Site Infections

Surgical site infections (SSIs) are commonly encountered by surgeons and intensivists and contribute significantly to postoperative morbidity [10]. They are the most common reason for hospital readmission among surgical patients and, if not treated appropriately, disrupt the normal healing process and may progress to a necrotizing infection. The Centers for Disease Control and Prevention (CDC) classifies SSIs as: superficial incisional infection, deep incisional infection, and organ space infection [10]. Superficial incisional SSIs involve only the skin or subcutaneous tissue of the incision while deep incisional SSIs the deep soft tissues (fascial and muscle layers). Organ space infections do not constitute soft tissue infections. Superficial incisional infections are the most common type of surgical site infections.

Pathogenesis of SSI

The initiation of a SSI requires the contamination of the wound site, with bacteria present at the completion of the surgical procedure. Development of a SSI specifically relates

to the pathogenicity and inoculum of microorganisms present, balanced against the host's ability to create an immune response. Well-perfused tissues and body regions have a much lower infection rate than tissues and body regions with limited perfusion. Numerous patient-related and process-/procedure-related risk factors for developing an SSI have been identified [103]. A variety of alterable risk factors for SSIs have been identified and include preoperative nutritional status, smoking, appropriate and timely antibiotic prophylaxis, maintenance of normothermia, maintenance of normoglycemia, proper intraoperative sterile technique, and prevention of incisional fluid collections [104, 105]. While systemic antibiotic prophylaxis given prior to incision has been shown to reduce postoperative infections, extending therapy beyond the time of surgery has little or no effect. This observation is most likely due to the inability to deliver systemic antibiotics to the surgical site once an incision is made and tissue hemostasis obtained.

The majority of all SSIs are caused by gram-positive pathogens, including (1) *Staphylococcus aureus*, (2) coagulase-negative staphylococcus, and (3) *Enterococcus* spp. Gram-positive organisms cause the vast majority of infections in clean surgical procedures. However, a variety of other pathogens may also cause SSI, particularly in clean-contaminated, contaminated, and dirty procedures. The frequency of particular pathogens is significantly influenced by the body region and type of surgery. Gram-negative bacilli are common causes of infection, particularly *Escherichia coli* surgery involving the gastrointestinal tract, genitourinary tract, or the perineum. Fungi and anaerobes may cause SSIs, particularly in compromised hosts.

Therapeutic Approach for SSI

Surgical site infections are most appropriately treated by prompt and wide opening of the surgical incision. For superficial SSIs, opening of the incision is usually adequate, and antibiotics are not required unless significant inflammatory changes are present in the surrounding tissue. Antimicrobial therapy is recommended for deep incisional surgical site infections if systemic signs of sepsis are present, if source control is incomplete or in immunocompromised patients.

Antibiotic therapy for patients with SSIs who have undergone clean operations should be directed against gram-positive organisms unless particular risk factors for other pathogens are present. The increased incidence of MRSA supports consideration of agents that cover this pathogen until identification and sensitivity data returns. Patients with SSIs following procedures on the gastrointestinal, the genitourinary tract, or the perineum antimicrobial therapy should cover both gram-positive and gram-negative organisms.

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Anemia in the Surgical ICU

25

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Definition and Epidemiology of Anemia in the ICU

Definition of Anemia

The definition of anemia has attracted considerable interest, as several studies have shown that anemia is associated with poorer outcomes in a variety of patient populations, including the critically ill [1, 2]. Based on recommendation of an expert committee some four decades ago, the World Health Organization (WHO) has defined anemia in men and women as a hemoglobin (Hb) <13 g/dL and <12 g/dL, respectively [3, 4]. These general definitions have been applied in most settings, including critical care.

The WHO definition is a reflective of hemoglobin distribution in studied populations, and it has been challenged recently in a population study of 26,530 adults in the town of Tromso in Norway which found that the prevalence of anemia among women was two to three times higher if the WHO criteria were used rather than the constructed reference range of <11.4 g/dL for women. This study provided confirmatory evidence of the gradual decline in mean Hb with age and a postmenopausal decrease of mean Hb among women [5].

Some experts in the field have advocated for new lower limits of normal hemoglobin concentrations to use as reasonable benchmarks for anemia for clinicians to use today (Table 25.1) based on a number of observational studies [6]. But these new definitions have not yet been evaluated in critically ill patient population. A potential definition of severe anemia as <8 g/dL was advocated by a panel of experts convened by the National Institute of Aging in 2004 [7], but further validation studies are needed in general or critically ill populations.

Epidemiology of Anemia in the ICU

Anemia (Hb <13 g/dL) is a common finding among critically ill patients within the intensive care unit (ICU) setting. Studies have demonstrated that up to two-thirds of patients presenting to an ICU may be anemic upon admission, that almost 95 % have anemia by ICU day 3, and that this anemia can persist for up to 6 months in over 50 % of patients beyond discharge [1, 8–14].

In the Audit of the Transfusion in Intensive Care in Scotland (ATICS) study, admission Hb was the factor most strongly associated with the persistence of anemia to ICU discharge. Interestingly, the APACHE II score and ICU length of stay were not independently associated with anemia on ICU discharge [15]. In a study of 155 critically ill patients with an ICU length of stay of 30 days or longer (median 49 days), Hb decreased significantly from mean 11.1 ± 2.5 g/dL on ICU admission to 9.0 ± 1.1 g/dL on ICU day 21. The majority

Table 25.1 Proposed lower limits of normal hemoglobin concentration in adults [6]

Group, age	Hemoglobin, g/dL
White men, years	
20–59	13.7
60+	13.2
White women, years	
20–49	12.2
50+	12.2
Black men, years	
20–59	12.9
60+	12.7
Black women, years	
20–49	11.5
50+	11.5

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Table 25.2 Blood transfusion in the critically ill patients across studies

	N	Mean ICU admission Hb, g/dL	ICU transfusion rate	Mean pre-transfusion Hb, g/dL	Mean transfusions per patient, units
CRIT study, USA [8]	4892	11.0±2.4	44.1 %	8.6±1.7	4.6±4.9
ABC trial, Western Europe [13]	3534	11.3±2.3	37.0 %	8.4±1.3	4.8±5.2
TRICC investigators, Canada [18]	5298	9.9±2.2	25.0 %	8.6±1.3	4.6±6.7
North Thames Group, UK [20]	1247	–	53.4 %	–	5.7±5.2
ABA Multicenter Trials Group [19]	666	–	74.7 %	9.3±0.1	13.7±1.1
CRIT study, USA, trauma cohort [17]	576	11.1±2.4	55.4 %	8.9±1.8	5.8±5.5
ATICS study, Scotland, UK [15, 22]	1023	10.6±1.3	39.5 %	7.4–7.9	1.2–1.9
SOAP study, Europe [21]	3147	–	33.0 %	–	–
Prolonged acute mechanical ventilation [23]	4344	11.1±2.4	67.0 %	8.2±1.4	9.1±12.0

(62 %) of patients received a mean of 3.4±5.3 red blood cell (RBC) units at a mean Hb trigger of 7.7±0.9 g/dL after this period. Transfused patients had significantly greater acuity of illness, phlebotomy volumes, ICU length of stay and mortality, and a lower Hb than those who were not transfused. Small increases in phlebotomy (3.5 mL/day) were associated with a doubling in the odds of being transfused after ICU day 21 [16]. This anemia in critically ill and injured patients is associated with worse clinical outcomes [8, 17].

RBC transfusions are also common in critically ill patients (Table 25.2) [8, 13, 15, 17–23]. Another retrospective analysis of critically ill patients from 139 hospitals in the USA confirmed that anemia, and in particular declining Hb concentration, is associated with a higher likelihood of RBC transfusion (odds ratio [OR] 2.315, 95 % confidence interval [CI] 2.288–2.342) [24]. RBC transfusion is associated with risk and little evidence of benefit [25].

Pathophysiology

Oxygen Delivery and Consumption

Among the many functions of blood and circulatory system, perhaps the most critical and time-sensitive one is delivering oxygen to the tissues and organs throughout the body. While reaching every single cell residing in the furthest corners of body is a daunting challenge in itself, the bigger challenge is to maintain the supply consistent with the demand, which can be rapidly changing severalfold within minutes, while responding to many other changes such as the oxygen content and pressure in the respiratory tract and changes in hemoglobin (Hb) level, as is the case in anemia [26].

Once the oxygen makes its way down to the airways and crosses the alveoli, its effective delivery and distribution to the tissues will be dependent on harmonized collaboration of three key components: a far-reaching circulatory system, a tireless pump, and an effective carrier [27]. Blood carries oxygen mainly in two forms: bound to Hb within the red blood cells and dissolved in water. Each Hb molecule in adults is a tetramer of two alpha and two beta chains, with each individual chain hosting a heme molecule. The Hb-oxygen association is essentially a chemical reaction which involves the iron ions in the center of heme molecules. The rest of the Hb molecule – consisting of over 140 amino acids per chain – is responsible for supporting and modulating this central reaction. Each Hb molecule can bind one to four molecules of oxygen, which translates to about 1.39 mL oxygen per gram of Hb when fully saturated under physiological condition [28]. The value measured in practice is often slightly lower, down to around 1.31 mL, due to the presence of other forms and conformations of Hb [29]. In contrast, oxygen solubility in plasma is around 0.031 mL per liter per each 1 mmHg partial oxygen pressure (PO_2) [27, 28, 30]. The total oxygen content of blood (CaO_2) can be estimated using the equations below:

$$\text{Total Hb-bound oxygen} = \text{Hb concentration} \times \text{Oxygen saturation}\left(SO_2\right) \times \text{Hb oxygen binding capacity} \quad (25.1)$$

$$\text{Total water-dissolved oxygen} = PO_2 \times \text{water oxygen solubility} \quad (25.2)$$

And from 25.1 and 25.2 above:

$$CaO_2 = \text{Total Hb-bound oxygen} + \text{Total water-dissolved oxygen} \quad (25.3)$$

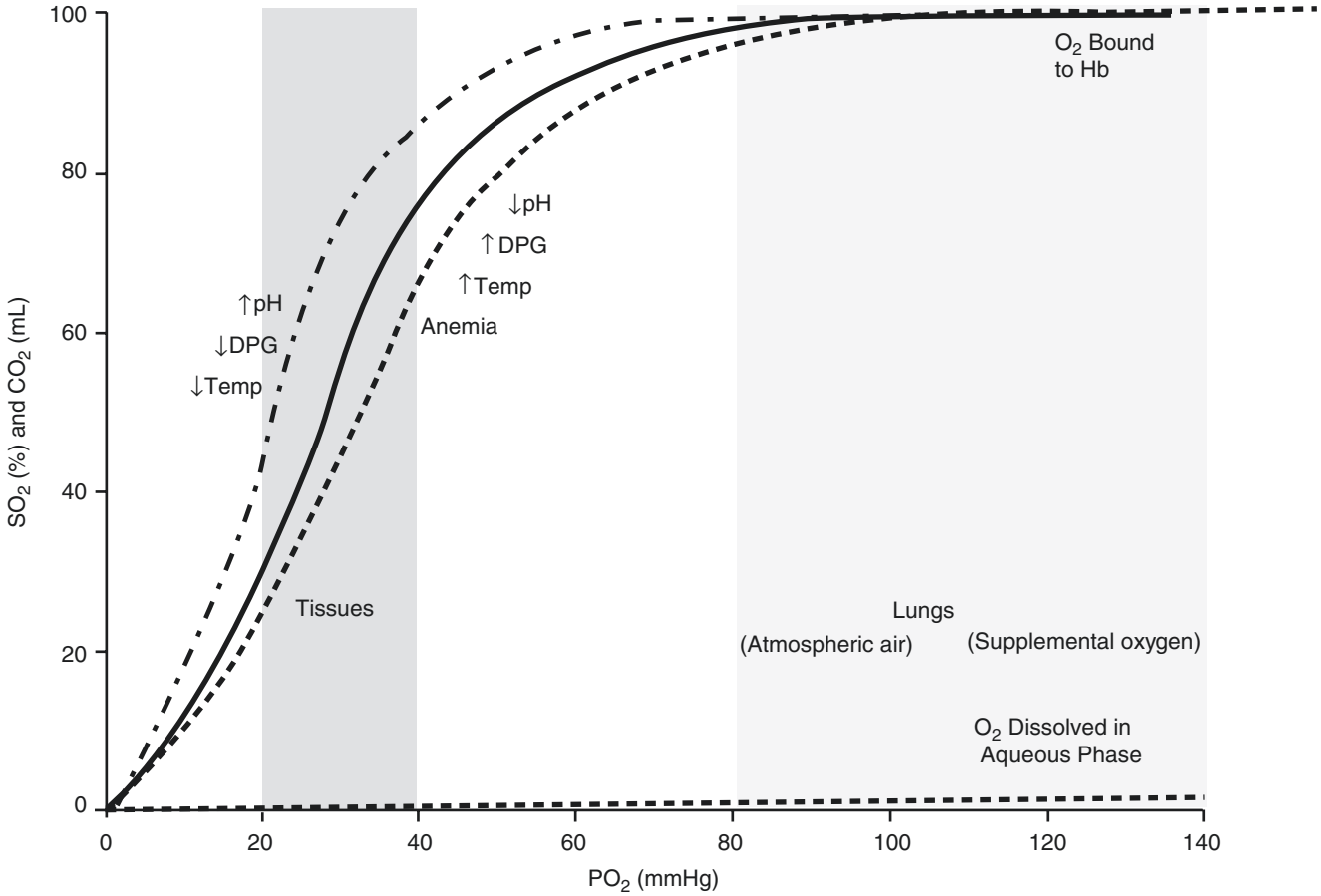

Fig. 25.1 Blood as an oxygen carrier. Relationship between partial pressure of oxygen (PO_2) and Hb-oxygen saturation/content as well as oxygen dissolved in the aqueous phase (plasma and cytoplasm of blood cells) is depicted. The vertical axis represents both the Hb-oxygen saturation (SO_2,%) and the Hb-bound and water-dissolved oxygen content (CO_2, mL) of a 150 mL hypothetical aqueous solution containing 75 g Hb at 37 °C. The *dashed gray lines* represent the shift to the left or right in Hb-oxygen dissociation curve as a result of changes in pH, 2,3-diphosphoglycerate (2,3-DPG), temperature, and anemia. *Dashed black line* represents the oxygen dissolved in the aqueous phase of blood

Considering that the Hb-oxygen-binding capacity is 1.39 mL/g, the calculated Hb-bound oxygen will be expressed in mL per L blood (if Hb concentration is expressed in g/L) or in mL per dL blood (if Hb concentration is expressed in g/dL). Oxygen saturation (SO_2) is usually expressed in %, but should be converted to decimal (e.g., 98 % saturation converted to 0.98). SO_2 in arterial blood (which is commonly denoted as SaO_2) is around 100 % (or 1 for use in the equation). Likewise, water oxygen solubility is about 0.031 mL per liter or 0.0031 mL per dL blood per each 1 mmHg of PO_2. Based on the above, 1 L of arterial blood with Hb concentration of 150 g/L (in which PaO_2 is around 100 mmHg and Hb molecules are fully saturated with oxygen, i.e., $SO_2 = 1$) can carry around 208.5 mL oxygen bound to Hb and around 3.1 mL oxygen dissolved in water. Thus, over 98 % of the oxygen carried by blood is normally bound to Hb [27, 28, 30].

One important aspect of oxygen transportation that is not accounted for in these simple equations is the Hb-oxygen association (or dissociation) curve. Unlike dissolving of oxygen in water which is directly related with PO_2 according to Henry's law (Eq. 25.2, Fig. 25.1), oxygen binding to Hb is dependent on availability of heme sites, which will reach a plateau sooner or later as all the oxygen-binding sites become occupied. Furthermore, Hb is a complex macromolecule that undergoes conformational changes in response to oxygen binding and the presence of other effectors. It has been long-recognized that Hb molecules generally exist in one of two conformational states – the T (tense) state and the R (relaxed) state, with the R state having a higher affinity for oxygen compared with T state [31].

Hb undergoes conformational changes as oxygen binds to the available heme site on each of the subunits, shifting from T state to R state and modulating the affinity of other available heme sites for oxygen. As a result, binding of oxygen is facilitated at higher PO_2 (e.g., at the alveolar capillary beds in the lung), while its release is facilities at lower PO_2 (e.g., at target tissues). This behavior is portrayed in the characteristic sigmoid Hb-oxygen association curve (Fig. 25.1). On the other hand, Hb molecules undergo allosteric regulation through interactions with other molecules and ions such as H^+ (pH) and 2,3-diphosphoglycerate (2,3-DPG) and

environmental parameters such as temperature, further modulating their affinity for oxygen in response to their vicinity. Increased temperature and levels of H^+ (lower pH) and 2,3-DPG – common at sites of increased oxygen consumption and/or low availability – decrease the affinity of Hb for oxygen and facilitate the release of oxygen, while release of oxygen from Hb molecules is inhibited in the presence of lower levels of H^+ (higher pH) and 2,3-DPG and lower temperature [30]. These changes result in shift of the Hb-oxygen association curve to the right and left, respectively (Fig. 25.1) [27, 30, 32].

The precise modulation of the affinity of Hb molecules for oxygen turns Hb into a highly efficient and specialized oxygen carrier that senses its surrounding and responds accordingly. As a result, Hb molecules react to scenarios of increased demand (e.g., physical activity or when fighting an infection) and reduced supply (e.g., anemia) by shifting the oxygen dissociation curve to the right (Fig. 25.1), off-loading their oxygen content easier and more readily when and where it is needed most [30, 32].

Besides modulation of Hb-oxygen affinity which affects how readily oxygen is released from Hb at any given PO_2, the real drive behind moving oxygen from the blood into the tissues is the PO_2 gradient: oxygen simply flows from higher PO_2 to lower PO_2 [33]. This gradient has been investigated in animal models as it spans from the arterioles (PO_2 around 80 mmHg), to the capillary (PO_2 around 60–30 mmHg), to the interstitial space (PO_2 around 30 mmHg) and eventually into the cells (PO_2 around 20 mmHg [34, 35], with the PO_2 gradient between the capillary and the interstitial space as the one driving the oxygen to be released from Hb molecules. This so-called transmural PO_2 gradient can be very small, as low as 1 mmHg/μm [36]. Nonetheless, given that Hb normally resides within the red blood cells (RBCs) in the blood and the blood is a non-Newtonian fluid [37], its rheological characteristics, namely, RBC nonsteady and heterogeneous flow, deformity and uneven distribution in microvasculature come into play as well. Recent models of moving RBCs through capillaries have shown that PO_2 across the RBC membrane can be greater than the PO_2 in plasma between the RBCs by as much as 30 mmHg, and the PO_2 in plasma drops by 9 mmHg over a distance of 50 μm [38]. Hence, the effective PO_2 gradient that is responsible for driving oxygen from the Hb molecules within the RBCs to the interstitial space and the cells into the mitochondria where it is eventually consumed can be markedly different from what is grossly measured at high level.

Oxygen delivery pathway ends primarily at the mitochondria, where over 90 % of the oxygen consumption by the body takes place, with oxygen being used as the ultimate electron acceptor to complete the aerobic respiration pathways and generate ATP [39]. Body oxygen consumption (VO_2) is the difference in oxygen content of the inspiratory air and the expiratory air. From a clinical point of view, VO_2 can be measured by multiplying cardiac output (CO) by the difference in oxygen content of systemic arterial and venous blood (CvO_2):

$$VO_2 = CO \times \left(CaO_2 - CvO_2 \right) \tag{25.4}$$

VO2 is often compared with another important parameter, oxygen delivery (DO_2), which is the total amount of oxygen delivered to the body per unit of time, and is a function of cardiac function (represented by CO) and the oxygen content of arterial blood:

$$DO_2 = CO \times CaO_2 \tag{25.5}$$

The key in maintaining adequate oxygen supply to the body is to ensure that DO_2 exceeds VO_2 at the systemic circulation level and, more importantly, at the level of microcirculation at individual tissues throughout the body. The difference between VO_2 and DO_2 can be expressed by the oxygen extraction ratio (O_2ER):

$$O_2ER = VO_2 / DO_2 \tag{25.6}$$

Normally DO_2 far exceeds VO_2 by a factor of 3–5, resulting in O_2ER of around 20–30 %. It should be remembered that the 20–30 % is an average range for the whole body and the O_2ER of individual organs and tissues can be markedly different. Notably in heart muscle, the O_2ER is much higher, around 60 % at rest and more as demand rises during exercise [29].

The large headroom in O_2ER across various tissues means that oxygen demand of tissues can still be met despite significant variations in DO_2, as is the case of anemia, a concept that is termed "supply independency." In contrast, conditions such as critical illness and septic shock are typically associated with increased VO_2, which can get dangerously close to DO_2, leading to a situation known as "supply dependency" (usually considered when O_2ER >50 % at rest). In this case, minor variations in either VO_2 or DO_2 of tissues can result in local oxygen demand exceeding the supply, leading to tissue ischemia and injury [40].

Red Blood Cell Life Span and Regulation of Red Cell Mass

RBCs live for around 120 days in the circulation. This life span is astonishingly long, when the far distances the RBCs travel, narrow capillaries they navigate (some even narrower than their own diameter), and shear stress they endure continuously are taken into consideration [31, 41].

The aging of RBCs is a complex process involving several phenomena that gradually erode the functionality and viability

of RBCs and lead to their removal from the circulation and destruction by macrophages. Being carriers of oxygen – an evolutionary toxin [42] – it is not surprising that RBCs are faced with significant oxidative stress in the form of various reactive oxygen species. RBCs are equipped with highly effective cytosolic antioxidant systems including glutathione peroxidase, catalase, and peroxiredoxin-2 that can neutralize many of these reactive oxygen species [43]. However, these protective systems have relatively limited access to the cell membrane, where auto-oxidation of membrane-bound Hb molecules may lead to stiffness and reduced fluidity of cell membrane, impairing the deformability of the RBCs – a key characteristic required for their survival [44]. Accumulating cytoskeletal damage further contributes to the problem. Other hallmarks of RBC aging include loss of membrane surface area, increased vesiculation and loss of cell volume (including loss of Hb content), increased cell density, and biochemical changes (e.g., decreased 2,3-DPG and lowered hexokinase and glucose-6-phosphate dehydrogenase activity) leading to diminished cellular energy level (reduced ATP), increased Hb-oxygen affinity, and reduced ability to neutralize oxidative stress [43, 45, 46].

Eventually, these and other signs of aging reach a critical level that alerts the molecular biosensing systems in the spleen and reticuloendothelial system to remove the aged RBC [47]. The oxidative stress and the resulting RBC aging process may become more pronounced when Hb molecules are partially oxygenated, as seen in hypoxic conditions [44]. Some deleterious aspects of aging may occur sooner in the lifetime of RBCs during critical illness, accelerating their demise, a factor that may contribute to higher prevalence of anemia and more therapeutic challenges in these patients [31, 41].

In addition to the aging of the RBCs, some RBCs are removed untimely through two other processes: eryptosis and neocytolysis [41]. Eryptosis is the premature death of mature RBCs. Its rhyming with apoptosis is not accidental as the phenomenon shares similarities with the extensively studied phenomenon of programmed cell death [48]. Eryptosis is in part triggered by the same oxidative stressors that lead to RBC aging, and it is characterized by a suicidal cascade of biochemical changes that result in cell vesiculation and shrinkage, cell membrane blebbing, and cell membrane phospholipid scrambling, which involves abnormal redistribution of components of the cell membrane which exposes some normally internal components (e.g., phosphatidylserine) to the outside of the RBC [41, 48]. The now-exposed internal molecules such as phosphatidylserine act as ligands for receptors on macrophages that signal them to bind the RBCs harboring the ligands and engulf them [49]. This process can be an effective way of eliminating defective cells with less "collateral damage" (compared with hemolytic pathway), reducing the potential for inflammation and other consequences of hemolysis [48], but when excessive, it can also contribute to the emergence of anemia [41, 48].

Neocytolysis is the process of selective removal of new RBCs just released from the bone marrow following a sudden reduction in the level of erythropoietin, as is physiologically encountered during rapid descent from altitude [41, 50]. Neocytolysis and eryptosis can be considered as tools for the body to rapidly adjust the RBC mass in response to the environmental factors and pathophysiological conditions [41].

Given the limited life span of RBCs and the associated large-scale turnover, maintaining the 20–30 trillion RBCs that normally reside in the body at any given time requires production of around 200 billion new RBCs every day, corresponding to around 15–20 mL of packed RBCs or 30–40 mL of blood with hematocrit of 50 %. This baseline production can be boosted up to ten times if needed (e.g., following acute anemia and heavy blood loss) in otherwise healthy, iron-replete individuals [41].

These numbers are indicative of the great logistics required to support hematopoiesis. Production of new RBCs requires adequate supply of iron, zinc, folic acid, and vitamin B_{12}, among other factors, and shortage of any of these can lead into impaired erythropoiesis and various types of anemia. The process is under tight regulation by a number of factors including erythropoietin, androgens, catecholamines, cortisol, and thyroxine, which act collectively to ensure that the supply of new RBCs keeps up (or down) with the demand while adapting to a host environmental, metabolic, and pathophysiological changes [41]. This ongoing regulation can respond effectively to acute changes (a rapid stress responds) and chronic conditions [51]. As a result, the mass of RBCs in the circulation is controlled to maintain an adequate supply of oxygen to the tissues.

It should be remembered that the impact of these regulators goes beyond erythropoiesis. The level of erythropoietin – produced by liver in fetus and kidney in adults – is primarily controlled by the oxygen-carrying capacity of blood, and it is stimulated by hypoxia, which works on hematopoietic cells to promote proliferation of progenitor cells and their differentiation and inhibit their apoptosis. In addition to these hematopoietic cells, the receptors for erythropoietin have been found on many other cells in endothelia, smooth muscles, heart, and nervous system, where it can impact ion flux, neurotransmitter synthesis, angiogenesis, ventilation, protection against ischemia, and more [52].

Mechanisms of Compensation

Several compensatory mechanisms assist body to maintain oxygen supply to the tissues in face of anemia. While the deleterious effects of anemia (even mild or moderate) on worsening the clinical outcomes of patients are well

documented [2, 27], reduced hematocrit of blood might not have an immediate negative impact on tissue DO_2. The way blood behaves in microcirculation can be markedly different from macrocirculation, and as RBCs file one after another to pass through capillaries with decreasing diameter, a point is reached where effective hematocrit of blood is significantly lower than the systemic hematocrit of blood, and it stays relatively unchanged over a wide range of changes in the latter (the Fahraeus effect) [53].

The body is equipped with accurate "oxygen sensors" which continuously monitor the level of oxygen delivery to the tissues and alert body of any deviations. These oxygen sensors exist and act at various levels throughout the body, ranging from subcellular level (e.g., the hypoxia inducible factor (HIF) signaling pathway) [54] to the tissue level (e.g., the chemoreceptors of aortic and carotid bodies and oxygen sensors in the renal cortex) [55–57]. One of the early response to anemia is elicited in the kidneys, where reduced PO_2 results in increased production of erythropoietin, working to enhance erythropoiesis to restore RBC mass [58]. Compensation of anemia occurs at various other levels and involves a plethora of mechanisms affecting literally every stage of oxygen delivery pathway from respiratory system to inside the cells where oxygen is consumed.

In anemia, CaO_2 is reduced while SaO_2 usually remains unchanged. As a matter of fact, a severely anemic patient can still have a SaO_2 of near 100 %, which simply means all oxygen-binding sites on available Hb molecules are occupied by oxygen molecules, but here the limiting factor is the reduced number of available Hb molecules. Even though availability of oxygen in alveoli is usually not the limiting factor in anemia, the body still responds to anemia by increasing respiration and ventilation. Additionally, ventilation-perfusion matching is improved through nitric oxide (NO)-mediated mechanisms, further ensuring PaO_2 and SaO_2 are maintained at the maximum level [59].

Another level of compensatory mechanisms takes place in the cardiovascular system. As discussed previously, DO_2 is a product of CO and CaO_2 (Eq. 25.5). Therefore in theory, any decrease in CaO_2 (e.g., resulting from anemia) can be neutralized by the same level of increase in CO. CO itself is a product of pulse rate and stroke volume [60]. During anemia, hypoxia sensors of chemoreceptors activate the sympathetic nervous system which increases CO, mediated by reduced afterload, increased venous return and preload, and positive inotropic and chronotropic changes increasing contractility of heart muscle and pulse rate. Reduced afterload is due to systemic vasodilatation and decreased vascular resistance, which resulted from a host of other changes, namely, increased NO activity, hypoxia-induced vasodilatation, increased recruitment of microvasculature (and even new angiogenesis in chronic anemia), as well as the reduced viscosity of diluted blood. These changes may even lead to left ventricular hypertrophy over time [60]. Reduced viscosity of blood in anemia can further help local perfusion by increasing the regional blood flow at the tissue and organ level leading to increased O_2ER [26]. On the other hand, maintaining microvascular perfusion and functional capillary density is dependent on maintaining a minimum level of blood viscosity, and extreme hemodilution may undermine this, further reducing DO_2 [61].

At the cellular and subcellular levels, compensatory mechanisms occur at RBCs as well as the target cells that consume oxygen. During anemia, the oxygen dissociation curve of Hb within the RBCs is shifted to the right following increased accumulation of 2,3-DPG, reduced pH, and other NO-mediated signaling events in RBCs at tissues [62–64]. This results in reduced affinity of Hb for oxygen and easier unloading of oxygen at tissue sites at relatively higher PO_2. Hence, despite reduced DO_2, oxygen extraction ratio increases, maintaining the oxygen supply. This phenomenon can be seen in experimental models in the brain where oxygen extraction can increase from a baseline of about 30 % to almost 50 % during anemia [65]. Nonetheless, dependence on increased O_2ER means that this strategy can only be helpful in tissues where baseline O_2ER is not high and there is some headroom to increase it. Organs with high baseline O_2ER such as heart may have very limited room to further increase it, and therefore they need to rely on another strategy – increased local blood flow – to maintain oxygen supply consistent with the demand during anemia [66, 67].

HIF signaling pathway – known as the master regulator of hypoxic cell signaling – plays an important role in compensation of anemia and hypoxia [68, 69]. Even a small reduction in tissue PO_2 can result in stabilization of HIF, an otherwise short-lived transcription factor, which activates and promotes the transcription of a host of other hypoxia response genes [68]. These hypoxia response genes are involved in modulating cardiovascular adaptation to anemia [69], promoting erythropoiesis through increased production of erythropoietin [70], promoting angiogenesis through inducing vascular endothelial growth factor (VEGF) [71], and increasing glucose transport to the cells and shifting cellular metabolism from aerobic to anaerobic (glycolytic) [72]. Studies have indicated that during acute anemia, cardiac oxygen consumption may increase at the expense of reduced oxygen consumption to other organs [73]. This shift makes sense given the critical role of heart in cardiovascular compensation of anemia and can be viewed as an attempt by the body to shift a limited resource (oxygen) from organs with less demand to those with highest and most critical need for it. This redistribution is also dependent on HIF-mediated metabolic adaptations at cellular level [73].

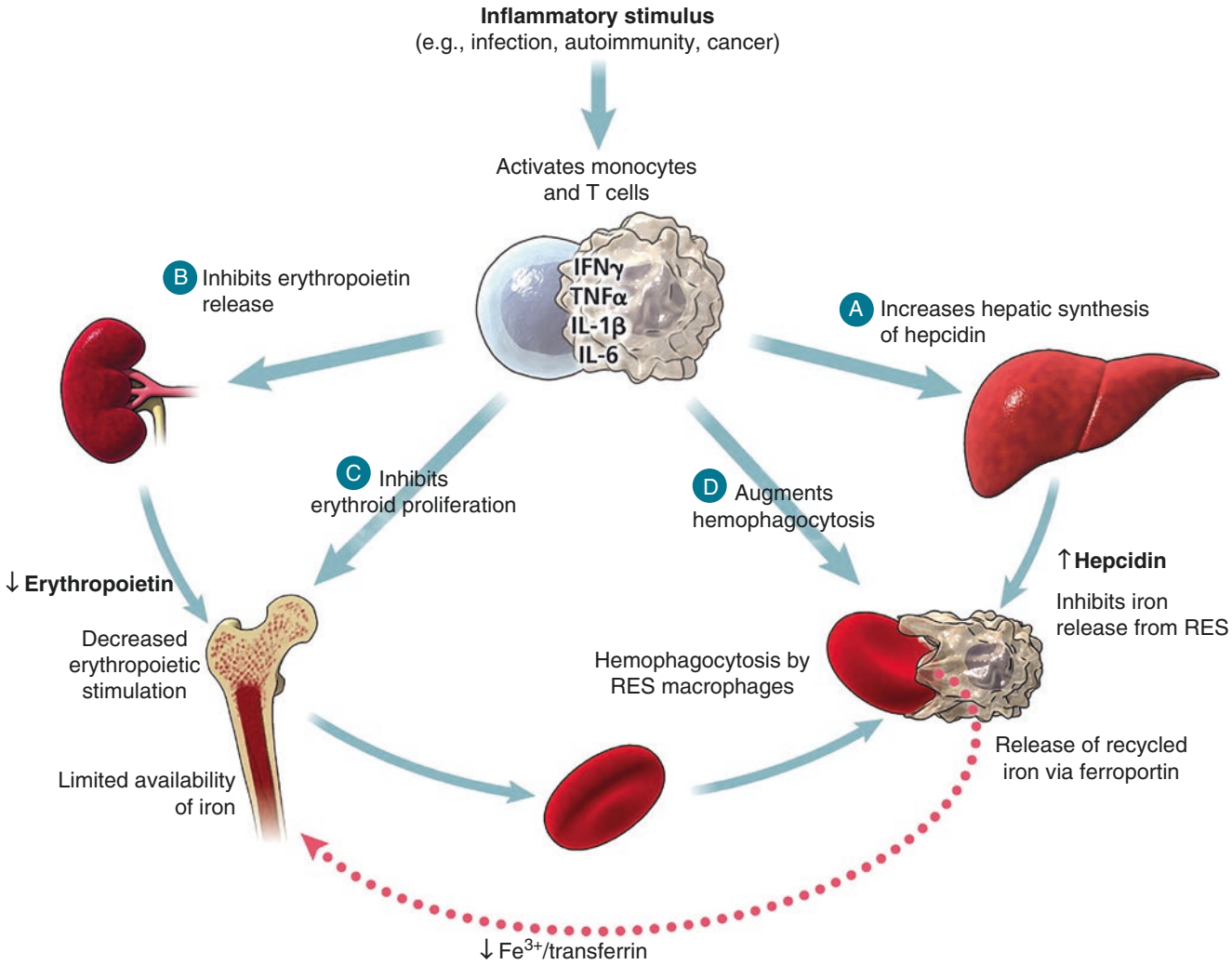

Fig. 25.2 Underlying mechanisms of anemia in critical care and trauma. In inflammatory diseases (including critical care, trauma, tissue injury, and hemorrhage), cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in Hb levels and inability to recover from anemia: (**a**) induction of hepcidin synthesis in the liver (especially by interleukin-6 [IL-6] and endotoxin). Hepcidin in turn binds to ferroportin, the pore that allows egress of iron from reticuloendothelial macrophages and from intestinal epithelial cells. Binding of hepcidin leads to internalization and degradation of ferroportin; the corresponding sequestration of iron within the macrophages limits iron availability to erythroid precursors. (**b**) Inhibition of erythropoietin release from the kidney (especially by interleukin-1β [IL-1β] and tumor necrosis factor α [TNFα]). Erythropoietin-stimulated hematopoietic proliferation is in turn reduced. (**c**) Direct inhibition of the proliferation of erythroid progenitors (especially by TNFα, interferon-γ [IFNγ], and IL-1β). (**d**) Augmentation of erythrophagocytosis by reticuloendothelial macrophages (by TNFα). *RES* reticuloendothelial system (From Zarychanski and Houston [75]. This work is protected by copyright and the making of this copy was with the permission of Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law)

Mechanisms of Anemia in Critical Care

While the role of inflammatory processes in the development of anemia in critically ill patients is often underscored (the so-called anemia of inflammation) [41, 74], anemia in these patients is almost always multifactorial. A number of underlying factors include pathologic iron homeostasis related to hepcidin, impaired erythropoiesis, shortened red blood cell life span, blunted erythropoietin response, RBC loss, and hemodilution (Fig. 25.2) [75, 76].

RBC Loss

Critically ill patients are at risk of losing significant amounts of blood. This is related to both (1) phlebotomy-related blood loss

for diagnostic laboratory testing and (2) acute blood loss and hemorrhage. Hb concentration decreases on average by 0.52 g/dL/day in non-bleeding ICU patients [10]. Mean daily blood loss related to diagnostic laboratory testing has been reported to be as much as 40 mL per day, contributing to 17–40 % of total blood loss in the ICU [13, 77]. Increased phlebotomy volume is associated with severity of illness, number of blood draws, and type of diagnostic testing tubes used. It has been documented that phlebotomy-related blood loss is associated with significant increased risk for RBC transfusion in critically ill patients with prolonged ICU length of stay [16].

A number of strategies can be used to reduce RBC loss in ICU patients. The use of closed blood conservation devices to reduce phlebotomy-associated blood loss is associated with reduced RBC transfusion requirements and decreased anemia in ICU patients [78–81]. Another effective strategy is to use pediatric or low-volume adult blood sampling tubes for blood draws [82]. A recent study compared the use of low-volume vs. conventional volume blood sampling tubes in 248 adult critically ill patients admitted to a surgical ICU. Low-volume sampling tubes were associated with significantly reduced phlebotomy volume (174 ± 182 mL vs. 299 ± 355 mL, $p = 0.001$). Daily blood draws also were less, 22.5 ± 17.3 mL vs. 31.7 ± 15.5 mL, $p < 0.001$. On the other hand, the difference in RBC transfusions was not statistically significant (4.4 ± 3.6 units vs. 6.0 ± 8.2 units, $p = 0.16$), but this may have been related to inadequate sample size of the study [83]. Patients should have daily assessment to eliminate any unnecessary diagnostic laboratory testing in the ICU, and standing orders and lab tests that are not likely to affect the course of management should be avoided.

Acute blood loss and hemorrhage are another etiology of anemia in the ICU. In a study of 211 ICU patients, 21 % had at least one episode of clinically significant hemorrhage. Of these patients, 65 % had one episode, 20 % had two episodes, and 15 % had three or more episodes of hemorrhage during their ICU stay [15].

Impaired Erythropoiesis: Reduced RBC Production and Shortened RBC Life Span

Another key reason for decrease of hemoglobin concentration in ICU patients is bone marrow suppression and inappropriate erythropoietic response [84–88]. Erythropoiesis is tightly regulated by erythropoietin circulating concentrations which are normally increased in states of anemia. A major feature of the anemia of critical illness is a failure of circulating erythropoietin concentrations to increase appropriately in response to the reduction in Hb concentration (Fig. 25.2) [84, 86, 87, 89]. This blunted endogenous erythropoietin response has also been documented in trauma patients [90].

During critical illness, there is reduced transcription of the erythropoietin gene by inflammatory mediators (IL-1, TNF-alpha, and TGF-beta). These inflammatory cytokines also directly inhibit RBC production through interactions with erythroid progenitor cells. Vasopressor agents also directly inhibit hematopoietic precursor maturation [91].

It has also been documented that a sudden and continued drop in erythropoietin production and concentrations with the onset of any acute inflammatory condition may promote neocytolysis (selective removal of young circulating RBCs just released from the bone marrow) and eryptosis (the premature death of mature RBCs) [50]. Eryptosis can be triggered by excessive oxidant RBC injury and is inhibited by erythropoietin which extends the life span of circulating RBCs. Excessive eryptosis can lead to anemia [48].

These observations suggest that treatment with pharmacological doses of an erythropoietin-stimulating agent (ESA) might raise the Hb concentration and as a result reduce allogeneic RBC transfusion requirements in critically ill patients. With the increasing adoption of restrictive transfusion strategies in critical care setting, the impact on reduction in RBC transfusion may become negligible [92]. Nonetheless, a meta-analysis of five randomized trials reported that there may be a dose-response ESA effect as the use of higher doses of ESAs resulted in a greater decrease in the number of units of blood transfusion [93].

ESAs are currently not indicated for treatment of anemia in general critically ill patients, but are indicated in those with chronic kidney disease and acute renal failure. Interestingly, analysis of the trauma cohort from two multicenter randomized controlled trials confirmed a survival advantage for critically ill trauma patients with ESA treatment [92, 94, 95].

Diminished RBC production can be due to nutritional deficiencies, but this is rare in ICU patients. Few studies have investigated this issue in critically ill patients. In one small study, only 2 % of patients were documented to have folate or B12 deficiency [86].

Iron Homeostasis and Hepcidin

Iron studies in critically ill patients consistently demonstrate low serum iron and transferrin saturation with high serum ferritin levels, likely to be related to the inflammatory state [96]. While absolute iron deficiency may not be very common in ICU patients and it can be difficult to diagnose in these patients [86], most critically ill patients have functional iron deficiency (FID) with low iron availability for endogenous RBC production. The percentage of hypochromic red cells and reticulocyte hemoglobin content are the best established tests for diagnosis of FID. Erythrocyte zinc protoporphyrin (eZPP) measurement is also a sensitive index of FID but is less sensitive to acute changes in iron availability, and it is essential that measurements be made on washed cells [97].

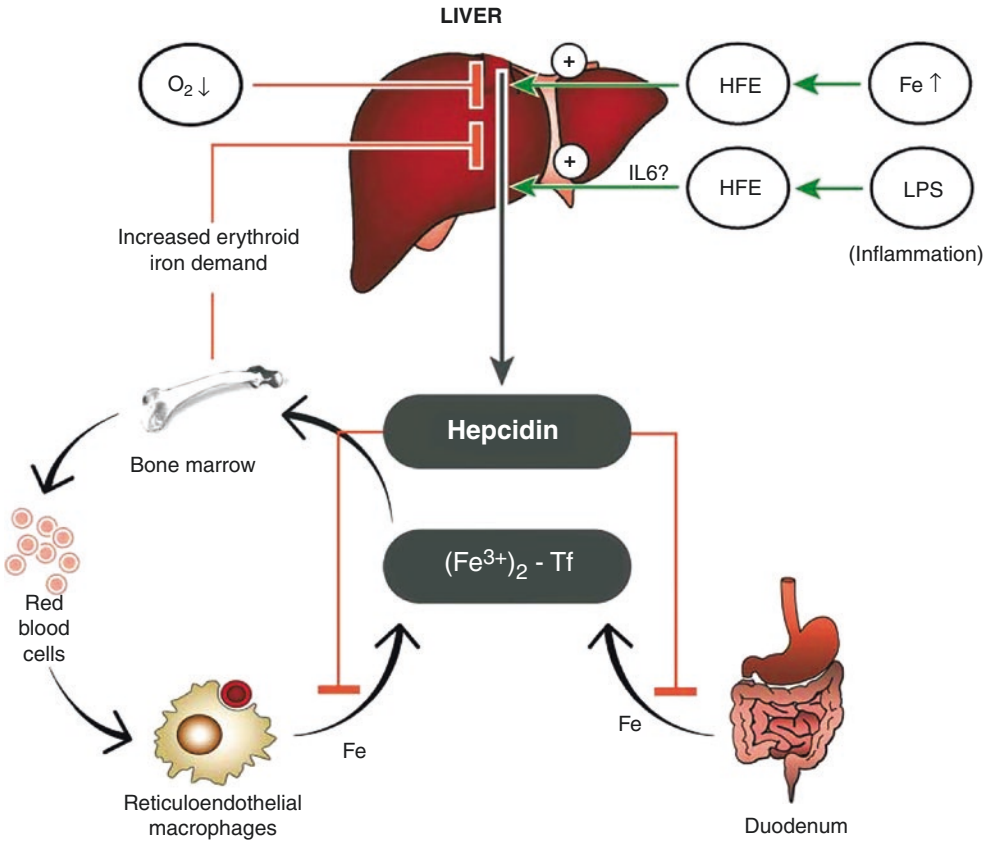

Fig. 25.3 Hepcidin induces functional iron deficiency in anemia of inflammation. Hepcidin reduces iron availability via two mechanisms: (1) decreased absorption of iron across the gastrointestinal tract and (2) decreased release of iron from the reticuloendothelial system

Numerous pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha, and others) impair iron homeostasis and normal reticuloendothelial system functioning and decrease intestinal absorption of iron via regulatory feedbacks [98, 99].

Recently, the role of hepcidin, a liver-derived 25-amino-acid peptide that is known as the master regulator of iron homeostasis, has gained more attention. Hepcidin is upregulated in inflammation, in infection, or when excess iron is detected, resulting in reduced iron bioavailability [100, 101]. Hepcidin mediates iron homeostasis by binding to the iron exporter ferroportin, inducing its internalization and degradation, with resultant decreased absorption of iron through the gastrointestinal tract and decreased release from the reticuloendothelial system (Fig. 25.3). Hepcidin is downregulated by iron deficiency, anemia, and tissue hypoxia [100, 101]. Additionally, hepcidin levels rise to extremely high levels after trauma and are positively correlated with injury severity and duration of anemia [102]. Erythropoietin stimulation via ESA treatment results in decreased hepcidin expression [103]. Further studies document that hepcidin is an important modulator of the acute inflammatory response [104, 105].

New studies are now targeting the hepcidin-ferroportin axis to develop new treatment strategies for anemia of inflammation [106, 107]. It has been documented that pharmacological ESA doses can overcome the erythropoietin resistance present in anemia of inflammation. Furthermore, a single ESA injection can cause rapid suppression of serum hepcidin concentrations in humans [108, 109].

Hepcidin neutralization has been proposed as a therapeutic treatment for anemia of inflammation, and several hepcidin antagonists are being developed and tested [110]. The hepcidin inhibitor NOX-H94 (a structured mirror-image RNA oligonucleotide) has undergone clinical trials to treat anemia associated with chronic disease [111]. LY2787106 is a humanized antibody designed to bind to hepcidin and neutralize its function and has been undergoing trial in patients with cancer-associated anemia (NCT01340976). PRS-080 is a type of anticalin (non-antibody proteins that can specifically bind to antigens similar to antibodies), and it specifically binds human hepcidin with subnanomolar affinity, and it is also considered for human study. The results of these clinical trials will help determine the efficacy of hepcidin antagonists as novel therapeutics for iron-restricted anemia and anemia of inflammation.

Most recently, a new hormone (erythroferrone, ERFE) has been identified that mediates hepcidin suppression (Fig. 25.4) [112]. ERFE mediates hepcidin suppression to allow increased iron absorption and mobilization from stores. Interestingly, ERFE is produced by erythroblasts in response to erythropoietin treatment [112]. These experimental findings suggest that ESA treatment, via modulation of both hepcidin and ERFE, may have significant impact on the acute inflammatory response in critical illness.

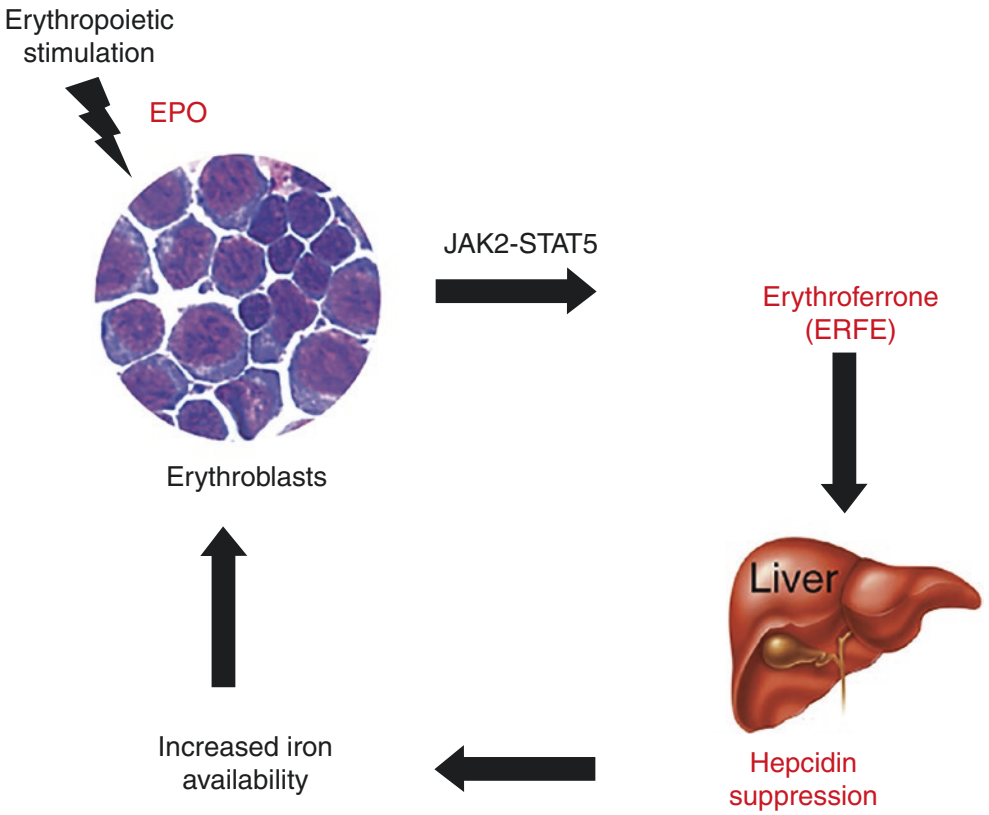

Fig. 25.4 Proposed role of the erythroid factor erythroferrone (ERFE). Prior studies suggested that high levels of EPO cause hepcidin suppression indirectly by inducing the secretion of erythroid regulators from the bone marrow, which in turn act on the liver to suppress hepcidin expression and increase iron delivery from dietary absorption and stores. A new hormone and erythroid regulator, erythroferrone (ERFE) has been identified that suppresses the hepatic synthesis of the principal iron-regulatory protein hepcidin, resulting in increased iron uptake. Erythroferrone production by erythroblasts is greatly increased when RBC synthesis is stimulated, such as after bleeding or in response to anemia. In normal volunteers, erythropoietin administration was sufficient to profoundly lower serum hepcidin levels in less than a day without any significant changes in serum iron concentrations, and its action was presumed to be mediated via ERFE (Reprinted by permission from Macmillan Publishers Ltd: Kautz et al. [112], copyright 2014)

Hemodilution

Anemia in ICU patients can also be in part related to hemodilution due to crystalloid fluid resuscitation for other disease processes (e.g., hypovolemic and septic shock, gastrointestinal, and other body fluid losses). It is important to consider the impact of crystalloid fluid resuscitation with resultant hemodilution on the development of anemia in the ICU and to decrease fluid resuscitation.

Management/Treatment of Anemia

The initial management of anemia begins with avoidance of any red blood cell loss. Patients in the ICU are at high risk for iatrogenic causes of blood loss, most likely from phlebotomy. Blood collection can lead up to 70 mL of blood taken from the patient on a daily basis. The body normally produces only 0.25 mL/kg of blood on daily basis [113]. In an average 70 kg patient, this is only 17.5 mL of RBC production daily. Clinical institutions have multiple methods to help reduce blood volumes withdrawn for laboratory testing. A goal of using small-volume or pediatric phlebotomy tubes can be instituted. The use of ordering routine multiple daily phlebotomies for blood sampling should cease, and lab testing should be initiated only when clinical signs or symptoms indicate the need. Nursing practices can implement closed-loop systems that return blood that is ordinarily wasted back to the patient. Point-of-care and inline bedside microanalysis of blood or noninvasive hemoglobin monitoring with pulse co-oximetry are other ways to monitor hemoglobin for anemia while minimizing blood loss [114].

In surgical patients where ongoing blood loss is expected, various methods for blood cell recovery are available. Continuous autotransfusion systems collect the shed blood from surgical fields via drains placed during surgical wound closure. The devices then filter, wash, and spin the collected blood in order to isolate RBCs to autotransfuse back to the patient. These devices are more commonly used for orthopedic and cardiac procedures. While in the general population

of patients with normal initial hemoglobin and hematocrit, these devices have not shown to consistently decrease costs or need for transfusion [115], in the setting of a critically ill patient who has higher risks of anemia for multiple other risk factors, the use of these devices could be considered appropriate.

Further assessment should include the evaluation of other therapies being administered to the patient that might be leading to blood loss or anemia. Many medications that are prescribed in the ICU can cause anemia via two pathways: hemolytic anemia or suppression of endogenous production and release of renal erythropoietin. Immune-mediated hemolytic anemia can be seen after administration of cephalosporins, beta-lactams, NSAIDS, antineoplastics, quinine, and methyldopa. The most common medications causing immune-mediated hemolytic anemia are piperacillin, cefotetan, and ceftriaxone [116]. Medications causing nonimmune-mediated hemolytic anemia that are more commonly used in the ICU are nitrofurantoin, phenazopyridine, primaquine, and sulfa drugs [117]. Treatment for drug-dependent, antibody-induced, macrophage-mediated hemolytic anemia is the discontinuation of the offending medication. For drug-independent hemolytic anemia, corticosteroids are the recommended first-line therapy [118]. Medications administered in the ICU can also suppress the release of erythropoietin. Such medications include angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, theophylline, and beta-adrenergic blockers [41].

The critical care clinician should remain vigilant and continue to monitor for possible new bleeding sources in the surgical ICU patient. Critically ill patients are at risk for bleeding complications and ongoing blood loss. In a study of 100 ICU patients, a bleeding evaluation tool was used to examine the frequency, severity, and causes of bleeding complications in the medical surgical ICUs. Researchers reported that of the 100 patients, 90 % experienced bleeding, resulting in 480 separate bleeding events. One in five patients suffered from a major bleeding event, with a median length of time of 4 days. Interestingly, only 15 % of bleeding events were at the surgical site. More often, the site of bleeding was at the insertion site of a vascular catheter (38 %) and endotracheal tube site (16 %). Six percent of bleeds were gastrointestinal in nature [119]. Some correctable causes of ongoing blood loss include thrombocytopenia, acquired coagulopathies, and GI bleeding. Thrombocytopenia in the ICU can be multifactorial. Conditions leading to decreased overall number or decreased platelet activity include hemodilution from red blood cell transfusion due to massive blood loss, platelet consumption (from bleeding, trauma, or disseminated intravascular coagulation [DIC]), platelet destruction secondary to immune response in the septic patient, decreased platelet production caused by liver disease, suppressed bone marrow or viral infection, and increased splenic sequestration. Medications are also likely culprits in diagnosing the cause of thrombocytopenia in a critically ill patient. In the cardiac surgery patient, especially those requiring mechanical assist devices, there is continued consumption of platelets. Post-cardiac bypass patients routinely have thrombocytopenia secondary to sequestration and platelet activation and adhesion to synthetic surfaces of cardiac bypass machines [120, 121].

DIC is a much less common cause of anemia in the ICU, but the clinician should remain watchful for signs, especially in patients with severe sepsis or trauma. DIC is defined as a clinical state with abnormally low platelet count caused by consumption of platelets and other coagulation factors. Laboratory testing will reveal prolonged coagulation times. Mechanisms include aberrations in endothelial function and loss of balance between procoagulant, anticoagulant, and fibrinolytic factors in the body. The presence of DIC is considered an independent predictor of mortality in the hospitalized patient. While bleeding and anemia will be the most obvious clinical signs, there is often an underlying end organ damage occurring secondary to microvascular thrombosis [114]. Successful treatment of DIC is a challenge, since the underlying cause is usually difficult to absolutely eliminate acutely. Improvements have been made in the prevention of DIC by correcting acidosis, hypothermia, and avoiding hemodilution.

While limiting blood loss will help prevent worsening of anemia, there are other multiple factors that hamper the process of erythropoiesis in the critically ill patient. The ICU patient can be seen as a patient suffering from multiple inflammatory processes that impair RBC proliferation, iron metabolism, and erythropoietin production. One theory is that this is a broad-based evolutionary response to sequester and deny iron from invading microorganisms [41]. Iron homeostasis is impacted by numerous pro-inflammatory cytokines, including IL-1, IL-6, and tumor necrosis factor (TNF)-α, leading to impaired regulatory feedback between iron body needs and intestinal iron absorption [98]. Hepcidin, which is upregulated by pro-inflammatory cytokines, will lead to decrease duodenal iron absorption and block iron release from macrophages. This will then limit iron availability for progenitor cells. Pro-inflammatory mediators also lead to reduced transcription of the erythropoietin gene and transforming growth factors, creating another hurdle for RBC production [74]. Patients in shock suffer from further inhibition of hematopoietic precursor maturation secondary to high levels of vasoactive agents such as norepinephrine and phenylephrine [91].

Since there is consistent evidence that a major feature of the anemia of critical illness is the failure of circulating erythropoietin to increase appropriately in response to reduced hemoglobin levels, research into the effects of using

exogenous erythropoiesis stimulating agents (ESAs) to treat anemia of critical care is ongoing [87]. Three main trials by Corwin and colleagues are among the largest studies to date on this topic. EPO-1, the pilot study, included 160 adults from a multidisciplinary ICU. It demonstrated a reduction in red blood cell transfusion and a rise in hemoglobin with ESA treatment using a dose of 300 units/kg/day for 5 days and then every other day. Exclusion criteria were extensive and included vasopressor requirements and high levels of ventilatory support [122]. The second study EPO-2 enrolled 1,302 patients. A lower dose of 40,000 units weekly of ESA was administered. This study as well showed a reduction in red blood cell transfusion and maintenance of higher hemoglobin concentration, but no further clinical benefit or harm was identified [94]. The third trial (EPO-3) enrolled 1,460 patients who were given a dose of 40,000 units weekly. In this larger study, no difference was seen between rates of RBC transfusion between the two groups [92]. This may be related to a more restrictive transfusion practice across the board. Some benefits were seen in the subgroup analysis of trauma patients. Of note, the intervention group had a higher rate of thrombotic events, but in a post hoc analysis, this risk was not increased among patients receiving standard prophylactic or therapeutic doses of heparin [41]. Iron repletion was not standardized in these studies, and it is not known if the patients would have had improved outcomes if appropriate levels of iron were achieved to ensure appropriate erythropoiesis. The optimal dosing regimen and route of administration (intravenous versus subcutaneous) of ESAs in critically ill patients for the treatment of anemia have yet to be determined. Additional prospective clinical trials with larger sample size are needed to investigate population pharmacokinetic and pharmacodynamic parameters of ESAs, which should also incorporate alterations in iron metabolism associated with critical illness and inflammation and other patient characteristics, such as age, weight, and use of vasopressors [123]. Considered together, the clinical evidence for ESA therapy in critically ill patients suggests a decrease in mortality in trauma patients (but this effect does not appear to be related to a reduction in RBC transfusions) and an increase in the frequency of adverse events, particularly in patients with cancer or chronic renal failure. Therefore, exogenous administration of ESAs is used with caution in critically ill patients unless chronic conditions (such as chronic kidney disease) are present, and a thorough workup suggests that ESAs may be beneficial [114].

As mentioned above, it is not just stimulating the production of RBC which is necessary to have successful erythropoiesis. The body must have the building blocks available to produce progenitor cells. Diminished RBC production can also be due to nutritional deficiencies seen during this state of inflammation. In one study, 9 % of ICU patients were iron deficient, with an additional 2 % each to B12 and folate deficiency [86]. While iron has been shown to promote the growth and virulence of a number of microbes responsible for nosocomial infections in animal studies, evidence linking iron with increased risk of infection from human studies is lacking [41]. There have been some smaller studies examining iron supplementation in the critical care population. In a retrospective study of 27 surgical patients receiving intravenous iron therapy matched to control subjects, there did not appear to be any higher rates of bacteremia [124]. In another study of 863 post cardiopulmonary bypass patients, treated with both intravenous iron and ESA as needed or with blood transfusions, there was no difference in subsequent infection rate [125]. Intravenous iron supplementation may have better efficacy than enteral administration because of the block of intestinal absorption by hepcidin and compliance issues [41].

Transfusion Indications in the ICU

The fastest way to increase hemoglobin levels is by transfusing RBC. More than one-third of all ICU patients will receive a blood transfusion, and when ICU stay is longer than 1 week, greater than 70 % of patients will receive a blood transfusion (Table 25.2) [8, 13, 15–23]. The primary reason to prescribe a blood transfusion in the non-bleeding patient is to improve oxygen delivery and carbon dioxide removal. Oxygen delivery is determined by cardiac output, hemoglobin concentration, and oxygen saturation. Increasing hemoglobin concentration should improve oxygen delivery to the tissues, but in studies where blood transfusions were given to patients with acute respiratory distress syndrome (ARDS), sepsis, and trauma, any improvement was not shown in oxygen uptake [126–129]. This lack of improvement in oxygen delivery may be due to partially reversible biochemical and structural changes that occur in stored blood [41].

In 1999, Herbert et al. published a study comparing a restrictive transfusion policy (goal Hg 7–9 g/dL) to a liberal transfusion policy (goal Hg 10–12 g/dL) on mortality rates. The Transfusion Requirements in Critical Care (TRICC) trial randomized 838 patients admitted to the ICU without evidence of active bleeding to a restrictive transfusion strategy (transfusion to maintain hemoglobin >7 g/dL) versus a liberal strategy (transfusion to maintain hemoglobin ≥10 g/dL). Patients met criteria if they were euvolemic after initial fluid resuscitation. The restrictive transfusion treatment was associated with decreased rates of inhospital mortality compared to those seen with the liberal transfusion strategy. This benefit was most obvious among the less critically ill patients (APACHE II score ≤20) and <55 years old. Before the TRICC trial, critically ill patients were routinely transfused to a hemoglobin of 10 g/dL. This was one of the initial studies that led to updated transfusion guidelines [18]. While blood transfusions are clearly indicated in the setting of

hemorrhagic shock, we must further investigate when it is appropriate to transfuse each patient. In a review of 45 observational studies reporting the impact of transfusions on patient outcome (mortality, infections, acute respiratory distress syndrome [ARDS]) in populations of trauma, general surgery, orthopedic surgery, acute coronary syndrome, and ICU patients, Marik and Corwin identified RBC transfusion as an independent predictor of death, infectious complications, and ARDS [25]. More specifically for critical care patients, many of these studies have continued to document the harm of transfusions.

In the ABC study, 3,500 ICU patients, 37 % of which received a transfusion, were included. Older patients and patients with longer ICU stays were more likely to receive a transfusion. Both ICU and overall mortality rates were significantly higher in patients who had received transfusions versus those that had not received a transfusion (ICU rates: 18.5 % vs. 10.1 %; overall rates: 29.0 % vs 14.9 %). When comparing similar degrees of organ dysfunction, patients who had a transfusion had a higher mortality rate. For matched patients in the propensity analysis, the 28-day mortality was 22.7 % among patients with transfusions and 17.1 % among those without [13].

In 2004, the CRIT study showed among 4,982 ICU patients that the total number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and increased mortality. Patients who received transfusions also had more total complications and were more likely to experience a complication during their hospitalization [8].

As ICUs across the world began to adopt more restrictive transfusion guidelines, the SOAP observational study of 3,148 European ICU patients showed direct relation between the number of blood transfusions and the mortality rate, but in multivariate analysis, blood transfusion was not significantly associated with a worse mortality rate. Furthermore, in 821 pairs matched according to a propensity score, there was a higher 30-day survival rate in the transfused patients compared with other patients [21]. One confounder is the higher use of leukoreduced red blood cells in the SOAP study compared with the ABC study [13, 21]. Is it possible that the SOAP study is showing that when a restrictive transfusion treatment plan is followed, the benefits of a needed transfusion will outweigh the risks?

Clinical practice guidelines for RBC transfusion in the critically ill and trauma patient published in 2009 have created a framework for intensivists to guide transfusion decisions [130]. As mentioned above, RBC transfusion is indicated for patients with hemorrhagic shock. Of special note, the guidelines advise against the use of a "transfusion trigger" of any number. Decision for RBC transfusion should be based on an individual patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters. When RBC transfusion is indicated in the absence of acute hemorrhage, only one unit at a time should be transfused and the patient should be reevaluated for further need of blood transfusions [130].

The guidelines also address the more specific subpopulations of critically ill patients. In a mechanically ventilated patient, no benefit to a "liberal" transfusion strategy has been recognized, but transfusion should be considered if Hg is less than 7 g/dL. For the critically ill trauma patients who are adequately resuscitated, transfusion can be indicated at an Hg of 7 g/dL. Again, there is no benefit in a "liberal" transfusion strategy for the critically ill trauma patients. Patients with stable cardiac disease in the ICU as well can tolerate a Hg of 7 g/dL, but RBC transfusion may be beneficial in patients with acute coronary syndromes (ACS) who are anemic (Hg 8 g/dL) on hospital admission [130].

Risks of Transfusions

Understanding the possible side effects of the transfusion is an important aspect of making transfusion decisions. Current data demonstrate that approximately 50 % of all blood product transfusions take place in the perioperative setting, underscoring the potential risks to the surgical critical care patient. Pulmonary edema, fever, acute transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM), hypothermia, coagulopathy (dilutional), thrombocytopenia, and transfusion errors (incorrect blood components) are some of the adverse events associated with transfusion of blood components. If a patient requires repeated transfusion of RBCs for treatment of chronic conditions, it can lead to iron overload and resulting end organ damage [131].

TRALI

One the most common (and clinically identifiable) causes of transfusion-related morbidity and mortality is TRALI – transfusion-related acute lung injury. The term was coined in 1983. TRALI is described as a clinical state characterized by pulmonary edema (noncardiac in nature), hypoxemia, respiratory distress, and new bilateral pulmonary infiltrates on chest X-ray which occur within minutes to 6 h after transfusion. Other signs and symptoms include fever, tachycardia, cyanosis, hypotension, and frothy sputum [132]. Researchers report an occurrence of approximately 8.1 cases per 100,000 units of blood components transfused [133], although evidence suggests that the incidence can be significantly higher as the condition is believed to be underdiagnosed and underreported [134]. The risk of acquiring TRALI increases with

age, illness severity, and in cardiac patients, higher with increased length of time for cardiopulmonary bypass [135]. According to US Food and Drug Administration and other sources, TRALI is the second or third most frequent cause of death from transfusion [136]. Not surprisingly, the risk of developing TRALI increases with the number of units transfused. Blood components with the highest plasma content (i.e., FFP) or those containing antibodies against human leukocyte antigens (HLA) I and II and human neutrophils represent the highest risk of triggering TRALI, but any blood component can lead to this adverse event. The HLA antibodies are mostly present in blood which has been donated by women who have been previously pregnant [137]. There have been efforts to restrict female plasma donors to the blood supply which might decrease the incidence of TRALI.

The current management of TRALI is mainly supportive. Since hypoxemia is a main part of the clinical picture, supplemental oxygen support will likely be needed even if the patient does not require intubation. A high proportion of patient will require ventilatory support with "lung protective" small tidal volume settings [132]. If hypotension occurs, fluid resuscitation is often appropriate. This is one reason why it is important to distinguish the cause of the pulmonary edema. The additional intravenous fluid would worsen a patient with cardiac-related pulmonary edema or TACO (see below), but can be beneficial to a patient with TRALI and hypotension. Only anecdotal evidence has been provided for the use of corticosteroids [132]. Overall prognosis for a patient with TRALI is good. Mortality is relatively low (6–10 %) when compared with acute lung injury. For patients who do survive the initial episode, there is a return to baseline pulmonary function within days, and long-term function does not seem to be affected.

TACO

Transfusion-associated circulatory overload (TACO) is considered an under-recognized and serious transfusion complication. TACO occurs when a patient is unable to compensate for rapid or high-volume infusions of blood products. Risk factors include patients who are predisposed to volume overload, such as those with congestive heart failure, renal failure, and respiratory failure who require large or multiple transfusions [114]. TACO is often seen more commonly in patients who are 3 years or younger or 61 years or older. Respiratory distress and/or cyanosis associated with pulmonary edema presents within 2 h of transfusion. Elevated blood pressure, tachycardia, and increased pulmonary wedge pressure are the typical stigmata. TACO can be precipitated by even a single unit of RBC or other blood product. Clinical consequences include prolonged hospitalization, greater intensity of care, and death [138]. The incidence of TACO appears to be rising over the past years, but this is most likely related to increase reporting. In a study the prevalence of TACO is estimated to be 1 in 68 (95 % CI, 1 in 250 to 1 in 27) patients receiving plasma. These patients on average received multiple units of plasma (mean 4.0 units; SD 2.3 units) before TACO developed [139]. In another 2-year prospective cohort study of 901 ICU patients, researchers reported that TACO developed in 6 % of patients who received a transfusion [140].

TRIM

Since the 1980s, the risk of disease transmission through blood transfusions has massively declined due to the adoption of pathogen reduction technologies and increased hemovigilance systems. While the most common noninfectious side effects include TRALI, TACO, and hemolytic transfusion reactions, there is also the risk of transfusion-related immunomodulation (TRIM) which can increase the risk of acquiring nosocomial infections. The cause of suppression of immune system by blood transfusions is not clear, but likely is multifactorial and leads to a downregulation of the recipient's immune function. This can explain the long-recognized observation that transfusing patients undergoing allogenic renal transplantation can reduce the risk of rejection [141]. Likewise, it can be theorized that TRIM can lead to an increased rate of cancer recurrence and of postoperative bacterial infection, but exact causality has not been established yet by clinical trials. "Old" blood transfusions (red blood cell units with longer storage times) are associated with increased risk of acquiring nosocomial infections in critically ill trauma patients [142]. It is possible that the soluble mediators that concentrate in stored RBCs can be implicated in the initiation of the immune suppression cascade [114]. Further investigation into how the biochemical, structural, inflammatory, and physiological properties of RBCs change with storage and the possible effects of these changes on clinical outcomes in patients who receive transfusions is needed [143]. Based on more recent studies, there is data to suggest that TRIM is a biologic effect strongly associated with the infusion of allogeneic leukocytes. Leukoreduction is a proven method and plasma depletion is a proposed method to significantly reduce TRIM and its clinical effects [144].

Anemia After ICU Care

Many patients are discharged from the ICU and subsequently from the hospital with persistent anemia. A study looked at 1,023 sequential ICU admissions from admission to discharge or death in the ICU over 100 days, representing 44 % of all ICU admissions in Scotland during the study period.

The median transfusion trigger used in the absence of bleeding was 7.8 g/dL and 766 patients admitted to the ICU survived to discharge. The prevalence of anemia at ICU discharge was 87 % [14]. In 2006, a 3-year observational cohort study followed ICU survivors from the hospital. The median time from ICU discharge to hospital discharge was 13 days (IQR 6–22, range 1–119). At the time of discharge from the ICU (using the last recorded Hb concentration), 77 % of the patients met criteria for the diagnosis of anemia. Of the patients who were anemic, 32.5 % had a hemoglobin level less than 10 g/dL and 11.3 % had a hemoglobin level less than 90 g/dL. A longer stay in the ICU and the hospital was a risk factor for anemia. Multivariate regression analysis showed that patient age, gender, APACHE II score, and ICU length of stay were not independent predictors after including the ICU discharge hemoglobin level [145]. Critically ill patients who survive to discharge may likely be suffering from other serious illnesses such as cancer, renal failure, chronic cardiac disease, and other chronic inflammatory diseases, during which anemia is associated with poor quality of life and higher morbidity [145].

Many patients who survive the ICU continue to suffer reduced quality of life after hospital discharge, often associated with symptoms typical of anemia such as fatigue and breathlessness. In a 6-month prospective observational cohort study of intensive care survivors with moderate to severe anemia at the time of ICU discharge, erythropoietic and inflammatory markers were measured at regular intervals over 6 months to assess red cell production and factors limiting recovery from anemia. Thirty patients were recruited of which 19 completed the study, 6 died during the study period, and 5 only completed part of the follow-up; 47 % of the patients who completed the study at 6 months from discharge from the ICU had recovered from their anemia. The median time to recovery was 11 weeks. On the other hand, 53 % of patients continued to suffer from anemia at 6 months. An inappropriately low erythropoietic response to anemia was observed in almost all patients in the study. Patients with delayed recovery or persisting anemia during the 13 weeks following ICU discharge had higher levels of circulating inflammatory markers (IL-6 and C-reactive protein) and did not exhibit reticulocytosis during the weeks following discharge [146].

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Coagulopathies and Anticoagulation

26

Jeremy W. Cannon

Introduction

Derangements in hemostasis—inherited, acquired, and iatrogenic—result in significant morbidity and mortality in critically ill patients. For the intensivist at the bedside, challenges in managing coagulopathy stem from the broad spectrum of disorders and the complexity of the tests required for a precise diagnosis to guide appropriate therapy [1].

With advances in molecular biology, we now appreciate that the classic coagulation cascade consisting of intrinsic, extrinsic, and common pathways significantly oversimplifies the complexity of the hemostatic system (Fig. 26.1) [2–4]. Basic science is also unraveling the mystery of conditions like acute coagulopathy of trauma, while recombinant coagulation factors allow us to replace specific deficiencies. At the same time, our patients now frequently present to us having been started on new types of anticoagulant medications which cannot be easily reversed. With these numerous recent developments, a multidisciplinary approach to managing coagulopathic patients in the ICU is often warranted.

The following chapter summarizes our current understanding of the most common disorders of coagulation encountered in the ICU and attempts to provide a practical guide to both diagnosis and management of these complex and challenging conditions. For common diagnoses that involve platelet dysfunction, refer to the chapter on "Thrombocytopenia."

Assessing the Coagulopathic Patient

A history of known coagulopathic conditions should be obtained during the initial patient evaluation. On review of systems, important indicators of an undiagnosed coagulopathic condition include significant bleeding after dental extractions or surgical procedures, heavy menses, or a history of easy bruising or petechial rashes [5]. A thorough list of the patient's active medications should also be obtained to identify anticoagulant and antiplatelet medications as well as those that increase bleeding risk when combined with these agents (e.g., selective serotonin reuptake inhibitors) [6–8].

Physical examination is critical to the complete assessment of the coagulopathic patient. Early identification of bleeding is paramount. Hemorrhagic shock can present in many different ways to include unexplained tachycardia, new onset tachypnea, and even altered mental status suggestive of delirium. Physical examination includes a rapid but thorough external examination of any wounds, the extremities, and the bedding to evaluate for external blood loss and sites of so-called "compressible" hemorrhage. Ultrasound evaluation of the thorax and abdomen can identify intracavitary bleeding. Nasogastric lavage and rectal examination should be used to assess for occult gastrointestinal bleeding. Physical findings consistent with coagulopathy include petechiae, subconjunctival hemorrhage, ecchymosis, and deep hematomas.

Relative to the complex array of plasma proteins involved in both the pro- and anticoagulation arms of hemostasis, our ability to measure the hemostatic properties of a patient's blood remains rather basic [9, 10]. The most common laboratory tests related to hemostasis performed in ICU patients are summarized in Table 26.1. For the acutely bleeding patient, the battery of labs should include a blood type and crossmatch, complete blood count (CBC), prothrombin time (PT) with international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen level, and a D-dimer. Additionally, a "blue top" sample should be sent for thromboelastography (TEG) or thromboelastometry (TEM), if available. Additional studies should be obtained in select instances when the cause of the patient's bleeding diathesis remains unclear.

Care should be taken to avoid collecting samples for these laboratory tests in the vicinity of intravenous infusions, especially from central venous catheters. If seemingly

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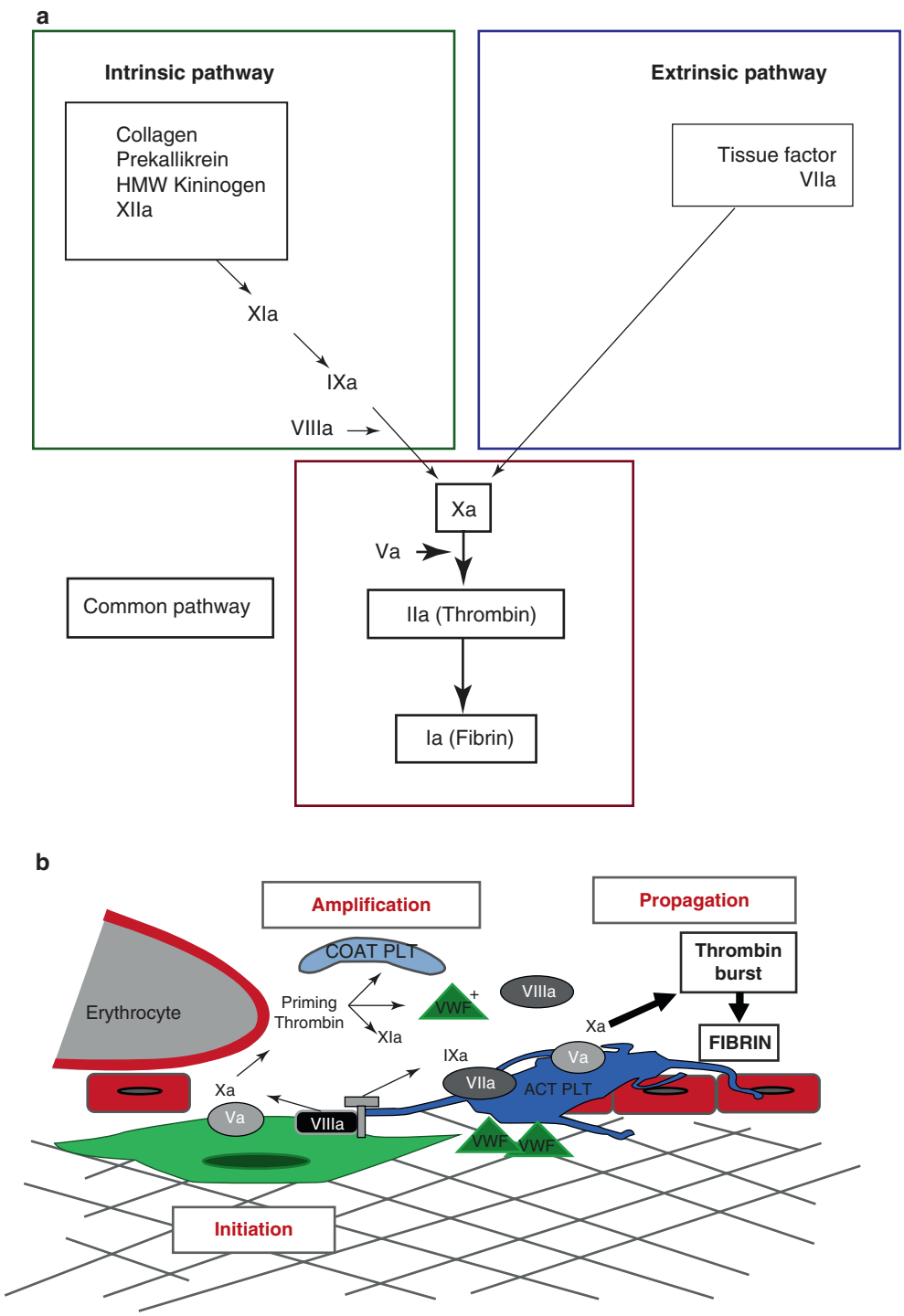

Fig. 26.1 The coagulation cascade. Traditionally, this has been conceived as an intrinsic and extrinsic pathway merging into a common pathway (**a**). However, we now understand that this is a vastly complex system of both enzymes and cells all working in concert to rapidly control hemorrhage when needed as illustrated by the so-called cell-based model of coagulation (**b**)

spurious results return, the first step should be to repeat the abnormal laboratory test for confirmation. Of note, these assays are performed at normal body temperature; so they may not accurately reflect the in vivo clotting function in hypothermic (or febrile) patients.

The prothrombin time (PT) is a measure of the extrinsic and common pathway factors including I (fibrinogen), II (prothrombin), V, VII, and X. Due to slight variations in the normal ranges across institutions and systems, the international normalized ratio (INR) was developed to standardize results. The INR is calculated as $(PT_{test}/PT_{normal})^{ISI}$ where ISI is the International Sensitivity Index which varies slightly depending on the assay. A normal INR is generally considered 1 ± 0.2.

The activated aPTT is used to assess the function of the intrinsic and common coagulation pathways. The aPTT is

Table 26.1 Common coagulation tests in ICU care

Test	Measure	Comment
Prothrombin time (PT), international normalized ratio (INR)	Extrinsic and common coagulation pathway	Used to monitor warfarin therapy
Activated partial thromboplastin time (aPTT)	Intrinsic and common coagulation pathway	Used to monitor heparin therapy
Anti-factor Xa assay	Focused assay of Xa activity	Used to monitor LMWH and heparin therapy
Activated clotting time (ACT)	Used to measure heparin effect when PTT is super-therapeutic	Most commonly used to monitor heparin during cardiopulmonary bypass and ECMO
Thrombin time (TT), thrombin clotting time (TCT)	Fibrin generation	Used as a complementary study when PT and PTT results are abnormal
Mixing studies	Assess for factor deficiency vs. inhibitor; performed by mixing equal parts of the patient's plasma with normal plasma	If coagulation test abnormalities correct with mixing, a factor deficiency is present; if abnormalities remain, an inhibitor (e.g., antibody or medication) is present
Thromboelastography (TEG), thromboelastometry (TEM)	Clot formation, propagation, and strengthening	Results available in near real time

LMWH low molecular weight heparin

commonly used to monitor heparin dosing with a therapeutic goal of between 1.5 and 2.5 times normal. Because there is no INR equivalent for the aPTT, the therapeutic range should be determined at each institution. Direct thrombin inhibitors (DTI) also prolong the aPTT. Low molecular weight heparins (LMWH) typically do not prolong the aPTT. Common patterns of abnormal PT/INR and aPTT results are suggestive of specific medication effects or disease states [11]. These common patterns are summarized in Table 26.2.

The anti-factor Xa activity (anti-Xa) assay can be used to monitor heparin and low molecular weight heparin (LMWH) dosing. There is growing evidence that this assay offers multiple advantages over aPTT for monitoring heparin therapy [12]. This assay can also be used to determine the therapeutic effect of a direct factor Xa inhibitor (Xa-I) in patients reportedly taking one of these medications. For heparin monitoring, the anti-Xa is drawn as a random level while for LMWH monitoring, the level is drawn 4 h after the medication dose. LMWH does not require monitoring but should be considered in obese patients and those with decreased renal clearance.

Activated clotting time (ACT) measures clot formation time (in seconds) in the presence of an activating agent (e.g., kaolin). This test has generally been replaced by the aPTT for most indications. It still has utility in cases where precise anticoagulation monitoring is needed above the aPTT assay limit such as during cardiopulmonary bypass [13].

TEG and its close counterpart TEM generate a tracing of the multiple phases of whole blood clot formation. These tests have been available for decades but have recently gained increased use in guiding hemostatic resuscitation [14]. The availability of real-time results from these tests as the assay is progressing makes them particularly useful in guiding therapy in the ICU. A sample TEG-based treatment algorithm is presented in Fig. 26.2.

Thrombin time (TT), also known as thrombin clotting time (TCT), measures the conversion of fibrinogen to fibrin at the end of the common coagulation pathway. Prolonged TT values suggest an abnormality in fibrinogen, hypo- or hyper-fibrinogenemia, or the presence of a thrombin inhibitor, including heparin. If heparin effect is suspected as the cause of a prolonged TT, a reptilase time (RT) can be sent for confirmation. If the RT is normal, then the prolonged TT is due to heparin.

Mixing studies are used to determine if abnormal coagulation study results are due to a factor deficiency or an inhibitor of coagulation (e.g., a medication or an antibody). These are conducted by mixing a sample of the patient's plasma with

Table 26.2 Patterns of abnormal PT/INR and aPTT in coagulopathic patients

Test result		
PT/INR	aPTT	Potential causes
Increased	Normal	Warfarin administration
		Vitamin K deficiency (mild–moderate)
		Liver disease
		Factor VII deficiency/inhibitor
Normal	Increased	Heparin administration
		von Willebrand disease (moderate–severe)
		Factor VIII, IX, XI, XII deficiency/inhibitor
		Lupus anticoagulant
Increased	Increased	Warfarin + heparin administration
		Fondaparinux administration
		Direct factor Xa inhibitor administration (variable)
		DTI administration
		Anticoagulant overdose
		Vitamin K deficiency (severe)
		Liver disease
		Fibrinogen, prothrombin, factor V, X deficiency/inhibitor
		DIC

aPTT activated partial thromboplastin time, *DTI* direct thrombin inhibitor, *DIC* disseminated intravascular coagulation, *INR* international normalized ratio, *PT* prothrombin time

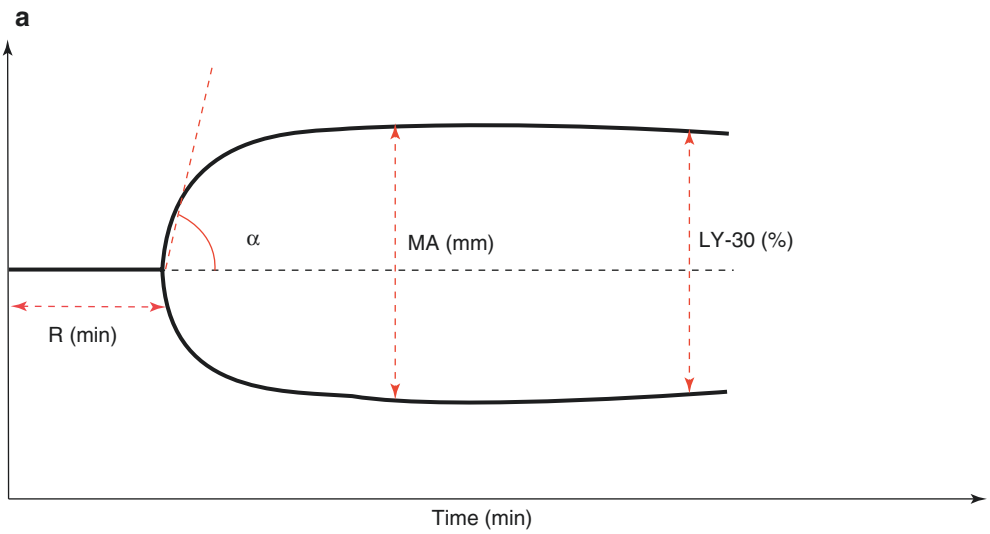

Fig. 26.2 Examples of a normal TEG tracing (**a**) and a TEG-based treatment algorithm for abnormal values (**b**). Reaction time (*R*) corresponds to the initiation phase of clotting; angle (α) corresponds to the rate of clot expansion and strengthening; maximal amplitude (*MA*) corresponds to the maximal clot strength; lysis at 30 min (LY-30) corresponds to the degree of fibrinolysis at 30 min. *CRYO* cryoprecipitate, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *PLT* apharesis platelet unit, *TXA* tranexamic acid. Low Amicar dose is 5 g IV × 1 followed by 1 g/h until LY-30 <3 %. High Amicar dose is 10 g IV × 1 followed by 1 g/h until LY-30 <3 %. *Check heparinase TEG; if R normalizes, heparin effect is present

b

R	α	MA	LY-30
10–14 min-->2 FFP	<50°-->10 CRYO, 2 FFP, or fibrinogen (60–70 mg/kg)	40–50 mm-->1 PLT	3–8 %-->Low Amicar or TXA
>14 min*-->4 FFP or PCC		<40 mm-->2 PLT	>8 %-->High Amicar or TXA

normal pooled plasma in a 1:1 ratio and then repeating the abnormal study. If the study results return to normal, the abnormality is likely due to a factor deficiency. Conversely, if the results do not normalize, this indicates that the abnormality is due to a coagulation inhibitor. Common examples of such inhibitors include heparin and antiphospholipid antibodies (associated with both hyper-and hypocoagulable states).

Point of care testing (POCT) at or near the patient's bedside is now available for many of these tests. Examples include INR, ACT, and TEG/TEM [15, 16]. A new INR testing device has also recently been approved for home use with excellent accuracy [17, 18]. These tests require strict adherence to quality control standards to assure study validity.

Common Acquired and Medication-Induced Coagulopathies in the ICU

Liver Disease

Critically ill patients with both acute liver failure and chronic liver disease manifest significant abnormalities in coagulation [19, 20]. Deficiencies in both procoagulant and anticoagulant factors, abnormal platelet numbers and function, hyperfibrinolysis, and frequent episodes of infection result in a mixed and dynamic picture of both hyper- and hypocoagulability in these patients. Patients with liver disease manifest abnormal coagulation laboratory values and can present with both acute hemorrhage (e.g., bleeding varices) and acute thrombosis (e.g., portal vein thrombosis).

These patients should not be considered "auto-anticoagulated" [20]. To determine the status of coagulation in a patient with liver disease, the following tests should be obtained: platelet count, PT, aPTT, TT, fibrinogen, and D-dimer. There is growing evidence that the INR varies significantly among laboratories in the presence of liver disease, thus calling the use of the MELD score (based on a locally measured INR) for organ allocation into question [21, 22]. TEG appears to have significant utility in managing coagulopathy in liver disease [23].

Management of patients with liver disease who are bleeding or who are undergoing invasive procedures should be guided by specific laboratory findings where possible. However, empiric therapy is required in some instances, such as vitamin K deficiency, as it is impossible to determine if the observed abnormalities are due to lack of synthetic function or lack of substrate. In general, blood products are overused in patients with liver disease with little demonstrated benefit [24]. Alternatives to FFP infusion include more liberal use of cryoprecipitate or fibrinogen concentrates (targeting a fibrin-

ogen level of ≥120 mg/dL), prothrombin complex concentrates (PCCs), antifibrinolytics (e.g., ε-aminocaproic acid or tranexamic acid), and desmopressin. These agents, when used judiciously, decrease the risk of volume overload while more directly correcting the coagulopathic abnormality.

Cirrhotic patients with venous thromboembolism (VTE) complications require careful consideration of the risks of bleeding weighed against the risk of further clot propagation. Portal vein thrombosis (PVT) significantly worsens patient outcomes. Consequently, PVT prophylaxis should be considered in at-risk patients [25]. Furthermore, when PVT is diagnosed, therapeutic anticoagulation should generally be initiated [26]. Patients with liver disease also develop other forms of VTE including deep venous thrombosis and pulmonary embolism. Prior to initiating therapeutic anticoagulation, an assessment for esophageal and gastric varices should be performed. If these are present, the risk of bleeding on therapeutic anticoagulation is considered high and should be weighed against the risk of thrombus propagation or migration [27]. The ideal anticoagulation regimen in these patients is debated due to the frequency of low levels of antithrombin in patients with cirrhosis and the difficulty in monitoring warfarin therapy. In most cases, a LMWH regimen monitored with anti-Xa levels is safe and effective.

Acute Traumatic Coagulopathy

Acute traumatic coagulopathy (ATC) is precipitated by a large soft tissue injury burden combined with hypoperfusion. This results in activation of the protein C pathway, shedding of the protective endothelial glycocalyx leading to "autoheparinization," Weibel-Palade body degradation with release of tissue plasminogen activator (tPA), and possibly platelet hypofunction mediated by ADP [28, 29]. ATC may be further exacerbated by iatrogenic coagulopathy from indiscriminant crystalloid resuscitation.

Up to one third of severely injured patients present with ATC. Clinically, patients with ATC have an elevated PT (>18 s)/INR (>1.5) or aPTT (>60 s), low fibrinogen, and some degree of fibrinolysis. Treatment of ATC often begins empirically, however, based on patient risk factors or the appearance of diffuse bleeding during damage control surgery [30]. This is done by activating the hospital's massive transfusion protocol (MTP) and administering predetermined blood product ratios (along with calcium repletement) and select hemostatic adjuncts [31]. As laboratory results begin to return during ongoing resuscitation, this empiric therapy can be refined with specific product replacement. [Of note, although many trauma centers are now advocating the use of TEG/TEM to guide hemostatic resuscitation in trauma patients [14, 32, 33], a recent Cochrane review concluded that TEG/TEM should only be used in the context of research [34]]. Crystalloid infusions should be minimized while hypothermia and acidosis are aggressively avoided as all of these factors decrease the function of the coagulation enzymes.

Need for MTP can be anticipated by using a number of clinical and laboratory factors. These include INR >1.5, systolic blood pressure <90 mmHg, hemoglobin <11 g/dL, base deficit ≥6, FAST+, heart rate ≥120 beats/min, and penetrating mechanism. Of these, INR >1.5 has the highest positive predictive value, and two or more positive triggers together predict a need for MT with a sensitivity of 85 % [35]. POCT for INR in trauma patients may, thus, be justified [16].

The ideal blood product ratio within an MTP has not been precisely defined. The recently completed randomized, prospective PROPPR study found no difference in 24-h and 30-day mortality between bleeding trauma patients treated with a 1:1:1 ratio of plasma:platelets:RBCs as compared to a 1:1:2 strategy [36]. However, the 1:1:1 group had fewer early deaths due to exsanguination and no increase in complications over the 1:1:2 group. Thus, one approach is to target as close as possible to a 1:1:1 ratio and administer more hemostatic blood products (i.e., plasma and platelets) generously early in the resuscitation [37].

Hemostatic adjuncts such as tranexamic acid (TXA) and recombinant VIIa (rVIIa, NovoSeven) should generally be limited to those patients with significant blood loss as indicated by a high probability of receiving a MT. The large CRASH-2 study on TXA does not have clear applicability to trauma care in established trauma centers [38] although military data suggests a mortality data if given early to severely injured patients [39]. No mortality benefit has been found with rVIIa [40]; however, it may reduce transfusion requirements in blunt trauma patients [41]. PCCs (e.g., Kcentra) are indicated for the reversal of known warfarin therapy in trauma patients who are bleeding [42, 43].

Post Cardiopulmonary Bypass

Cardiopulmonary bypass activates platelets, the coagulation cascade, and complement. Intraoperative anticoagulation with heparin partially counteracts these effects. However, residual activation of these complex systems along with residual heparin effect, hypothermia, and hemodilution all contributes to postoperative coagulopathy in cardiac surgery patients [44]. About 30 % of patients require a postoperative blood product transfusion, and about 10 % develop significant bleeding which increases postoperative mortality [44, 45]. In such cases, sources of surgically correctable hemorrhage should always be considered and discussed with the cardiac surgeon.

For the assessment of nonsurgical coagulopathic bleeding, essential laboratory testing in the postoperative

cardiac patient includes a CBC, PT/INR, aPTT, TT, fibrinogen level, and a TEG/TEM. A prolonged aPTT and TT suggests residual heparin effect which can be reversed with protamine in a patient with excessive bleeding. Elevated PT/INR indicates deficient levels of vitamin K-dependent factors including factor VII which can be corrected with FFP. Fibrinogen levels less than 100–150 mg/dL should be treated with FFP or cryoprecipitate. Thrombocytopenia or evidence of depressed platelet function on a TEG (i.e., low MA) can be treated with platelet transfusion. Further therapy should be guided by repeat testing if bleeding continues.

Pregnancy

Pregnancy results in a hypercoagulable state which persists for up to 3 months postpartum. This is due to an increase in procoagulant proteins including factor VIII and von Willebrand factor, a decrease in protein S activity, and the mechanical compression of the gravid uterus primarily on the left iliac venous system. Pregnant patients diagnosed with VTE should be treated with weight-based LMWH or a heparin infusion. LMWH should be dosed according to actual weight rather than predicted or ideal body weight. Treatment should continue a minimum of 6 weeks postpartum for a total duration of at least 3 months of therapy [46]. Warfarin can safely be used as treatment after delivery even during breastfeeding.

Antiphospholipid Syndrome

This is an acquired autoimmune syndrome typically characterized by a hypercoagulable state [47]. Patients with antiphospholipid antibodies usually present with multiple venous or arterial thrombotic events or with fetal loss. Those with antiprothrombin antibodies present with bleeding. A small subset of patients experience catastrophic antiphospholipid syndrome (CAPS) resulting in multi-organ failure from diffuse microvascular thrombosis.

The diagnosis of antiphospholipid syndrome (APS) is made when antiphospholipid antibodies are detected in the appropriate clinical setting [48]. Screening tests consistent with the presence of an antiphospholipid antibody include a prolonged aPTT and dilute Russell viper venom time.

Initial treatment of venous thrombotic events in these patients consists of anticoagulation with heparin or LMWH transitioned to warfarin. Duration of therapy depends on the certainty of the APS diagnosis. Those patients with strongly positive test results should be maintained on lifelong anticoagulation.

Heparin and LMWH

"Iatrogenic coagulopathy" due to anticoagulant medications is very common in the management of surgical ICU patients. Factors that increase bleeding risk in these patients include high anticoagulation doses, combined therapy with NSAIDS or antiplatelet agents, and underlying patient factors. For unfractionated heparin, a treatment protocol based on aPTT or anti-Xa should be used to minimize wide swings in heparin dosing. LMWH does not require monitoring except in unique circumstances (e.g., obesity or pregnancy).

Patients receiving over 35,000 units/day of heparin to achieve a therapeutic aPTT are considered heparin resistant [49]. Causes of heparin resistance include antithrombin (AT) deficiency, increased elimination (e.g., aggressive diuresis) and elevations in factor VIII. In such cases, monitoring heparin therapy with anti-Xa levels results in a lower heparin dose with no difference in outcome [50]. If high doses are still required, AT levels can be measured in many large medical centers, and low levels (e.g., $\leq$60 % predicted) can be supplemented with FFP or AT concentrate. Be aware that dosing AT concentrate carries a risk of bleeding if excessive doses are given; so consideration should be given to consulting a hematologist if considering AT repletion.

Management of bleeding on heparin or LMWH depends on the severity of bleeding and the risk of discontinuing anticoagulation. If a patient on heparin or LMWH develops significant bleeding (e.g., suspected hemorrhagic stroke, hematemesis, hematochezia, or large blood loss from surgical or traumatic wounds), immediately discontinue the medication and send the standard battery of anticoagulation labs (including TT and RT). To measure any underlying coagulopathy independent of heparin, a TEG with heparinase can also be ordered.

Heparin has a very short half-life (30–60 min); so reversal with protamine is generally not required. However, in extreme circumstances, protamine can be given at a dose of 1 mg per 100 units residual heparin given slowly (e.g., <5 mg/min) [43]. If no heparin boluses have been given recently, the amount of residual heparin can be roughly approximated as the current heparin infusion rate (e.g., if a patient is on a heparin infusion at 1,500 units/h, 15 mg IV protamine will fully reverse the heparin). Alternatively, a default dose of 25 mg protamine can be used. Protamine also partially reverses LMWH but has no effect on the indirect Xa inhibitor fondaparinux (Arixtra), other Xa-Is, or DTIs.

Patients on heparin or LMWH frequently undergo invasive bedside and surgical procedures. A full discussion on the management of both prophylactic and therapeutic doses of these medications in the periprocedural period is provided below.

Warfarin

Warfarin inhibits the γ-carboxylation of the vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X, resulting in a prolonged PT and INR. Warfarin has a narrow therapeutic window and variable absorption based on diet and other patient factors. Consequently, warfarin dosing can vary up to 50-fold between patients. Warfarin therapy requires frequent monitoring with INR levels checked either in a laboratory or at home.

A number of scenarios can arise in patients on warfarin requiring intervention. The urgency of intervention is dictated by the INR relative to the patient's upper therapeutic range and whether the patient is bleeding (Table 26.3) [51, 52]. The FDA recently approved a four-factor PCC (Kcentra) for urgent reversal of warfarin in adult patients with acute bleeding. This is a pooled plasma product which contains factors II, VII, IX, and X. It can be administered in a low or standard dose depending on the INR. The advantage of this approach is that it achieves rapid reversal with a very small volume infusion as compared to FFP. For inpatients who need to resume or start warfarin, all planned invasive procedures should have been completed before warfarin administration and the INR monitored daily until a stable dose is achieved.

Table 26.3 Management of bleeding in patients on warfarin based on INR levels

INR	Bleeding	Management
>9	–	Hold warfarin until INR_{THER} and re-assess; oral vitamin K (2.5–5 mg PO × 1)
	+	Reverse with IV vitamin K (10 mg QDay × 1–3 days given over 10 min); standard dose 4-factor PCC (50 units/kg IV × 1)
>5–9	–	Hold warfarin until INR_{THER} and re-assess; consider oral vitamin K (1–2.5 mg PO × 1)
	+	Reverse with IV vitamin K (10 mg QDay × 1–3 days given over 10 min); standard dose 4-factor PCC (50 units/kg IV up to 5,000 units × 1)
>INR_{THER}-5	–	Reduce warfarin dose or hold warfarin until INR_{THER} and then reduce dose; no specific reversal
	+	Consider reversal with vitamin K (10 mg IV QDay × 1–3 days over 10 min); standard dose 4-factor PCC (50 units/kg IV up to 5,000 units ×1)
2-INR_{THER}	+	Low-dose 4-factor PCC (25 units/kg IV up to 2,500 units × 1)
1.5–2	+	Consider FFP or low-dose PCC if the patient is volume sensitive

FFP fresh frozen plasma, *INR* international normalized ratio, INR_{THER} upper therapeutic limit for the patient, *PCC* prothrombin complex concentrate

Novel Anticoagulants

A number of DTIs and Xa-I inhibitors have recently been approved for use in cerebrovascular accident (CVA) prevention and treatment of VTE [53]. The IV DTI argatroban is also used for prophylaxis and anticoagulation in patients with heparin-induced thrombocytopenia (HIT). DTIs can be monitored with aPTT with 1.5–3× the upper limit of normal representing therapeutic anticoagulation. Xa inhibitors also prolong the aPTT and the anti-Xa assay. Oral DTIs and Xa inhibitors do not generally require monitoring; however, these assays can be used to determine the drug effect level in patients who are bleeding or who cannot provide a reliable medication history.

Both DTIs and Xa inhibitors have long half-lives (relative to heparin) and only one (dabigatran) has a direct antidote [54]. This combination makes the management of bleeding in patients on these medications especially challenging [43]. The characteristics of the most common oral novel anticoagulants and a recommended management strategy for bleeding in these patients are presented in Table 26.4.

Inherited Coagulopathies in the ICU

Inherited disorders of coagulation are uncommon relative to acquired and medication-induced coagulation abnormalities. Nonetheless, these abnormalities in coagulation present significant management challenges in critical care and warrant specific discussion. The most common inherited coagulopathy is von Willebrand disease VWD. Other factor deficiencies (e.g., hemophilia A) are much less common but present more significant management challenges in critical illness. Although these conditions generally present early in life, acquired forms of these conditions can present later in life with variable phenotypic manifestations.

Table 26.4 Characteristics of novel oral anticoagulants and the management of bleeding on these medications

Medication	Class	Half life	Dialyzable	Bleeding management
Dabigatran (Pradaxa)	DTI	14–17 h	Y	Charcoal (within 2 h), idarucizumab (Praxbind), dialysis, FEIBA
Rivaroxaban (Xarelto)	Xa-I	5–13 h	N	Charcoal (within 2 h), PCC
Apixaban (Eliquis)	Xa-I	8–15 h	N	Charcoal (within 3 h), PCC

DTI direct thrombin inhibitor, *PCC* prothrombin complex concentrate, *Xa-I* direct factor Xa inhibitor

Von Willebrand Disease

Primary hemostasis involving platelet adhesion is facilitated by von Willebrand factor. This factor also carries factor VIII, thereby protecting it from degradation. Decreased levels or activity of this factor result in VWD which is the most common inherited bleeding disorder, diagnosed by laboratory criteria in up to 1 % of the population. However, clinically significant bleeding occurs in only 1 % of these patients [55]. VWD is transmitted in an autosomal dominant fashion and is divided into three disease types with multiple subtypes. VWD can also be acquired and should be considered in patients with a bleeding diathesis of uncertain etiology [56], especially while on extracorporeal therapy [57]. In patients with moderate to severe VWD, aPTT and bleeding time may be prolonged. Further testing for suspected VWD should consist of a von Willebrand factor antigen, von Willebrand factor activity, and a factor VIII activity.

Therapy depends on the type of VWD, the severity of symptoms, and the planned procedure [58]. For minor procedures in minimally symptomatic patients, IV or intranasal desmopressin is the first-line therapy for those who are desmopressin responsive. All others should be treated with a von Willebrand factor concentrate. Adjuncts to this therapy in patients with VWD include the use of oral or IV antifibrinolytics and topical hemostatic agents (e.g., thrombin-soaked Gelfoam).

Hemophilia A and B

Factor VIII (hemophilia A) and factor IX (hemophilia B) deficiencies are inherited coagulopathies transmitted in an X-linked recessive fashion. Mild forms of coagulopathy can present in carrier females as well. Severity of disease depends on the level of factor activity present. Prophylactic factor replacement therapy is recommended for patients with severe disease [59].

Perioperatively and following acute trauma with bleeding, emergent factor replacement to >50 % activity (and ideally up to 100 %) is indicated [58, 60]. Minor bleeding can be treated with a low dose of factor concentrate except in patients with mild hemophilia A where desmopressin is the treatment of choice. In hemophiliac trauma patients, joints should be monitored for hemarthrosis and extremities frequently assessed for deep hematomas that could progress to compartment syndrome. Antifibrinolytics can also be administered to further stabilize established clot. Patients with factor inhibitors require alternative treatment strategies such as use of activated PCC (FEIBA) or rVIIa [61].

Procoagulant Therapies

Transfusion therapy has long been the mainstay of managing coagulopathic bleeding. Early and appropriate component therapy with plasma, platelets, and cryoprecipitate can treat coagulopathy effectively, and these remain important tools in the armamentarium of critical care physicians [36, 37, 62, 63]. Furthermore, for severe bleeding, the use of these products in the context of an institutional MTP improves survival [31, 64].

Conversely, unscrupulous or inappropriate transfusion must be avoided as treatment with blood products carries a risk of bacterial or viral infection, transfusion reaction, fluid overload, and end-organ failure such as ARDS [65, 66]. Thus, it is prudent to avoid transfusion for minor laboratory abnormalities in a non-bleeding patient [67, 68]. In some cases, an alternative procoagulant therapy should be considered. A description of the important features of these alternative procoagulant therapies is provided in Table 26.5.

Anticoagulation Management in the ICU

During a course of ICU treatment, patients are frequently managed with VTE chemoprophylaxis. Some patients also develop indications for therapeutic anticoagulation. In all cases, a careful assessment of the risk of thrombosis must be weighed against the risk of bleeding over days to weeks or even months. Unfortunately, the risk of bleeding is poorly quantified which further complicates decision-making. Recent guidelines by the American College of Chest Physicians quantify the existing data on the risk of bleeding vs. the risk of VTE events in the general postoperative patient population [69]. Some specific scenarios of particular interest are discussed in the subsequent paragraphs.

VTE Chemoprophylaxis or Full Anticoagulation in Patients with Blunt Solid Organ Injury

Patients with blunt solid organ injuries often have a number of associated injuries and are at moderate to high risk for both VTE and bleeding. The timing of initiating VTE chemoprophylaxis has been hotly debated over the years as the rate of non-operative management in the adult population has increased. Recent evidence suggests that the historic tendency has been to unnecessarily delay VTE chemoprophylaxis. Retrospective data further indicates that bleeding from a solid organ injury is independent of VTE chemoprophylaxis initiation across all grades of solid organ injury [70]. Consequently, VTE prophylaxis should be considered early in the patient's course regardless of the organ injury grade.

Table 26.5 Common hemostatic adjuncts used in treating coagulopathy

Agent	Dose	Indications	Notes
Vitamin K	1–10 mg IV daily for 1–3 days	Vitamin K deficiency; prolonged reversal of warfarin	Low risk of anaphylaxis from IV dosing (3/100,000); it can be safely given at a rate of 1 mg/min
4-factor prothrombin complex concentrate (PCC, Kcentra)	25–50 units/kg	Urgent-emergent reversal of warfarin; treatment of bleeding in patients on oral Xa inhibitors	Contains factors II, VII, IX and X as well as protein C, protein S, antithrombin and albumin; warfarin reversal is FDA approved; the use for bleeding in patients on direct Xa inhibitors has not been studied on a large scale
Activated prothrombin complex concentrate (factor VIII inhibitor bypassing activity, FEIBA)	12.5–25 units/kg	Hemophilia prophylaxis; treatment of bleeding in patients on dabigitran	Contains factors II, VIIa, IX, and X; the use for bleeding in patients on direct thrombin inhibitors has not been studied on a large scale
Fibrinogen concentrate (RiaSTAP)	60–70 mg/kg (each vial contains 900–1,300 mg; so a full dose is approximately 3–4 vials)	Fibrinogen repletion	Pooled human product; lyophilized and treated for viral attenuation
rVIIa (NovoSeven)	90–120 mcg/kg IV	Hemophilia; hemostatic adjunct in trauma	No survival benefit in trauma; dose will be ineffective in acidemia (pH <7.1)
ε-Aminocaproic acid (Amicar)	Low dose: 5 g IV bolus × 1 followed by a 1 g/h infusion for 8 h or until hemostasis; high dose: substitute 10 g IV bolus	Fibrinolysis; hemostatic adjunct in VWD, hemophilia, liver disease	Not specifically studied in trauma patients
Tranexamic acid (TXA)	1 g IV bolus × 1 followed by a 1 g IV infusion over 8 h	Fibrinolysis; hemostatic adjunct in trauma, VWD, hemophilia, liver disease	Use within the first 3 h of severe injury; may lower the seizure threshold

Full anticoagulation in patients with solid organ injury has been examined in one small study limited to low-grade liver and spleen injuries [71]. In this report of 20 patients with both a blunt aortic injury and a grade 1 or 2 liver or spleen injury, there were no failures of non-operative management despite undergoing operative aortic repair on partial bypass with full anticoagulation. Thus, if full anticoagulation is required early post-injury (e.g., for management of a blunt cerebrovascular injury), this can likely be initiated safely in the setting of a low-grade solid organ injury. No data exists to guide decision-making in higher-grade injuries. Practically speaking, if full anticoagulation is strongly indicated, this should be started while the patient is under close surveillance with angiographic and surgical resources rapidly available.

VTE Chemoprophylaxis or Full Anticoagulation in Patients with Traumatic Brain Injury

One of the most contentious topics in all of critical care is the anticoagulation of neurotrauma patients. Some centers have created treatment guidelines with input from all the involved specialties to guide therapy in these difficult situations. This approach results in an institution-specific practice guideline that can serve as a reference point for patient management decisions at the bedside.

Based on the work of Norwood and Berne, there appear to be specific TBI injury patterns with an increased risk for progression [72], and VTE chemoprophylaxis may further increase this risk [73]. At the same time, the risk of VTE begins to increase significantly at 72 h post-injury [74]. One approach to the questions of (1) whether a given patient is a candidate for VTE chemoprophylaxis and (2) when that prophylaxis can be initiated is shown in Fig. 26.3. This approach ensures collaborative review of the CT findings to determine the presence of moderate- or high-risk criteria upon which both the neurosurgical and critical care teams can agree. Results of the Delayed vs. Early Enoxaparin Prophylaxis (DEEP) randomized, prospective study on patients in the low-risk group found no increased risk of clinically significant bleed progression with enoxaparin at 24 h post-injury over placebo [75].

No data exists on the safety of therapeutic anticoagulation in patients with acute traumatic brain injury. However, the same risk factors for bleed progression as discussed above can be applied to identify patients who should definitely not be started on early therapeutic anticoagulation (i.e., those with documented bleeding progression on CT, those with an indwelling ICP monitor or extraventricular drain, and those

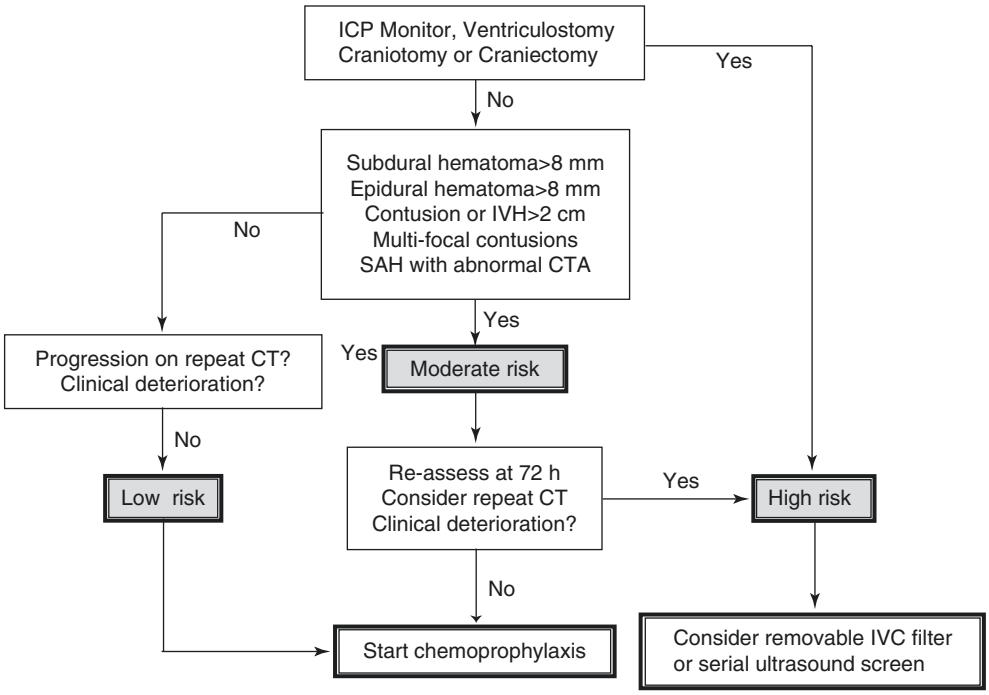

Fig. 26.3 Algorithm for risk stratifying TBI patients for VTE prophylaxis (Adapted from Phelan [92]). *CTA* CT angiography, *ICP* intracranial pressure, *IVC* inferior vena cava, *IVH* intraventricular hemorrhage, *SAH* subarachnoid hemorrhage

who have undergone a craniotomy or craniectomy). For those with a stable interval CT either with or without risk factors for bleeding progression, the timing of anticoagulation should be determined in consultation with neurosurgery. The decision of whether and when to resume pre-injury anticoagulation for atrial fibrillation CVA prevention is discussed below.

Atrial Fibrillation ATE Prevention

Patients with a history of atrial fibrillation are at increased risk of a thromboembolic CVA, while the recommended stroke prevention strategy—oral anticoagulation—increases the risk of bleeding, including intracranial hemorrhage (ICH), which can be equally disabling. A number of well-conducted studies and carefully considered guidelines have addressed this conundrum [76].

The risk of a thromboembolic CVA can be assessed with the CHA_2DS_2-Vasc score which is an acronym for *c*ongestive heart failure (CHF), *h*ypertension (HTN), *a*ge, *d*iabetes mellitus, *s*troke, *s*ex, and *vasc*ular disease. One point is assigned for CHF, HTN, age 65–74, diabetes, and female gender while two points are assigned for age ≥75 and stroke. Patients with a score of 0 are considered low risk for CVA (0.2 %/year), 1 intermediate risk (0.4 %/year), and ≥2 high risk (2.2–13.2 %/year). Anticoagulation is generally not recommended for patients with a score of 0. A score of 1 is more controversial with some recommending a nuanced approach depending on the specific risk factor (e.g., age carries a higher risk than gender). Thus some patients with a score of 1 may not be anticoagulated [77]. Those with a score ≥2 should be started on anticoagulation [78]. Traditionally, this is done with warfarin (following a heparin bridge in higher risk patients) although DTIs and Xa-Is are now used more commonly as they do not require monitoring and appear to carry a comparable or even lower overall bleeding risk compared to warfarin [79, 80]. As noted above, however, the anticoagulation effect of these agents cannot be easily reversed.

Another scoring system called HAS-BLED can also help estimate the risk of bleeding from anticoagulation. This acronym stands for *h*ypertension, *a*bnormal renal and/or liver function, *s*troke, *b*leeding history or predisposition, *l*abile INR on warfarin, *e*lderly (age >65), and *d*rugs (aspirin or NSAIDS; alcohol abuse). One point is assigned for each risk factor (up to 2 for abnormal organ function and up to 2 for drugs) [81]. A score of 0–2 represents a low risk of bleeding (1–2 bleeding events per 100 patient years) while a score of ≥3 is high risk (≥4 bleeding events per 100 patient years). Limitations include the wide range of bleeding severity and the fact that this scoring system has not been validated on surgical patients.

Patients on anticoagulation who have a major bleeding complication, such as an intracranial bleed, bear special mention. Following such a life-threatening complication, the patient's risk for future thromboembolism and bleeding should be reassessed. Patients at high risk for a thromboembolic stroke and low risk for bleeding should be resumed on anticoagulation following the establishment of hemosta-

sis. Those deemed high risk for recurrent bleeding may be reluctant to resume anticoagulation. Unfortunately, aspirin monotherapy affords minimal protection against CVA and carries a moderate bleeding risk [77]. Dual antiplatelet therapy with aspirin and clopidogrel offers slightly more protection against CVA but at the expense of bleeding risk that is comparable to full anticoagulation. A recent retrospective study of patients with an intracranial bleed on anticoagulation indicates that outcomes (mortality, CVA, recurrent bleeding) are significantly better in patients resumed on anticoagulation (within a median of 31 days of the index bleed) [82]. Although prospective data is needed to confirm these findings, this study does provide some guidance for discussing this issue with patients prior to hospital discharge. If the patient is undecided on anticoagulation or the care team feels this presents excessive risk, a short-term approach would be to start aspirin monotherapy (81 mg PO daily) if the patient should otherwise be considered for primary prevention with ASA (e.g., a Framingham Heart Study score of >10%) with short-interval primary care follow-up.

New-onset paroxysmal atrial fibrillation can present in the postoperative cardiac patient, trauma patients, and non-cardiac thoracic postoperative patients in the ICU. In addition to decisions about rate and rhythm control, the intensivist must decide on the need for and timing of systemic anticoagulation in these patients. In general, anticoagulation should be started when atrial fibrillation persists beyond 48 h [83], especially in patients with a CHA_2DS_2-Vasc ≥2. Those with one or no risk factors may benefit from a more selective approach. One study in non-cardiac thoracic surgical patients found no benefit to nonselective anticoagulation in patients with postoperative atrial fibrillation due to increased bleeding complications [84]. Closer examination of these results indicates that selective anticoagulation in those with a $CHADS_2$ score ≥2 may have been a safer strategy. If patients undergo electrical cardioversion, anticoagulation should be started prior to the procedure (time permitting) and continued thereafter.

ICU Procedures in Patients with Coagulopathy and Therapeutic Anticoagulation

The timing of therapeutic procedures in a coagulopathic patient and the management of anticoagulation in an ICU patient undergoing a bedside procedure depends upon the degree of coagulopathy or the indication for anticoagulation and the urgency of the procedure. There is considerable practice variability among expert intensivists and no clear guidance from the literature on these issues [85, 86]. Coagulopathic patients should undergo resuscitation aimed at reversing coagulopathy. Emergent monitoring and access procedures should not be delayed but should be performed by experienced providers to minimize mechanical complications which can lead to bleeding.

In the patient on therapeutic anticoagulation, a radial arterial line can be placed without holding or reversing the anticoagulation. Similarly, for a standard triple lumen central venous catheter placed under ultrasound guidance, anticoagulation can generally be continued. For insertion of larger catheters (e.g., hemodialysis access) on an elective basis, heparin can be held for 1–6 h prior to insertion or one dose of LMWH can be skipped with resumption of anticoagulation after successful, hemostatic placement of the line (provided the insertion was straightforward). Bedside percutaneous dilational tracheostomy (PDT) and percutaneous endoscopic gastrostomy (PEG) are elective procedures with a risk of bleeding [87]. Consequently, anticoagulation should be reduced or held around the time of these procedures. If this cannot be done safely (e.g., recent pulmonary embolism with right heart strain), the procedure should generally be deferred although some choose to continue anticoagulation through these procedures [88].

Mechanical Heart Valves

Guidelines for the perioperative management of anticoagulation for mechanical heart valves have been recently published [89]. Some minor procedures (e.g., cataract surgery and diagnostic endoscopy) can be performed with a therapeutic INR and thus do not require any special anticoagulation management [90]. For cases where the INR should be normal at the time of surgery, if the patient has a bileaflet mechanical valve in the aortic position with no additional risk factors for arterial thromboembolism (ATE), bridge anticoagulation is not warranted. Warfarin should be held for 5 days preoperatively, and an INR is checked the day prior to surgery. If it is still elevated beyond the surgeon's comfort level, vitamin K (1 mg PO) can be given. Warfarin can be restarted 12–24 h postoperatively once hemostasis is assured. Patients with a bileaflet aortic valve and additional thromboembolic risk factors are at moderate risk for ATE, and the need for bridging anticoagulation should be tailored to the individual patient and the type of surgical procedure being considered. Those with a mechanical mitral valve are at high risk for ATE and require bridge anticoagulation therapy with heparin or LMWH while warfarin is held. If heparin is used for bridge anticoagulation, it should be held 4–6 h before surgery. For bridge LMWH, the last dose should be given 24 h prior to surgery. Bridging heparin or LMWH can be resumed at the preoperative dose once hemostasis has been assured approximately 24 h after low-bleeding-risk surgery and 48–72 h after high-bleeding risk surgery [89].

Pulmonary Embolism with an Absolute Contraindication to Anticoagulation

Patients with an absolute contraindication to anticoagulation who develop a pulmonary arterial thrombosis or embolism should be considered for a removable IVC filter [69]. Although IVC filters increase the risk of DVT [91], the patient may not tolerate another VTE event. The IVC filter can be removed once the patient is started on therapeutic anticoagulation. In patients on bed rest or other causes of decreased mobility, delayed removal until their mobility improves is also reasonable.

Presumed Pulmonary Embolism in a Patient with Hemodynamic Instability or Cardiac Arrest

Patients who develop a massive pulmonary embolism with hemodynamic compromise should be considered for thrombolysis [92]. Diagnostic imaging with CT angiography is often not possible in these circumstances. If available, TTE or TEE should be obtained to assess for right heart strain. In a patient with PEA arrest or profound hypotension together with right heart strain, thrombolysis should be administered. One convenient dosing regimen is tPA 50 mg IV as a bolus followed by another 50 mg bolus if the first proves ineffective [93]. Anticoagulation should then be continued in patients who are successfully resuscitated.

Summary

Management of coagulopathy and anticoagulation in the ICU presents many nuanced challenges to the ICU physician. Early recognition and treatment of hemorrhage is critical in the management of coagulopathic patients. Although empiric therapy is sometimes required, laboratory analysis provides the most appropriate therapeutic guidance. Specific management depends on the patient's condition and the available resources. Those patients who present on anticoagulation or who develop a need for anticoagulation require special consideration. Rapid reversal in anticoagulated patients who are bleeding will minimize the risk of complications. Novel anticoagulants present special challenges in this regard. Those patients who require resumption of anticoagulation in the ICU or who need treatment for a VTE should be evaluated in a multidisciplinary fashion to ensure the patient's care is optimized over both the short and long term.

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Thrombocytopenia in the Surgical Intensive Care Unit

27

Noelle N. Saillant and Carrie A. Sims

Introduction

In contrast to the traditional depiction of platelets as quiescent cells that form the scaffold of an active clot, platelets participate in complex cellular interactions that make them a critical director of hemostasis. They are also active participants in the host response and crucial mediators of vascular integrity.

As immunologically active cells, platelets bind and internalize antigens, release microbiocidal granules, and assist in leukocyte migration. Interestingly, the total surface area of circulating platelets is greater than that of all other leukocyte subtypes, thus making platelets a formidable modulator of immunity [4].

Platelets also mediate the health of the endothelium and contribute to the integrity of the vascular wall through functional contact and release of local trophogens. With persistent severe thrombocytopenia, the endothelium thins and develops gaps between cells, leading to bleeding and capillary leak that may further compound the microvascular dysfunction associated with thrombocytopenia [5].

Finally, platelets are essential mediators of clot formation. A new *cell-based* model of thrombus formation emphasizes the complex interactions of platelets, the endothelium, and coagulation factors (see Fig. 27.1) [6]. In this model, platelets serve as the scaffold for assembly of two complexes at the platelet surface: the tenase complex and the prothrombinase complex. The sequestration of coagulation factors into the tenase and prothrombinase complexes at the platelet surface provides the necessary foundation to produce thrombin en masse for "thrombin burst" and active clot formation.

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Hemostasis requires a sufficient number of *functional* platelets; however the threshold platelet count is unclear. Moreover, platelet function is poorly characterized by clinically available tests [7].

Clinical Presentation

Patients with thrombocytopenia frequently develop petechiae, mucosal bleeding, bullae, purpura, and superficial ecchymoses [8]. The risk of clinically significant "bleeding events" such as intracranial hemorrhage, gastrointestinal bleeding, airway bleeding, and spontaneous retroperitoneal bleeding increases substantially as the platelet count falls. In a study of 329 adult ICU patients, Vanderschueren et al. found that the observed bleeding incidence was 21.4 % for patients whose platelet count was $<150\times10^9$/L versus 4.1 % in patients without thrombocytopenia. Platelet nadirs below 100×10^9/L increased the incidence of bleeding events to 52.6 % [9].

The risk of spontaneous intracranial bleeding, however, was only increased once the platelets fell below 10×10^9/L, a nadir present in less than 2 % of critical patients [1, 9, 10]. Although low platelet count was associated with more bleeding events in this series, the platelet nadir may be a marker of illness severity rather than the direct cause of dysfunctional coagulation. As such, the percent fall in platelet count rather than the absolute nadir might be a superior marker of microvascular dysfunction and risk of death serving as a clinical indicator that deserves attention in ICU patients [1].

Etiologies of Thrombocytopenia in the ICU

The cause of thrombocytopenia in most ICU patients is often multifactorial and includes one or more of the following: decreased production, increased destruction, enhanced consumption, increased sequestration, and overall dilution.

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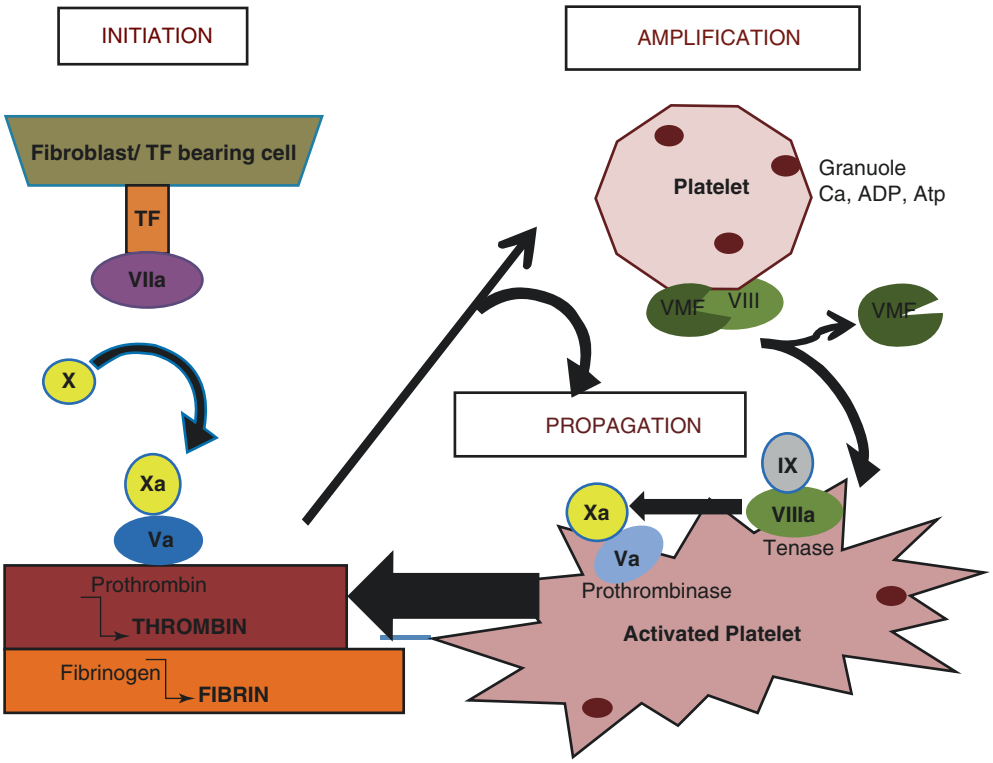

Fig. 27.1 Cell-based model of hemostasis proposed three overlapping phases of coagulation occurring at cellular surfaces: initiation of coagulation begins at the tissue factor-bearing cell, amplification of coagulation is directed at the platelet surface as the platelet becomes activated, and propagation on the activated platelet surface to create "thrombin burst" with significant clot production [6]

Decreased Production

Platelets are produced in the bone marrow by progenitor cells known as megakaryocytes. Megakaryocytes are stimulated by the hormone thrombopoietin and must shed 100×10^9/L platelets daily in order to maintain normal platelet levels [12]. In the ICU, primary bone marrow failure is rare and is associated with congenital disorders such as TAR syndrome (thrombocytopenia and absent radii syndrome), congenital amegakaryocytic thrombocytopenia, and Fanconi anemia. More commonly, secondary marrow failure in critically ill patients is multifactorial and occurs as a slow decline in platelet function over time with nadirs often $<20 \times 10^9$/L [13]. Infections, classically of viral origin (e.g., parvovirus, varicella, HIV, EBV), may lead to aplastic anemia or direct marrow suppression. Medications may also lead to thrombocytopenia from marrow suppression. In particular, antiepileptic drugs (e.g., phenytoin, valproic acid), antibiotics (e.g., penicillins, cephalosporins, vancomycin), and H2 blockers (cimetidine, ranitidine) are some of the common medications known to cause thrombocytopenia by this mechanism. Rarely, thiazides and estrogens can cause isolated megakaryocyte aplasia or hypoplasia. Lastly, adequate nutritional stores of cobalamin, folate, and iron are essential for platelet production, and specific nutrient deficiencies may contribute to insufficient production [13].

Increased Destruction, Consumption, or Dilution of Platelets

Sepsis and Disseminated Intravascular Coagulation

The leading cause of thrombocytopenia in the ICU is sepsis, affecting 20–50 % of ICU patients [11, 14]. The mechanism for sepsis–associated thrombocytopenia, however, is complex. Severe inflammation leads to both platelet and endothelial activation with consumption of circulating platelets in microthrombi. In addition, high circulating levels of macrophage colony-stimulating factor stimulate monocytes and macrophages to engulf platelets, leukocytes, erythrocytes, and other precursor cells leading to their pathological destruction [3]. Bacterial pathogens, such as *S. Pneumoniae*, can also lead to thrombocytopenia by producing enzymes that cleave platelet surface glycoproteins. This alteration in platelet surface glycans leads to hepatic sequestration and premature platelet clearance [15].

Disseminated intravascular coagulation (DIC) is the ultimate manifestation of coagulation dysfunction and results in significant thrombocytopenia. This disorder is present in upward of 25 % of patients with septic shock but may also be triggered by injury, obstetrical emergencies, and other inflammatory conditions [14]. DIC results from cytokine release leading to the dysfunctional activation of the coagulation cascade. Inappropriate thrombin generation and the

expression of tissue factor leads to microvascular thrombi while consumption of coagulation factors, platelets, and activation of fibrinolysis leads to a concomitant bleeding diathesis. Laboratory findings are significant for low platelet counts, prolonged coagulation tests, elevated byproducts of fibrin degradation, and diminished levels of protein C and antithrombin. End-organ dysfunction ensues, as the patient suffers both thrombotic and hemorrhagic complications. Purpura fulminans is a cutaneous complication of acquired depletion of protein C, protein S, and antithrombin III during severe DIC. The skin evolves from a painful hyperemic area to frank necrosis. Classically, febrile viral infections, as well as *Meningococcus* and *Staphylococcus* infections, lead to purpura fulminans. However asplenia and liver disease may also cause these lesions.

Application of scoring systems in conjunction with early treatment of DIC may lead to improved mortality [16, 17]. The International Society of Thrombosis and Hemostasis (ISTH) proposed a simple cumulative score of five points based on abnormal laboratory values for the platelet count, prothrombin time (PT), fibrinogen, and D-dimer. Overall the scoring system is 93 % sensitive and 98 % specific in the setting of overt DIC; however the utility of this scoring system in patients with more insidious presentation has been questioned (see Table 27.1) [3, 18]. In response to these concerns, the Japanese Association for Acute Medicine (JAAM) published a DIC scoring system that is more capable at recognizing non-overt DIC earlier than the ISTH model (see Table 27.2) [16].

Heparin-Induced Thrombocytopenia (HIT)

Certain therapeutic agents may cause thrombocytopenia by suppressing bone marrow production, whereas other medications (e.g., antibiotics, antiepileptic drugs, diuretics, and quinines) can directly lead to immune-mediated platelet destruction. Heparin is perhaps the most notable offending agent. Heparin exposure can lead to a clinically nonsignificant thrombocytosis (HIT type 1) or a highly morbid syndrome of platelet activation and consumption (HIT type 2). HIT type 1 is a direct, non-immunologic heparin effect that leads to *asymptomatic p*latelet aggregation and a resultant *mild* thrombocytopenia (~100,000 × 10^9/L). HIT type 2, on the other hand, is a life-threatening condition that occurs when a heparin-induced antibody binds to platelet factor 4 (PF4) leading to platelet phagocytosis. Additionally, the binding of the heparin antibody to the PF4 complex activates platelets causing a 40-fold increase in venous and arterial clotting complications [19–21]. HIT type 2 affects 1–5 % of ICU patients with an associated mortality ranging from 2 to 20 % [1]. Classically, there is a 50–60 × 10^9/L decrease in platelet count that occurs 7 days post heparin exposure; however at least 10 % of patients will still have an absolute platelet count over 150 × 10^9 [8]. Previous exposure to heparin products within 3 months may accelerate this processing leading to HIT symptoms before 7 days. Clinically, patients are more likely to develop venous thrombi including pulmonary emboli with a 4:1 predominance over arterial complications [8, 20, 21].

Currently, diagnosing HIT type 2 relies on both a positive ELISA assay for heparin-dependent anti-PF4 antibodies and followed by a confirmatory serotonin release assay (SRA). This two assay approach attempts to maximize both speed and specificity. Although the HIT ELISA is rapid and very sensitive, it is not very specific. In fact, very high percentages of false positives in ICU patients have been observed in the setting of hemodialysis (1–3 %), vascular procedures (20 %), and cardiac surgery (50 %) [3]. In contrast, the SRA test has a sensitivity and specificity over 95 % but is labor intensive and may take days to complete [22]. Thus, the ELISA is performed first as a screening test and, if positive, the SRA is used to confirm the diagnosis.

The pretest probability of a positive HIT is predicted by the Warkentin 4 Ts scoring system (see Table 27.3) with a

Table 27.1 ISTH scoring system

Parameter	Result	Score
Platelet count	>100 × 10^9/L	0
	<100 × 10^9/L	1
	<50 × 10^9/L	2
PT	<3 s prolonged	0
	>3 s but <6 s	1
	>6 s	2
Fibrinogen	>1.0 g/L	0
	<1.0 g/L	1
D-Dimer/FDP	No increase	0
	Moderate increase (250–5,000)	1
	Strong increase (>5,000)	2

A total score of ≥5 = DIC [18]

Table 27.2 Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis [16]

Criteria	Score
Systemic inflammatory response syndrome criteria	
≥3	1
0–2	0
Platelet count (cells/μL)	
<8,000 or 50 % decline in 24 h	3
≥8,000 and <120,000 or >30 % decline in 24 h	1
≥12,000	0
Prothrombin time	
≥1.2	1
<1.2	0
Fibrin/fibrinogen degradation products (mg/L)	
≥25	3
≥10 and <25	1
<10	0

Table 27.3 Warkentin scoring system clinical probability of HIT

4 Ts	0 points	1 point	2 points
Thrombocytopenia	Platelet count decreased >30 % or nadir $<10\times10^9$/L	Platelet count decreased 30–50 % or nadir $10–19\times10^9$/L	Platelet count decreased >50 % or nadir $\geq20\times10^9$/
Timing of drop in platelet count	Platelet count decreased <4 days Without recent exposure (w/in 3 months)	C/w immunization but unclear Hx Onset after day 10 or <1 day with recent exposure (w/in 3 months)	Clear onset 5–10 days or decrease within 1 day With recent exposure (<30 days)
Thrombosis or other clotting complication	None	Progressive/recurrent thrombosis Non-necrotizing skin lesions Suspected but unproven thrombosis	New thrombosis Skin necrosis Acute reaction post infusion
Other causes of thrombocytopenia	Definite	Possible	None apparent

High HIT is likely (6–8 pts), intermediate HIT is possible (4–5 pts), and low HIT is unlikely (≤3 points) [22]

score of >2 indicating that a HIT laboratory test should be performed. However this scoring system has not been validated in ICU patients and is not meant to substitute for clinical judgment when deciding whether to order an ELISA screening assay [20, 23].

Other Drug-Induced Hemolytic-Thrombolytic Syndromes

Other commonly used ICU medications that have been associated with drug-induced immune thrombocytopenia (DITP) include vancomycin, penicillin derivatives, sulfonamides, trimethoprim-sulfamethoxazole, rifampin, haloperidol, amiodarone, acetaminophen, naproxen, ibuprofen, and furosemide [24, 25]. The cross-reactivity of drugs with the immune system may take place via multiple mechanisms. Drugs may bind to larger macromolecules such as proteins and become "haptens." The resulting hapten complex then induces antibody formation. This phenomenon has been observed with penicillins and cephalosporins. Similarly, medications such as quinine, NSAIDs, and antiepileptic drug exposure may prime the immune system to react against platelets through drug-dependent antibody formation.

Pharmacologic agents may change the processing of glycoproteins of platelets by macrophages, introducing new cross-reactive peptides that trigger thrombocytopenia. Sulfamethoxazole, penicillamine, procainamide, and, more recently, some monoclonal antibodies have been implicated in this regard. Regardless of etiology, the clinical consequences of DITP typically manifest after a sensitization period of 7 days. Reexposure to the drug may lead to a more precipitous manifestation within hours to days. The clinical symptoms of DITP range from a mild, self-limited thrombocytopenia to life-threatening decreases in platelet count. Severe forms may cause hypotension and bleeding complications in the form of purpura, mucosal hemorrhage, as well as gastrointestinal and genitourinary bleeding. At times, DITP may produce syndromes akin to thrombotic thrombocytopenia purpura and hemolytic uremic syndrome. A detailed drug exposure history coupled with a high index of suspicion is critical to prompt diagnosis. After the offending agent is discontinued, symptoms typically subside within days; however, platelet counts sometimes take days to weeks to rebound. Treatment is typically supportive; however IVIG and plasmapheresis have been used for severe cases [26].

Immune Thrombocytopenia (ITP)

ITP is an autoimmune disease that results in IgG-mediated platelet destruction while leaving other cell lines unaffected. Although primary ITP presents without an associated triggering condition, secondary ITP is more frequently associated with viral infections (e.g., HIV, HCV, CMV), autoimmune diseases (e.g., SLE), lymphoid malignancies, and other conditions that disrupt the immunologic-hemostatic equilibrium. ITP frequently presents with moderate to severe thrombocytopenia. Given that there is no confirmatory diagnostic study, the diagnosis is made clinically after other causative agents have been excluded. The goal of treatment is to prevent bleeding complications, not to restore normal platelet counts. Treatment is recommended for patients with platelet counts $<30{,}000\times10^9$/L or bleeding complications. First-line therapy is glucocorticoids and/or IVIG. Rituximab (anti-CD20 monoclonal antibody) and other immunotherapeutics (azathioprine, cyclosporine A, cyclophosphamide, etc.) are considered second-line treatment for refractory ITP. Thrombopoietin receptor agonists are reserved as a third-line approach. Surgical consideration for splenectomy is warranted after failure of first-line therapeutics [27].

Thrombotic Microangiopathies (TMA)

Microangiopathies are a subset of nonimmune processes that share a common process of endothelial damage, microthrombi, platelet destruction, and hemolysis. Two prominent TMAs are thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS). TTP is characterized by a deficiency of ADAMTS-13, a metalloproteinase that cleaves von Willebrand factor (VWF). Uncleaved

VWF multimers are prone to activating platelets leading to microthrombi and subsequent end-organ dysfunction. The diagnosis of TTP is clinical and should be suspected in patients with hemolytic anemia, thrombocytopenia, fever, purpuric lesions, acute kidney injury, and neurologic dysfunction (e.g., headaches, delirium, strokes, and seizures). TTP may be differentiated from DIC and other causes of acute thrombocytopenia by the presence of schistocytes on the blood smear in conjunction with elevated LDH but a normal prothrombin time. Although serum levels of ADAMTS13 are neither sensitive nor specific for diagnosing TTP, a very low ADAMTS13 activity level is associated with worse outcome. Plasmapheresis and glucocorticoids are the recommended therapy. Rituximab is generally considered for refractory cases or for those with neurologic and cardiac sequela. Platelet transfusion is to be avoided due to a concern for continued microvascular platelet deposition unless severe bleeding or intracranial hemorrhage is observed [3, 28–30].

Hemolytic uremic syndrome (HUS), on the other hand, is a microangiopathic hemolytic anemia that is typically preceded by a diarrheal illness in children. Following infection, toxins from *Shigella* or *E. coli* (O157:H7) can both injure the endothelium. As a result, microthrombi are formed in arterioles and capillaries leading to hemolysis, thrombocytopenia, and organ dysfunction. Aside from supportive treatment, no therapies have been proven beneficial. Renal replacement therapy may be needed in severe cases.

In contrast, atypical HUS almost exclusively affects adults and is not associated with an antecedent bacterial infection. With atypical HUS, either a genetic or immune-mediated deficiency of factor H leads to uncontrolled and excessive activation of complement and subsequent thrombotic complications. First-line treatment is plasma exchange, with recommendations to begin within 24 h of presentation. Recently, the FDA-approved eculizumab, an anti-C5 monoclonal antibody, inhibits complement-mediated angiopathy for use in atypical HUS [3, 30].

Intravascular Hemolysis

Mechanical heart valves, cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO), balloon pumps, and other intravascular devices are associated with mechanical stress and shear forces across circulating element membranes. Cellular blood components may be injured as they traverse these devices leading to microangiopathic anemia and thrombocytopenia. Treatment is supportive coupled with timely device removal as appropriate.

Postsurgical Thrombocytopenia

A decline in the platelet count is frequently observed following major surgery and correlates with both the severity of blood loss and tissue injury. Although this phenomenon has been attributed to both platelet consumption and hemodilution, its underlying pathophysiology remains poorly characterized. In general, postsurgical thrombocytopenia typically nadirs by post-op day 4 and rarely requires intervention.

Trauma-Induced Coagulopathy (TIC)

Trauma-induced coagulopathy is a life-threatening disorder affecting over 25 % of severely injured patients [31, 32]. While the pathophysiology of TIC is multifactorial, platelet counts in the trauma patient are directly affected by consumption, hyperfibrinolysis, hemodilution, and cellular dysfunction. Importantly, both the number and functional quality of the platelets in circulation correlate with mortality after injury. In a study of 389 severely injured patients, Brown and colleagues noted that for every 50×10^9/L decrease in absolute platelet number, the risk of death increased by 17 % [33]. This association persisted even when platelet levels were within the normal laboratory range of $100–450 \times 10^9$/L. Moreover, platelet clotting is abnormal in up to 45 % of trauma patients on admission and was associated with a tenfold increase in early mortality [34]. When platelet function was specifically assessed by measuring aperture, Jacoby et al. found that platelets were activated but functionally in brain-injured patients and in non-survivors alike [35].

Sequestration

Typically, the spleen can sequester up to a third of circulating platelets. In conditions of hypersplenism (i.e., portal hypertension), the sequestration capacity is increased. This platelet pooling gives the appearance of thrombocytopenia even though the overall number of platelets within the body remains unchanged.

Evaluation of Thrombocytopenia

While the timing, speed of nadir, and duration are important clinical considerations, a diagnostic evaluation of thrombocytopenia is prudent when the platelet count drops below 100×10^9/L or if there is a 30 % decrease in the absolute platelet count. Although the clinical context should suggest the etiology for most patients, multiple mechanisms are not uncommon in ICU patients [11]. In general, a basic laboratory investigation should include a complete blood count, coagulation studies (PT, aPTT, INR), and a peripheral blood smear. If there is evidence of schistocytes on smear, then a bilirubin, LDH, haptoglobin, D-dimer, and fibrinogen may be additionally helpful. A bone marrow aspirate is not indicated and should be reserved as a diagnostic modality when there is evidence of dysfunction in multiple hematologic cell lines or when no clear etiology can be identified [11].

Treatment

Treatment of thrombocytopenia is largely supportive and is based on the underlying etiology [36]. The decision to treat thrombocytopenia should be based on assessment of the following:

- Central versus peripheral thrombocytopenia, with underlying etiologic consideration
- Risk of bleeding (procedures, surgical interventions, etc.) (see Table 27.4)
- The presence of active bleeding
- The risk of thrombosis
- The risk of platelet transfusion [i.e., transfusion-related acute lung injury (TRALI)], pathogen transmission, and allergic and hypotensive reactions
- Etiology of thrombocytopenia

The etiology of thrombocytopenia is the critical determinant regarding the utility of platelet transfusion. Specifically, some etiologies (HIT and TTP) may be made worse by platelet transfusion (see Tables 27.5 and 27.6).

Platelet transfusion should be considered when the platelet count is $<10\times10^9$ cells/L in order to decrease the risk of spontaneous bleeding. Prophylactic platelet transfusion can also be considered for invasive elective procedures. The threshold for transfusion will depend both on the degree of invasiveness as well as the risk associated with bleeding.

Table 27.4 Platelet transfusion thresholds [11]

Platelet count threshold	Recommendations
$<100\times10^9$/L	Platelet transfusion may be considered if:
	Central nervous system surgery
	Eye surgery
	Liver surgery
	Large vessel vascular surgery
	Polytrauma
$<50\times10^9$/L	Platelet transfusion is recommended:
	In severe hemorrhage
	Sepsis with risk of severe hemorrhage
	Invasive procedure
	Perioperative management of hemostasis
$<20\times10^9$/L	Platelet transfusion may be considered if:
	Central thrombocytopenia
Other	There is no evidence to support role for prophylactic platelet transfusion
	Platelet counts $>20\times10^9$/L
	(see exceptions above)
	DIC
	HIT
	TTP
	Antiphospholipid syndrome
	Hemolytic uremic syndrome (HUS)
	Posttransfusion purpura

Despite these consensus guidelines, it is important to note that platelets stored for transfusion may not perform as well as native in vivo platelets. Banked platelets develop a time-dependent dysfunction known as "platelet storage lesion" (PSL). PSL is characterized by derangements in platelet metabolism, reorganization of cell structure, and diminished aggregation response [37, 38]. Overall, these changes may reduce the effectiveness of platelet transfusion.

If transfusion is deemed clinically necessary, platelets should be ABO/ Rh1 compatible. Although pooled platelets may be used in most patients, single donor apheresis platelets should be used in alloimmunized patients. All platelets should be leukoreduced to minimize the risk associated with concomitantly transfusing white blood cells. In addition, patients who are immunocompromised or immunosuppressed should receive irradiated platelets in order to decrease the risk of graft vs. host disease.

Table 27.5 Treatment of the various etiologies of thrombocytopenia in the ICU patient [1, 3, 8–10, 13, 21, 22, 27, 28]

Pathology	Treatment
Sepsis	Source control, antibiotics, supportive care
Drug-induced thrombocytopenia	Withdrawal of offending agent
HIT	Platelet transfusion contraindicated*
	Withdraw heparin, LMWH, or heparin-coated devices
	A non-heparin anticoagulant should be administered
ITP	If platelet count <30,000 or bleeding complications
	First line: steroids and/or IVIG
	Second line: rituximab (anti-CD20 monoclonal antibody), immunotherapeutics. Splenectomy
	Third line: thrombopoietin receptor agonists
Thrombotic microangiopathy	Platelet transfusion contraindicated*
	Etiologically driven
	TTP: plasmapheresis and steroids; second line: rituximab
	Typical HUS: supportive therapy, RRT
	Atypical HUS: plasma exchange, second line: eculizumab
Mechanical/ sequestration	Supportive care
Trauma/postsurgical	Supportive care
	Transfusion guidelines as above

Table 27.6 Recommendation to withhold antiplatelet medications and antithrombotic prophylaxis [11]

Platelet count threshold	Recommendation
$<50\times10^9$/L	Consider withdrawing antiplatelet medications
$<30\times10^9$/L	Consider withdrawing antithrombotic prophylaxis

Conclusion

Thrombocytopenia is a common hematologic malady of the critical ill. Often multifactorial, a low platelet count or a significant nadir requires the attention of the clinician and serves as a harbinger of poor prognosis as well as a marker of illness severity. A structured evaluation is required to diagnose the underlying factors contributing to a low platelet count. Consensus guidelines regarding the treatment of thrombocytopenia and the optimal utilization of platelet transfusions are still evolving. Further research is needed to better understand platelet transfusion thresholds and the efficacy of platelet transfusion.

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Venous Thromboembolism in the Intensive Care Unit

28

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Abbreviations and Acronyms

AAOS	The American Academy of Orthopaedic Surgeons
ACCP	The American College of Chest Physicians
AHRQ	The Agency for Healthcare Research and Quality
CT	Computed tomography
DVT	Deep vein thrombosis
EAST	The Eastern Association for the Surgery of Trauma
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
INR	International normalized ratio
IVC	Inferior vena cava
LMWH	Low molecular weight heparin
PE	Pulmonary embolism
SC	Subcutaneous
SCDs	Sequential compression devices
TEDS	Thromboembolic deterrent stockings
US	United States
V/Q scan	Ventilation/perfusion scan
VTE	Venous thromboembolism

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT), pulmonary embolism (PE), or both, is common among critically ill surgical patients and potentially preventable. VTE remains a significant source of morbidity and mortality among patients in the intensive care unit (ICU) and among hospitalized patients in general. Each year in the United States (US), there may be as many as 350,000–900,000 cases of VTE, and more than 100,000 people will die as a result of VTE [1]. The Agency for Healthcare Research and Quality (AHRQ) has identified VTE prophylaxis as "the number one patient safety practice" to prevent inhospital death [2, 3]. Furthermore, the US Surgeon General has recognized VTE as "a major public health problem" and issued "A Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism" in 2008 [1]. Most recently, the AHRQ has placed "strategies to increase appropriate prophylaxis for VTE" on the list of top 10 "Strongly Encouraged Patient Safety Practices" [4, 5]. While high-quality evidence-based guidelines for VTE prophylaxis are available and strongly encouraged for adoption, studies continue to show that hospitalized patients are not routinely provided with risk-appropriate VTE prophylaxis [4, 6, 7].

Critical care patients are at even higher risk for VTE than other hospitalized patients secondary to additional risk factors commonly acquired in the ICU including pharmacologic sedation, vasopressor use, mechanical ventilation, immobilization, and central venous catheters [8–10]. Many patients in the ICU also have coincident VTE risk factors such as malignancy, major surgery, stroke, or traumatic injury. Diagnosis and management of VTE in ICU patients is particularly challenging for a number of reasons. First, the signs and symptoms associated with VTE are not reliable indicators of VTE in critically ill patients [11]. Second, ICU patients often have compromised cardiac and respiratory function, and even a relatively small PE may be catastrophic for patients with little or no reserve [10]. Third, ICU patients are frequently at risk for bleeding, and some may be unable to be anticoagulated for VTE treatment due to major surgery, traumatic injury, gastrointestinal bleeding, or thrombocytopenia. Despite these challenges, VTE prophylaxis is safe and guidelines exist to assist healthcare providers with individual risk assessment and effective prophylaxis regimens.

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All ICU patients without contraindications require risk-appropriate VTE prophylaxis because *all* ICU patients are at risk for VTE. It is important to recognize risk factors, prescribe and administer all doses of effective prophylaxis, and provide timely and accurate diagnosis and treatment for patients with VTE in the ICU.

Definitions

DVT refers to partial or complete occlusion of the venous system, typically of the lower extremities, from formation of venous thrombi. A distal DVT is confined to the deep veins of the calf, while a proximal DVT involves thrombosis at the popliteal vein or above. It is important to remember that the "superficial femoral vein" is still part of the deep venous system and any clot identified within this vein must be treated as a true DVT. PE refers to occlusion of the pulmonary vasculature and is thought to result from embolism secondary to DVT. However, more recent data suggest that primary thrombosis of the pulmonary vasculature may be the cause of some PE [12]. The severity of PE is related to the associated mortality risk and is typically stratified according to hemodynamics and imaging or biomarker assessment of right ventricular cardiac function. Massive or high-risk PE is associated with blood pressure less than 90 mmHg or at least a 40 mmHg decrease from baseline, signs of cardiogenic shock and/or cardiac arrest. Submassive or intermediate-risk PE is associated with preserved hemodynamics but evidence of right ventricular dysfunction and/or elevated cardiac biomarkers indicative of myocardial necrosis.

Incidence

Each year in the United States (US), there may be as many as 350,000–900,000 cases of VTE, and more than 100,000 people will die as a result of VTE [1]. Over one third of patients with DVT will experience PE [13]. Autopsy studies have identified PE in 7–27 % of critically ill patients postmortem, and in most of these cases, there was no clinical suspicion of PE before death [10]. In a study of mechanically ventilated ICU patients, all of whom received appropriate VTE prophylaxis, nearly 25 % were diagnosed with DVT when the group was screened with duplex ultrasound. In addition, 11.5 % of patients with DVT in this study were diagnosed with PE during their hospitalization [14]. A recent study examined ICU patients with sepsis and septic shock and found that 37 % were diagnosed with VTE, and all had received best practice VTE prophylaxis [15]. While incidence varies significantly based on specific risk factors, all ICU patients are at considerable risk for VTE.

Risk Factors and Risk Assessment

Virchow described the basic etiology of venous thromboembolism as vascular endothelial injury, venous stasis, and hypercoagulability. Critical care patients are at higher risk for VTE than other hospitalized patients secondary to risk factors commonly acquired in the ICU including mechanical ventilation, pharmacologic sedation, immobilization, vasopressor use, and central venous catheters. Many surgical ICU patients commonly have general risk factors as well including major surgical procedures, traumatic injury, and malignancy. Gastrointestinal, pancreatic, and colorectal malignancies in particular are associated with increased risk for VTE.

Mechanical ventilation decreases venous return and often requires sedation and immobilization, all of which may increase the risk of VTE. One study has demonstrated that ICU patients with DVT had longer duration of mechanical ventilation than patients without DVT, although there is no clear causal relationship [16]. This same study demonstrated that vasopressor administration is an independent risk factor for DVT and is likely related to reduced absorption of subcutaneous prophylactic heparin secondary to peripheral blood vessel constriction. Central venous catheters, especially femoral catheters, represent another important VTE risk factor. The incidence of thrombosis with subclavian vein catheters is 10 % or less but may be as high as 40–56 % with internal jugular vein catheterization and 10–69 % with femoral vein catheterization [9, 17]. One study has demonstrated that ICU patients who developed DVT had longer duration of central venous catheter use than patients who did not develop DVT [14]. Table 28.1 presents VTE risk factors commonly acquired in the ICU as well as other major and minor general risk factors.

Many different risk assessment models have been created to stratify patient risk for acquiring VTE during hospitalization. Some include bucket models (e.g., University of California (UC), San Diego, and Johns Hopkins systems), while others use a point allocation system (e.g., Caprini, Padua, Rogers, IMPROVE) [18–23]. The Caprini VTE risk assessment model was recently validated in critically ill surgical patients [24]. This model supports individual risk assessment for patients in the ICU based on a point allocation system related to the presence of specific risk factors. The American College of Chest Physicians (ACCP) recommends the Padua score for VTE risk assessment of nonsurgical hospitalized patients, although it does not differentiate explicitly between ICU and non-ICU patients [25].

Prevention

Guidelines for VTE prophylaxis provided by the ACCP are often considered the definitive resource [25]. Guidelines for specific populations at risk including trauma patients and orthopedic surgical patients are available from the Eastern Association for the Surgery of Trauma (EAST) and the

Table 28.1 Risk factors: venous thromboembolism in the intensive care unit

VTE risk factors commonly acquired in the ICU
Respiratory failure requiring mechanical ventilation
Cardiac failure (New York Heart Association Class III/IV)
End-stage renal disease
Sepsis, severe sepsis, and septic shock
Vasopressors
Pharmacologic sedation
Immobilization
Central venous catheters
Platelet transfusion
Thrombophilia (e.g., heparin-induced thrombocytopenia)
Other major VTE risk factors
Malignancy
Personal history of previous VTE
Family history of VTE
Prolonged surgical procedure (>2 h)
Major general surgery
Major traumatic injury
Hip or leg fracture
Hip or knee replacement
Acute spinal fracture
Acute spinal cord injury (<1 month)
Acute stroke (<1 month)
Pregnancy/postpartum (up to 6 weeks)
Known thrombophilia (e.g., factor V Leiden, lupus anticoagulant, anticardiolipin antibodies, antithrombin deficiency, protein C or S deficiency, etc.)
Other minor VTE risk factors
Older age
Immobility from prolonged sitting (e.g., airplane travel or prolonged car travel)
Laparoscopic surgery
Inflammatory bowel disease
Obesity
Pregnancy/antepartum
Acute infection
Varicose veins
Arteriovenous malformations
Tobacco use
Estrogen/selective estrogen receptor modulators (e.g., tamoxifen)
Contraceptives

VTE venous thromboembolism, *ICU* intensive care unit

American Academy of Orthopaedic Surgeons (AAOS), respectively [26, 27]. Evidence-based best practice VTE prophylaxis in the ICU varies based on the primary service (e.g., medicine, surgery, etc.) and other patient-specific risk factors.

Pharmacologic Prophylaxis

Most protocols use subcutaneous (SC) injection of unfractionated heparin or low molecular weight heparins (LMWHs) such as enoxaparin, dalteparin, or fondaparinux for VTE prophylaxis. Trauma and orthopedic literature typically supports the use of LMWH over unfractionated heparin [26]. Patients with unstable renal function or creatinine clearance less than 30 mL/min should receive unfractionated heparin instead of LMWH due to risks associated with bioaccumulation of some LMWHs in patients with reduced renal clearance. In ICU patients, LMWH may be preferable to unfractionated heparin. The PROTECT study was a randomized controlled trial comparing unfractionated heparin and LMWH as VTE prophylaxis in ICU patients [28]. There was no significant difference in proximal DVT between the two groups, but patients treated with LMWH had fewer PE events. A recent meta-analysis pooled data from eight randomized controlled trials (including PROTECT) to evaluate the use of LMWH versus unfractionated heparin prophylaxis in ICU patients [29]. This study concluded that LMWH was preferred over unfractionated heparin for VTE prophylaxis in ICU patients: the risk of any DVT, any PE, major bleeding, and/or mortality was decreased by 10 % among patients receiving LMWH versus unfractionated heparin (RR 0.90, 95 % CI 0.83–0.97, $p = 0.01$). However, when looking at each of these outcomes separately, LMWH was associated with a significantly decreased rate of DVT but no significant difference in PE, major bleeding, or mortality.

Most protocols recommend VTE prophylaxis throughout the inpatient hospitalization, but some literature supports extending prophylaxis to the outpatient setting for a limited duration after discharge from the hospital. This may be of particular use in patients at high risk for perioperative VTE including orthopedic surgery patients or those with major abdominopelvic oncologic resections. Dosing of unfractionated heparin is typically 5,000 units SC every 8 h for most (if not all ICU) patients, while the less frequent dosing every 12 h regimen may be appropriate for some patients at lower risk. Dosing for a common LMWH, enoxaparin, is typically once daily with 40 mg SC. VTE prophylaxis is typically administered 1–2 h before any major surgical procedure and resumed 12–24 h postoperatively. Contraindications to pharmacologic prophylaxis include active bleeding, high risk of bleeding, systemic anticoagulation, coagulopathy with international normalized ratio (INR) ≥1.5, or thrombocytopenia (platelet count <50,000).

Mechanical Prophylaxis

Mechanical prophylaxis may include sequential compression devices (SCDs) and thromboembolic deterrent stockings (TEDS). SCDs are preferred over TEDS alone, and TEDS may be associated with ulcers or skin breakdown, especially in patients with peripheral vascular disease or chronic lower extremity wounds and in ICU patients [30].

Patients with lower extremity wounds, casts, external fixation devices, or immobilizers may be unable to utilize SCDs or TEDS. Finally, compliance with these devices in surgical patients is poor even without any specific contraindications. Although very little data support its use, ambulation has been suggested as an effective adjunct to VTE prophylaxis when feasible [31]. However, this should never be considered an acceptable replacement to pharmacologic and/or mechanical prophylaxis in hospitalized patients.

Prophylactic Inferior Vena Cava Filters

Inferior vena cava (IVC) filters have been used as prophylaxis in certain high-risk patients without VTE who are unable to receive pharmacologic prophylaxis. The strongest data for this indication come from the trauma literature [32]. EAST offers a level III recommendation (based on retrospective data and/or expert opinion) that a prophylactic IVC filter may be considered in very high-risk trauma patients who are unable to receive pharmacologic VTE prophylaxis. This recommendation may apply to patients with both increased bleeding risk and an injury pattern rendering them immobile for a prolonged period such as severe closed head injury (Glasgow Coma Scale <8), incomplete spinal cord injury with paraplegia or quadriplegia, complex pelvic fracture with associated long bone fracture, or multiple long bone fractures [26]. ACCP recommends against the use of prophylactic IVC filters for primary prevention of VTE [25]. Prophylactic IVC filters are associated with higher mortality and higher risk of DVT in patients undergoing bariatric surgery [33]. IVC filters may be easily placed at bedside in the ICU using portable fluoroscopy and/or intravascular ultrasound techniques. Many IVC filters are retrievable and should be removed as soon as the patient's acute risk of VTE decreases. However, filter endothelialization may occur as soon as 3 weeks after placement, and many patients do not return for IVC filter removal, rendering the device effectively permanent.

Prescription and Administration Compliance

Despite evidence-based guidelines, many ICU patients are not prescribed and/or administered VTE prophylaxis. Current efforts focus on ensuring that healthcare providers prescribe optimal prophylaxis and nurses administer all prescribed doses. Even missing one dose of VTE prophylaxis is associated with VTE events [34]. One study recently showed that only 42 % of patients diagnosed with DVT during a hospitalization had received VTE prophylaxis [7]. It is important to note that not all VTE is preventable. Even when patients are appropriately prescribed and administered all doses of VTE prophylaxis, VTE may still occur [35]. One approach to improve documentation of VTE risk status and compliance with evidence-based guidelines is to utilize a mandatory computerized clinical decision support tool within the institution's provider order entry system. This approach has demonstrated dramatic improvements in prescription of risk-appropriate VTE prophylaxis for medical and surgical patients [19, 36].

Diagnosis

Signs and symptoms of VTE are nonspecific and may include findings common among critically ill patients including tachycardia, hypoxia, and fever. Furthermore, physical exam and history are not useful to rule out a diagnosis of VTE in the ICU because most critically ill patients with VTE are "clinically silent" and not detected by history or physical examination techniques [11].

DVT may cause local symptoms secondary to partial or complete occlusion of venous outflow including pain, edema, discoloration, or erythema of the affected area. PE may manifest with symptoms of dyspnea, tachypnea, substernal chest pain, diaphoresis, hemoptysis, tachycardia, agitation, hypotension, syncope, and/or cardiac arrest. Pleuritic chest pain is characteristic of smaller emboli, which travel more distally to cause pleurisy. Large, proximal emboli do not generally cause pleuritic chest pain. Other signs may include narrowed pulse pressure, jugular venous distension, acute pulmonary hypertension, or electrocardiographic evidence of acute right ventricle strain. A new right bundle branch block or an S1Q3T3 pattern on electrocardiogram may be indicative of PE, but the most common finding on electrocardiogram is sinus tachycardia. Any patient with clinical suspicion for VTE requires further workup to establish or rule out this life-threatening diagnosis.

Duplex Ultrasonography

DVT was historically diagnosed with invasive contrast venography, but in current practice, DVT is almost exclusively diagnosed with noninvasive duplex ultrasonography. DVT may be noted on contrast-enhanced CT scan or magnetic resonance imaging (MRI), but these tests are not frequently specifically used to diagnose DVT. Duplex ultrasonography makes use of B-mode imaging, color Doppler, and pulsed Doppler spectral analysis [37]. Acute and chronic DVT are easily distinguished utilizing duplex ultrasonography. Acute DVT demonstrates a noncompressible vein with hypoechoic thrombus, spongy texture, and increased vein diameter due to acute venous hypertension. Flow may be present around the acute thrombus, suggesting

incomplete attachment and possibility for embolization. Chronic DVT is hyperechoic, firmly attached to the vein wall, and often associated with valvular reflex. The vein remains noncompressible or partially compressible with chronic DVT. Complete duplex examination for lower extremity DVT involves the superficial and deep veins of both lower extremities.

Computed Tomography Angiography

Invasive pulmonary angiography via right heart catheterization was historically employed to diagnose PE. This invasive and costly procedure has been replaced with contrast-enhanced computed tomography (CT) angiography for the diagnosis of PE. Current multidetector helical CT angiography allows highly accurate diagnosis of PE [38]. Furthermore, improvements in imaging modalities allow visualization of segmental and subsegmental pulmonary arteries, although the clinical importance of treating peripheral pulmonary emboli is not certain. CT angiography may also identify radiologic parameters of interest. For example, increased right ventricular/left ventricular diameter ratio on transverse CT images may predict PE-related mortality [39].

Echocardiography

Severity of PE may be evaluated with transthoracic or transesophageal echocardiography. Echocardiography may also be appropriate for evaluating patients with suspected PE who are too unstable for transport to radiology for diagnosis by CT. Transthoracic echocardiography is noninvasive and easily applied at the bedside in the ICU, even in urgent settings with hemodynamically unstable patients. While the left main pulmonary artery is often obscured by the air-filled left main stem bronchus, Doppler techniques allow for estimation of pulmonary artery systolic pressure. Other echocardiographic findings suggestive of pulmonary embolism include right ventricular dilatation, right atrial dilatation, displacement of the intraventricular septum into the left ventricular cavity during systole, and pulmonary artery dilatation. Although it may be difficult to distinguish acute from chronic pulmonary hypertension based on these findings, other evidence of chronic disease such as right ventricular hypertrophy or valvular disease may suggest other underlying etiologies or comorbid conditions. Transesophageal echocardiography may not be feasible in patients with acute hemodynamic collapse, but this technique is also useful and often allows direct visualization of intraluminal thrombotic material in the main pulmonary artery or at its bifurcation.

Other Diagnostic Modalities

Ventilation/perfusion scan (V/Q scan) is a nuclear medicine test sometimes used to diagnose PE in patients who are unable to undergo contrast-enhanced CT secondary to renal insufficiency or severe contrast allergy. D-dimer assay is commonly used in emergency department patients and outpatients to rule out VTE due to its high sensitivity. Fibrin D-dimer measures the final product of the plasmin-mediated degradation of fibrin and is often elevated in patients with acute VTE. However, D-dimer is also common in many other conditions associated with fibrin production including malignancy, trauma, infection, inflammation, and postoperative state. As such, D-dimer has poor specificity and has little predictive value for ICU patients [11, 40]. A negative D-dimer can help rule out the diagnosis, but a positive test is certainly not confirmatory for VTE. Both V/Q scan and D-dimer assay must be utilized in conjunction with a pretest probability assessment such as the Wells score or the Geneva score to be clinically useful.

Screening in Asymptomatic Patients

Screening of high-risk asymptomatic patients remains a point of controversy, and practices among surgeons may vary significantly [41]. ACCP does not recommend routine screening for DVT in critically ill patients [25]. EAST recognizes that some patients at high risk may benefit from routine screening for DVT [26]. However, the clinical importance of asymptomatic DVT detected by routine screening remains unclear. Supporters of routine screening see benefit in performing a relatively inexpensive and noninvasive test (duplex ultrasonography), in order to diagnose and treat asymptomatic DVT before it progresses to symptomatic or fatal PE. Others feel that increased medical testing, associated costs, and treatment of asymptomatic DVT (which may never have come to clinical attention otherwise) incur not only the risk associated with anticoagulation, but also unnecessary costs. Surveillance bias ("the more you look, the more you find") is a common concern when screening asymptomatic patients for VTE. Studies have clearly shown that increasing screening is associated with increasing rates of VTE [42–45]. While national and regional bodies recognize low incidence of VTE as a marker of quality, this is a biased measurement since hospitals that less commonly screen patients for VTE are going to identify fewer VTE events regardless of associated healthcare quality.

Treatment of DVT

The mainstay of treatment for DVT is systemic anticoagulation. Anticoagulation prevents worsening of acute symptoms and sequelae including recurrent DVT, PE, and post-thrombotic

syndromes. Most protocols recommend rapid initiation of either weight-based intravenous unfractionated heparin infusion (ideally with a loading bolus) or subcutaneous LMWH. Long-term anticoagulation can continue with either LMWH or warfarin. Duration of therapy ranges from 3 months to lifelong therapy based on individualized patient characteristics and risk factors. Provoked DVT, or those cases where a clear risk factor such as traumatic injury or major surgery is present, may only require 3 months of anticoagulation. Spontaneous DVT without a clear risk factor is usually treated for 3–6 months. Patients with recurrent VTE, or those with an ongoing hypercoagulable state such as known thrombophilia or malignancy, should probably continue anticoagulation indefinitely. Rarely, patients with distal DVT and no predisposing risk factors for VTE may be managed with compression stockings alone, although this is most appropriate for ambulatory outpatients, rather than the ICU population. Repeat duplex ultrasonography after 2 weeks should be performed to ensure resolution of the clot. Propagation of the clot to the level of the popliteal vein or more proximal warrants transition to anticoagulation.

Thrombolysis or thrombectomy has been proposed for certain subsets of patients at low operative risk with proximal iliofemoral or femoral DVT, especially among young patients at high risk for post-thrombotic syndrome. A large, ongoing, multicenter, prospective randomized controlled trial (the ATTRACT study) should help resolve the question of whether pharmacomechanical catheter-directed thrombolysis benefits patients with large DVT [46]. Patients with a threatened limb from phlegmasia cerulea dolens or phlegmasia alba dolens should undergo thrombolysis or thrombectomy for the purpose of limb salvage. In patients with DVT and absolute contraindication to anticoagulation or in patients with recurrent DVT on adequate anticoagulation, IVC filter placement is indicated.

Treatment of PE

Treatment of PE in the hemodynamically stable patient begins with initiation of either weight-based intravenous unfractionated heparin infusion (ideally with loading bolus) or subcutaneous LMWH. However, standard VTE treatment with anticoagulation alone is not adequate for many patients with massive and submassive PE. In the setting of hemodynamic instability and/or right ventricular dysfunction, other aggressive and invasive therapies may be indicated. Systemic thrombolytic therapy such as intravenous alteplase or catheter-directed thrombolysis or embolectomy may be warranted. In patients with contraindications to anticoagulation such as intracranial hemorrhage or active bleeding, surgical embolectomy and/or IVC filter may be necessary. In some cases, particularly those with acute cardiorespiratory failure secondary to PE, extracorporeal membrane oxygenation (ECMO) has been suggested [47]. Similar to long-term treatment for DVT, provoked PE is often treated with anticoagulation for 3 months, spontaneous PE is frequently treated for 3–6 months, and patients with ongoing risk factors are most often treated indefinitely.

Impact

Prevention of VTE remains one of the most important patient safety practices in hospitalized patients, in particular for those in the ICU. However, even when patients are prescribed and administered VTE prophylaxis according to best practice guidelines, VTE may still not be preventable in as many as 50 % of cases [35]. National bodies including the Centers for Medicare and Medicaid Services and regional entities impose financial penalties when hospitalized patients develop VTE. Policy changes at the regional and national level should focus on a more impactful approach. Rather than measuring incidence of VTE alone, some experts argue for a pure process measure approach or combined process and outcome measure instead [43, 48, 49]. A true benchmark of patient safety and quality care should measure how frequently patients are prescribed and administered VTE prophylaxis according to best practice guidelines.

Conclusion

VTE is common among surgical patients with critical illness and represents a major source of morbidity and mortality. All ICU patients without contraindications require risk-appropriate VTE prophylaxis because *all* ICU patients are at risk for VTE. It is important to recognize risk factors, provide effective prophylaxis, and provide timely and accurate diagnosis and treatment for patients with VTE in the ICU.

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Glycemic Control and Insulin Resistance

29

Richard N. Lesperance and Oscar D. Guillamondegui

Type 2 diabetes has become an epidemic in the developed world. The US Centers for Disease Control and Prevention estimates that 29 million (9.3 %) US residents have diabetes. Up to 37 % of the US population (80 million) are pre-diabetics as measured by elevated hemoglobin A1C levels [1]. These pre-diabetics demonstrate increased peripheral insulin resistance and pancreatic β(beta)-cell dysfunction and are at increased risk for renal and vascular complications [2]. Additionally, patients without diagnosed diabetes may frequently experience hyperglycemia during critical illness. In epidemiological studies, 75 % of adult ICU patients demonstrated either hyperglycemia or insulin resistance [3]. Cytokines and other soluble inflammatory modulators cause decreased glycolysis and increased peripheral insulin resistance in critically ill patients [4]. Stress hormones such as catecholamines and glucocorticoids are increased during critical illness, or frequently administered exogenously, and promote hyperglycemia [5] (Fig. 29.1.) Additionally, glucose is a common component of IV infusions in the ICU and a major component of total parenteral nutrition, thus promoting hyperglycemia.

Acute hyperglycemia is common in critically ill patients admitted to the intensive care unit (ICU). Previously, hyperglycemia was thought to be an expected response to critical illness and not aggressively treated until glucose levels exceeded 200 mg/dl [6, 7]. However, over the last decade, hyperglycemia has been increasingly correlated with worse outcomes in a wide variety of critically ill patients, including those with myocardial infarctions [8], after non-cardiac surgery [9], and in the trauma population [10]. Elevated blood glucose has been shown to elevate the risk of surgical site infections and prolong hospital stays in postoperative patients [9, 11], presumably due to interference with normal neutrophil function [12–14]. The apparent deleterious effect of hyperglycemia in diverse ICU patients led to interest in strictly controlling serum glucose levels and the landmark randomized controlled trial (RCT) from the Leuven group in Belgium [15].

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Overview of Evidence Supporting Strict Glucose Control in the ICU

In 2001, researchers from the University of Leuven published the results of their RCT [15] comparing strict glucose control (80–110 mg/dl) to their conventional standard of care (180–200 mg/dl), in a primarily surgical ICU with a large proportion of cardiac surgery patients. Their study was prematurely halted after the planned interim analysis when the strict glucose control group demonstrated superior outcomes. The overall randomization of approximately 1500 patients demonstrated that the strict control group almost universally required insulin infusion to maintain euglycemic control, while in the conventional group, only 39 % required intravenous insulin infusion to meet glucose targets.

The improvements in the strict glucose control group were notable: a reported 42 % relative risk reduction for ICU mortality (4.6 % vs. 8 %) as well as a decrease in overall in-hospital mortality (7.2 % vs. 10.9 %) favoring intensive glucose control. Despite the overall cohort being heavily weighted toward cardiac surgery patients, the majority of mortality benefit occurred in patients remaining in the ICU for greater than 5 days. This group was heavily weighted to non-cardiac admissions. The mortality in this group was 10.6 % for the strict control group, as opposed to 20.2 % for the conventional arm. They also reported significant improvements in other aspects of intensive care management including rates of septicemia, time on ventilator support, and need for renal replacement therapy.

However, when the Leuven group used a similar protocol in a medical ICU [16], they found no improvement to overall mortality. Interestingly, when they looked at a (predefined) subgroup of patients staying in the ICU for 3 or more days,

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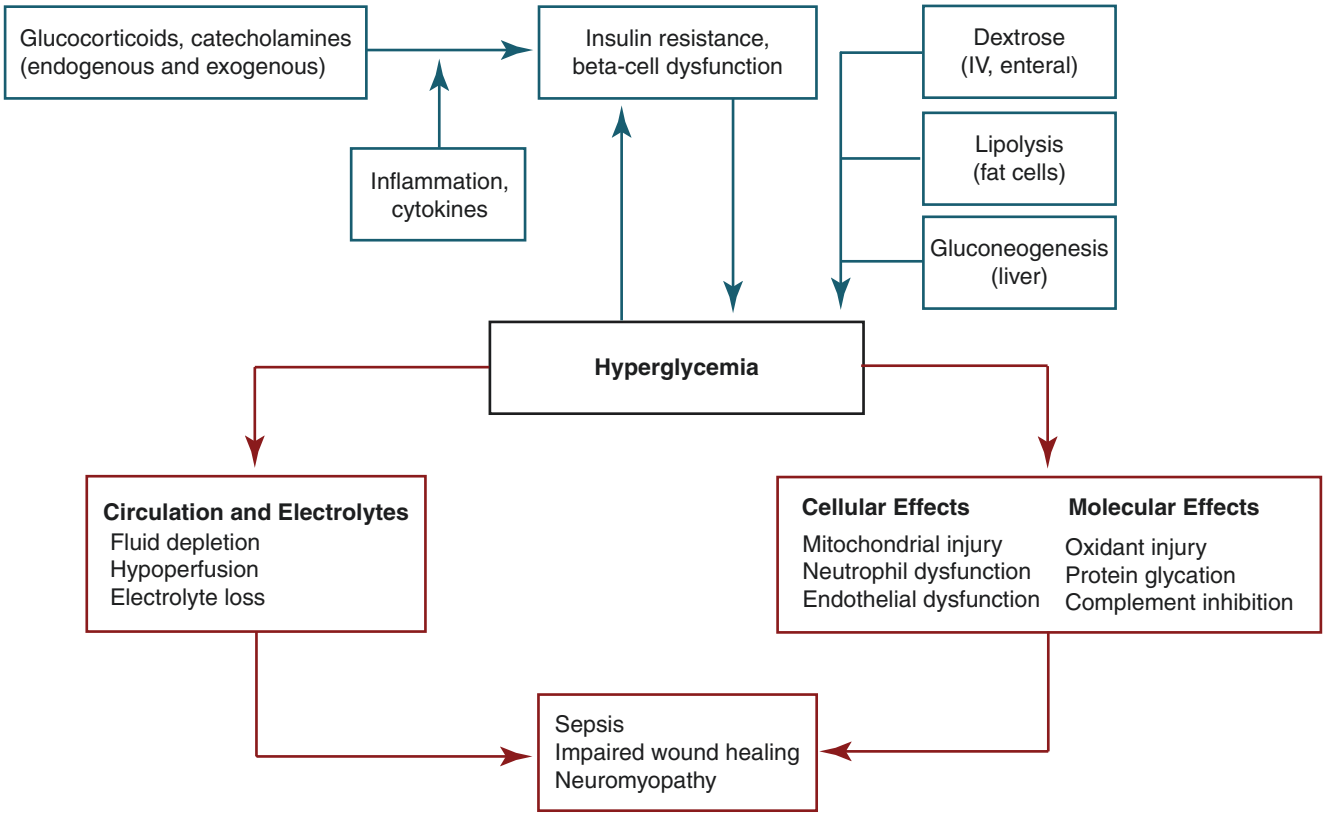

Fig. 29.1 Causes and effects of stress hyperglycemia (From Kavanagh and McCowen [73]. Copyright ©2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

there appeared to be a survival advantage (43 % vs. 52.5 %). This benefit, however, was offset by increased mortality among patients staying in the ICU for fewer than 3 days, a finding the authors could not explain in their study. Regardless of the lack of overall mortality benefit, patients receiving strict glucose control did show an improvement in the number of ventilator days, need for renal replacement therapy, and ICU length of stay.

Unfortunately, since the publication of those two single-center studies, multiple other investigators have been unable to replicate those benefits in larger multi-center trials, several of which are recounted here. The studies are summarized in Table 29.1.

The VISEP trial [17] was conducted among 18 academic centers in Germany. It examined both the use of intensive glucose control and pentastarch resuscitation, among patients presenting with sepsis and septic shock. The study was halted early, at the first planned safety analysis, due to an increased rate of hypoglycemic events (glucose ≤40 mg/dl) among patients randomized to intensive glucose control (17 % vs. 4.1 %.) Although the authors were unable to identify any of the hypoglycemic events as having directly caused death or disability, regression analysis did identify hypoglycemia as an independent risk factor for death by any cause. They did not find any mortality benefit to intensive glucose control, and they were unable to demonstrate improvements in ventilator time, ICU length of stay, or need for renal replacement therapy. The trial also elicited more "severe adverse events" in the strict glucose control group.

The Glucontrol trial [18] was another large multi-center randomized trial conducted mainly in European mixed medical/surgical ICUs. They compared strict glucose control (80–110 mg/dl) to a control group with a slightly tighter standard (140–180 mg/dl) than that utilized in the original Leuven studies. This study was also halted early, unfortunately, due to the high rate of "protocol violations" for glucose control. For example, only 39 % of the recorded blood glucose values were actually in the target range for the strict control group. Since these investigators analyzed all of their recorded glucose values, as opposed to the Leuven trials [15, 16] (which only analyzed the admission and morning values), no direct comparison of their accuracy compared to Leuven can be made.

Despite halting their trial early, Glucontrol did accrue over 500 patients per group. When they analyzed their data, they found no benefit of strict glucose control on mortality, organ failure, ventilator days or ICU duration. There was no distinguishable benefit noted with the patient subsets within or outside the determined glucose targets.

Table 29.1 Comparison of major randomized controlled trials of intensive glucose control

Study	Population	Intensive group	Control group	Hypoglycemia rates	Results
Leuven 2001 [15]	Single-center surgical ICU, 1500 patients	80–110	180—200	5.1 % vs. 0.8 %	Mortality benefit 4.6 % vs. 8 %, also better septicemia, ventilator LOS, and need for RRT
Leuven 2006 [16]	Single-center medical ICU, 1200 patients	80–110	180–200	18.7 % vs. 3.1 %	No mortality benefit, better ventilator LOS, and need for RRT
Glucontrol [18]	21 academic medical/surgical ICUs, 1100 patients	80–110	140–180	8.7 % vs. 2.7 %	Study halted early due to protocol violations. No mortality benefits
VISEP [17]	18 academic medical/surgical ICUs, 537 patients with sepsis or septic shock	80–110	180–200	17 % vs. 4 %	Trial halted early for increased rate of SAEs (11 % vs. 5 %) in intensive group
NICE-SUGAR [19]	42 medical/surgical ICUs, 6100 patients	81–108	144–180	6.8 % vs. 0.5 %	Increased mortality for intensive glucose control, 27.5 % vs. 24.9 %

ICU intensive care unit, *LOS* length of stay, *RRT* renal replacement therapy, *SAE* serious adverse event

The final large, multinational randomized trial was NICE-SUGAR [19], involving over 6,000 patients in mixed medical-surgical ICUs in Australia, New Zealand, and Canada. Patients were randomized to strict control of 81–108 mg/dl or a conventional group with targets between 144 and 180 mg/dl. Their primary outcome was a 90-day mortality. These investigators were able to define a mortality difference but, contrary to the Leuven trials, one that favored the conventional group. Patients receiving intensive glucose control had a 27.5 % 90-day mortality, as opposed to 24.9 % in the conventional group. Despite this study being conducted in mixed ICUs, when the results were analyzed by predefined subgroups, surgical patients benefited the most from looser blood glucose targets with a 31 % improvement in survival (odds ratio of 1.31).

To try and resolve these discrepant results, two large meta-analyses were performed including several smaller randomized studies in different environments. The first meta-analysis [20] did not include the data from the ongoing NICE-SUGAR study. The pooled results showed no mortality benefit to intensive glucose control and no improvement in organ failure, although there was a decreased risk of septicemia. The second meta-analysis included NICE-SUGAR data, as well as slightly different inclusion criteria for other studies, resulting in approximately 13,000 included patients [21]. They also found no overall benefit to mortality for the strict control group. In contradiction to the previous meta-analysis, this study showed the only group identified to receive a survival benefit to strict glucose control was those patients managed in surgical ICUs (odds ratio of 0.63 favoring intensive control, 95 % CI 0.44–0.91.) Both analyses identified a higher incidence of hypoglycemic events in patients receiving intensive glucose control.

Resolving the Differences Between Studies of Intensive Glucose Control

There have been several theories advanced to explain the discrepant results between the Leuven studies and subsequent studies. The initial Leuven study [15] had a much higher rate of IV glucose administration (200–300 g/day) than the Glucontrol, VISEP, and NICE-SUGAR studies provided.

A second theory is that the control group of the subsequent studies targeted a more physiologically appropriate blood glucose range (140–180 mg/dl) than the liberally set range of the initial Leuven study (which allowed patients to reach 215 mg/dl before starting therapy). The true benefit of the subsequent studies may not be the achievement of an artificial "normoglycemia" but simply the avoidance of excessive (>180 mg/dl) hyperglycemia. The exception to the lower conventional target range was the VISEP study, which used a range of 180–200 mg/dl, but since that study was halted early, it may have been underpowered to detect a difference.

Another possibility is a higher than expected mortality rate among patients in the initial Leuven study. The mean APACHE II score for both the intensive and conventional control groups was 9. For postoperative patients, this should yield an in-hospital mortality of 3.9 % [22], yet the (hospital) mortality in the two groups was 7.2 and 10.9 %. There are criticisms about the use of APACHE II, however, in comparing mortality estimates between different facilities, the APACHE II system was originally derived using a North American population [23], and this may be less reflective of the European cohort of critically ill patients. This may be related to patient selection bias. Additionally, entering data for the calculation of APACHE II scores is heavily dependent on medical staff training [24], and this may be affected by systematic differences in North American and European healthcare delivery systems. One similarity among all the

studies referenced above was the consistency of hypoglycemia identified within the strict glucose control group. Universally, the rate of hypoglycemia was higher than the conventional/liberal glucose control groups. In the initial Leuven trial, the strict glucose control group had a 5.1 % rate of hypoglycemia. In the subsequent trials, the rate varied from 6.8 to 19 % [4, 16–19]. As described below, hypoglycemia in the ICU is frequently correlated with mortality.

A final potential difference between the Leuven results and those achieved by subsequent investigators is the accuracy of the blood glucose measurements. Inaccurate measurements of blood glucose might result in higher rates of actual (if not measured) hypoglycemia (see the section on Glucose Measurement in the ICU, below). In the initial Leuven study, only arterial blood samples were used and were assayed on blood gas analyzers. In both the second Leuven trial and the subsequent larger RCTs described above, a convenience mix of blood gas analyzers and point-of-care finger stick monitors were used for the measurements of samples of both arterial and capillary origin.

The Role of Hypoglycemia and Glucose Variability in ICU Mortality

As stated above, a consistent finding in studies of intensive glucose control is an increased rate of hypoglycemia among patients targeted for tighter control. Hypoglycemia was not felt to contribute to mortality by the authors of the original Leuven study [15]. Since then, there have been increasing concerns that the impact of hypoglycemia reduces or eliminates any benefit obtained from intensive glucose control.

The neuroglycopenic effects of hypoglycemia are well known [25]. Severe hypoglycemia causes brain neuronal death in a pattern distinct from cerebral ischemia [26] and appears to worsen after reperfusion with glucose [27]. Even in the absence of overt hypoglycemia, patients with traumatic brain injury who undergo intensive glucose control have decreased brain glucose measured by microdialysis, accompanied by increased markers of cellular distress [28].

Hypoglycemia also interferes with adrenocortical responsiveness to ACTH during stress states [29, 30], which could presumably interfere with response to septic insults. Additionally, episodes of hypoglycemia decrease the adrenergic responsiveness to subsequent hypoglycemic insults. This progressive effect could interfere both with attempts to return to normoglycemia and also with response to sepsis, by decreasing endogenous catecholamine and corticosteroid response [31, 32].

Hypoglycemia may cause harmful cardiovascular effects through several mechanisms. Overnight asymptomatic hypoglycemia in diabetics has been associated with prolongation of the QTc interval and other conduction abnormalities and arrhythmias [33, 34]. Hypoglycemia causes an overall pro-inflammatory and pro-thrombotic state [35, 36]. Some of the mechanisms involved in cardiovascular risk may be from induction of platelet aggregation [37], and endothelial dysfunction and mitochondrial oxidative stress from interference with nitric oxide signaling [38, 39].

The first Leuven study [15] found increased rates of hypoglycemia in the intensive control group, but the authors felt there was no harm from these episodes. The subsequent studies, however, have correlated hypoglycemic events with an increased risk of mortality, even after correcting for disease severity [40, 41]. This suggests that hypoglycemia is not simply a marker of a sicker patient. Even relatively mild hypoglycemia (72–81 mg/dl) in ICU patients has been independently associated with death from cardiovascular or septic causes [42].

Aside from hypoglycemia, blood glucose variability is becoming increasingly appreciated as a marker of mortality. Most major studies of intensive glucose control evaluate their impact by looking at the mean serum glucose values, but this may obscure time spent hyper- or hypoglycemic [4] (see Fig. 29.2.) Standard deviation (SD) is used to express variability about a mean value in statistics. Several investigations have correlated higher SD in blood glucose values with ICU mortality, including patients who had “normal” mean glucose values [43, 44]. The standard deviation, however, does not discriminate between gentle changes in glucose levels over time, as opposed to vigorous fluctuations of hyper- and hypoglycemic states. Other investigators have used different measures of variability to account for this and found that they correlate better with mortality [45, 46]. It remains to be seen whether glucose flux is a possible target for intervention or simply another marker of underlying illness severity. Conversely, it is possible that lower glucose variability simply reflects more attentive medical and nursing care, and mortality benefits accrue from this “nursing Hawthorne effect” [47].

What Is the Appropriate Target for Glucose Control?

It is clear that the ICU practitioner must make every effort to avoid hypoglycemia, whether due to disease process or iatrogenic. The question of what blood glucose level to target however remains difficult, given the harmful effects of uncontrolled hyperglycemia. While it is obvious that blood glucose levels <81 mg/dl have been associated with poor outcomes, it is not certain at which level hyperglycemia becomes detrimental. Certainly, as outlined earlier, levels >200 mg/dl should be avoided. The results of the NICE-SUGAR study suggested that patients allowed to remain slightly hyperglycemic (144–180 mg/dl) had better out-

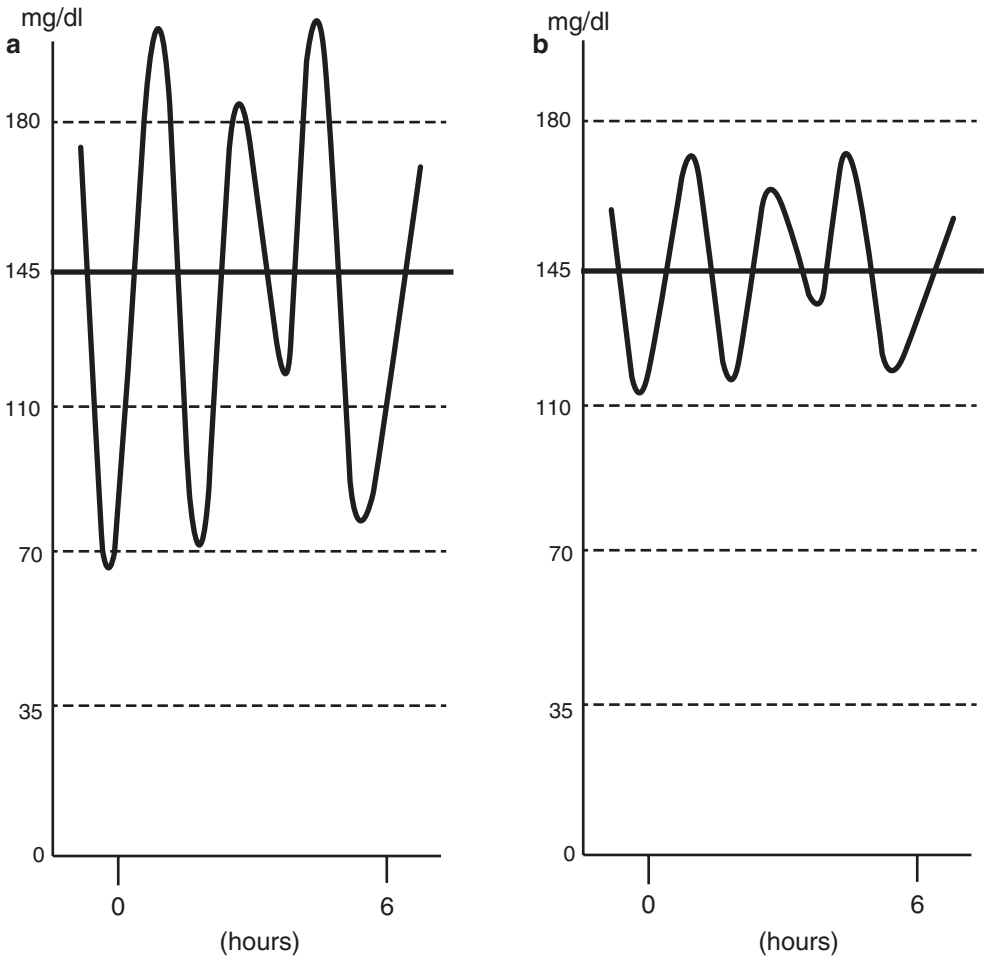

Fig. 29.2 Graphic representation of glucose variability. Both graphs represent patients with the same mean serum glucose values (*thick horizontal line*), but graph A represents higher variability with hypoglycemic episodes, despite a normal mean glucose (**a**) high variability (**b**) low variability (Modified with permission from the American College of Chest Physicians. Egi et al. [4])

Table 29.2 Current specialty society recommendations for blood glucose targets in ICU patients

Organization	Recommendation
Society of Critical Care Medicine [50]	<150 mg/dl, absolutely <180 mg/dl
Surviving Sepsis Campaign 2012 [70]	<180 mg/dl
American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement [71]	140–180 mg/dl
American College of Physicians [72]	140–200 mg/dl

comes than those who were artificially normalized. A recent Australian observational study [48] found that septic patients who developed mild hyperglycemia (155 mg/dl) actually had better outcomes than those who remained normoglycemic, suggesting that there may be some benefit to mild hyperglycemia. Acute mild hyperglycemia may indeed be an adaptive survival response [49] and only harmful when excessive or prolonged, much like tachycardia.

Multiple guidelines from specialist societies no longer advocate strict glycemic control. Most recommend a target range of 140–180 mg/dl (Table 29.2). The paradigm of glucose control has not quite turned full circle to allowing florid hyperglycemia, but certainly artificial strict "normalization" is no longer suggested practice.

Glucose Measurement in the ICU

An obvious problem with hyper- or (hypo)glycemia is that accurate treatment is impossible without precise measurement. Point of care (POC) glucometers are widely used for rapid bedside glucose determinations in ICU patients, but persistent concerns remain about their accuracy in critically ill patients [50]. They were designed to be used in an outpatient setting in noncritically ill patients. Samples analyzed by POC meters can be affected by anemia, elevated pO^2, or edema fluid [51]. Regulatory standards allow POC glucometers up to a 20 % error [50]; but in ICU patients, this is well within the range of the relatively mild (75 mg/dl) hypoglycemia that has been associated with adverse outcomes and

death. Several studies of POC glucometers used for bedside measurement and titration of insulin infusions have found that while most measurements will adequately correlate, a significant number will deviate from values obtained by central laboratory analysis [52]. Variability among values obtained from arterial and capillary samples, and those obtained from central lab-measured samples, is frequently large enough to change insulin infusion rates [53].

The source of the samples is just as important. Samples drawn from central venous catheters can be contaminated with glucose-containing infusions, or diluted by infusions without, even if infusions are temporarily paused or running in adjacent lumens of multi-lumen catheters. Laboratory managers have identified wide variances in repeat samples sent within 15 min from the same patient, suggesting a recognized error in sample handling by bedside personnel [54]. Capillary (finger stick) samples should be avoided if at all possible, since they have regularly been found to not correlate well with central samples in critically ill patients demonstrating shock or systemic edema [55, 56].

Recent Technological Developments

If episodic hypoglycemia or excessive glucose variability contributed to the increased mortality seen in studies such as NICE-SUGAR, then more accurate methods of measuring glucose and delivering insulin (or avoiding hypoglycemia) might conceivably deliver the promised benefits of tighter glucose control.

Significant physiologic response to insulin can occur in 10–15 min, but in most insulin infusion protocols, serum glucose is checked hourly. Measuring glucose more frequently might improve the accuracy of insulin infusions and possibly detect otherwise missed hypoglycemic episodes but would impose a heavy workload burden on busy bedside nurses. Continuous glucose monitoring (CGM) refers to a set of technologies that may allow more frequent or even real-time measurement of glucose [57, 58]. These technologies range from microdialysis membranes implanted in central venous catheters to devices implanted in the subcutaneous tissue utilizing RFID tags for wireless communication [59, 60]. Visual or audible alarms could alert bedside personnel to glucose readings outside of pre-set parameters. The expense of testing and adopting new systems may be offset to some extent by decreasing nursing workload in the ICU [61].

Computerized decision support systems (CDSSs) are computer-based advisers for dosing insulin infusions and have the potential to decrease variability in insulin dosing. Computerized protocols may allow "tighter" control of blood sugar with a lower incidence of hypoglycemic events, as compared to written protocols [62]. CDSS have been shown in prospective studies to increase compliance with strict glucose control targets while decreasing rates of hypoglycemia and glucose variability [63, 64].

There are multiple algorithms available which, when compared against hypothetical patients, vary widely in their prescribed insulin doses [65, 66]. Different algorithms may be appropriate for different categories of patients or clinical settings [60]. This may be the reason a recent large multicenter RCT using CDSS to achieve tight glucose control was (once again) unable to find a benefit [67].

Bringing together both CGM and CDSS is the concept of a "closed-loop" glycemic control system, also referred to as an "artificial pancreas." The processes of glucose monitoring, calculation of insulin infusion and administration, are automated without human input. Such "artificial pancreas" systems have been used in Japan for over 20 years for perioperative glucose control [68] but have not yet found widespread acceptance in ICUs elsewhere nor have they been tested against other systems in large-scale studies for safety, efficacy, or cost-effectiveness. Nonetheless, they offer the tantalizing prospect of delivering the benefits of strict glucose control without hypoglycemia while simultaneously reducing nursing workloads [57, 69].

Conclusion

Hyperglycemia is common in ICU patients with or without a history of diabetes and until 2001 not aggressively treated in most ICUs. Despite the widespread adoption of strict glucose control protocols due to the Leuven studies, subsequent studies failed to replicate their improved outcomes. Concerns persist that higher rates of hypoglycemia with strict glucose control may be the reason for lack of benefit and the higher mortality seen in the NICE-SUGAR trial. Most recommendations from critical care and endocrine specialty societies suggest glucose targets for ICU patients in the range of 140–180 mg/dl [50, 70–72], although the results of one meta-analysis suggest there may be a benefit to stricter control in surgical ICU patients [21]. Validated protocols should be used to dose continuous insulin infusions used in ICUs, and POC glucometers should be used cautiously in critically ill patients. The development of continuous glucose monitoring and closed-loop insulin delivery systems may reduce ICU nurse workload and reduce hypoglycemic events while still delivering tight glucose control.

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Critical Illness-Related Corticosteroid Insufficiency in the Intensive Care Patient

30

Noelle N. Saillant and Carrie Sims

Introduction

The ability of the human body to mount a hormonal response to severe physiologic stress is a critical adaptation needed to maintain homeostasis in the face of life-threatening illness. The so-called "fight or flight" response is primarily achieved via the hypothalamic-pituitary (HPA) axis and results in increased cortisol production. Cortisol enables alternative energy resources to be utilized rapidly, dampens the inflammatory response, and sustains hemodynamic stability through fluid retention and enhanced catecholamine sensitivity [1]. Although essential for survival in the acute phase, the HPA axis may become dysfunctional and maladaptive during prolonged phases of critical illness. Historically, the terms "absolute adrenal insufficiency" or "relative adrenal insufficiency" were used to describe the phenomenon of HPA axis dysfunction during critical illness. The use of these labels, however, has been discouraged by consensus opinion [2] in favor of the term critical illness-related corticosteroid insufficiency (CIRCI).

CIRCI is defined as a complex, proinflammatory state manifesting as "inadequate cellular corticosteroid activity" for the demand of the physiologic stress suffered by the patient [2]. The typical constellation of features includes a low ACTH value [3], an elevated plasma cortisol level, and resistance to corticosteroids at the tissue level [4–6]. Dysfunction may occur at any point in the HPA axis and results in inadequate cortisol production and/or diminished sensitivity to the corticosteroid hormones.

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Physiology of the HPA Axis

Corticosteroid secretion begins with the paraventricular nuclei (PVN) of the hypothalamus. Stimulated by the circadian cycle of the superchiasmatic nucleus (SCN), or by a stress signal, the PVN releases corticotropin-releasing hormone (CRH) and arginine vasopressin. CRH stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) that in turn stimulates the adrenal gland to secrete cortisol. Secreted cortisol can either bind to circulating proteins and thus remain inactive or may exist as a "free" hormone capable of binding to intracellular tissue glucocorticoid (GR) and mineralocorticoid receptors (MR). In the healthy state, the release of glucocorticoid has a circadian pattern based on ACTH secretion, with an early morning peak superimposed on basal secretion with smaller fluctuations throughout the day.

In response to acute stress, the HPA axis can be modulated to increase or decrease glucocorticoid production. For example, catecholamines enhance the HPA response to stress by stimulating CRH secretion. In turn, the release of CRH augments the release of norepinephrine. Free cortisol, on the other hand, downregulates the HPA axis and serves as a negative feedback to modulate its own release [1]. This tightly controlled system sensitively responds to external and internal stimuli (see Fig. 30.1).

The Systemic Effects of Cortisol

Cortisol is a glucocorticoid hormone that directly influences endocrine, metabolic, and immunologic functions. As part of the "fight of flight" response, cortisol enhances the availability of energetic substrates by antagonizing the effects of insulin. Decreased insulin sensitivity not only directly affects glucose utilization at the tissue level, but also promotes hyperglycemia by enhancing gluconeogenesis and glycogenolysis. Cortisol also modulates the immune response to physiologic stress. Glucocorticoid secretion dampens cell-mediated immunity, as

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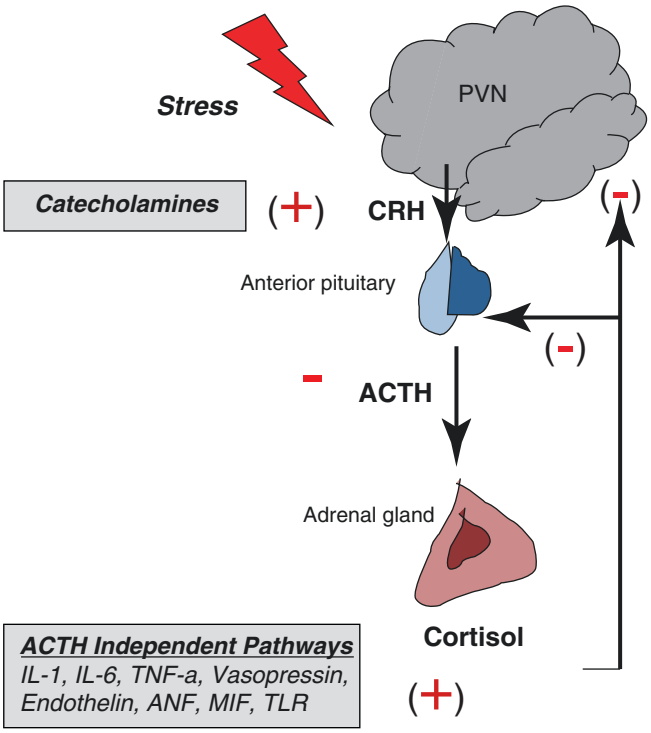

Fig. 30.1 The hypothalamic-pituitary axis (HPA axis). Stress signals the paraventricular nucleus (PVN) of the hypothalamus to produce and release the corticotropin-releasing hormone (CRH). CRH stimulates the anterior pituitary to release the adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal glands to produce and release the stress hormone cortisol. Cortisol then provides negative feedback to diminish the release of CRH and ACTH. Catecholamines are an alternative stimulus for CRH production. IL-1, IL-6, TNF-α, vasopressin, endothelin, ANF, MIF, and TLR may trigger ACTH release that is independent of hypothalamic control

well as decreases cytokine and histamine responsiveness. This immunologic downregulation prevents the proinflammatory reaction to sepsis or injury from becoming over exuberant. However, states of prolonged glucocorticoid excess may lead to profound immunosuppression. Lastly, cortisol is essential for maintaining vascular tone and stability. As an important regulator of ion homeostasis, cortisol is necessary for sodium retention and potassium wasting. Cortisol also enhances vascular smooth muscle tone and reduces nitric oxide-mediated vasodilation. Without cortisol, patients experience severe sodium wasting, hypovolemia, and decreased vascular tone that rapidly leads to cardiovascular disease and death [7].

Cortisol Synthesis

The production of cortisol primarily occurs in the adrenal zona fasciculata via the steroidogenic conversion of cholesterol to pregnenolone to cortisol [5]. Because the body does not store cortisol, any augmentation in cortisol level must be coupled with increased steroidogenesis and de novo synthesis. Thus glucocorticoid levels follow real-time bodily demand.

Critical Illness

Severe stress triggers the PVN to augment ACTH secretion leading to the increased production and release of cortisol [1]. However, in prolonged critical illness, there appears to be a paradoxic "ACTH-cortisol dissociation." Specifically, overall free plasma cortisol levels tend to be several-fold higher in critically ill patients, while ACTH values are notably lower in healthy patients. Theoretically, elevated free cortisol levels could be attributed to three possible mechanisms: increased production, increased liberation of free hormone, or diminished breakdown.

Increased cortisol production through the traditionally described pathway is unlikely to account for the elevated cortisol levels observed. Given that this is not from ACTH stimulation, the increased cortisol levels observed are the result of activating ACTH-independent pathways. It has been postulated that cytokines (IL-1, Il-6, TNF α), arginine vasopressin, endothelin, and atrial natriuretic factor may be responsible for activating this alternative pathway activation during severe stress [8, 9]. A second interesting association has linked macrophage migration inhibitory factor (MIF) and Toll-like receptors (TLR) to this dysfunction of the HPA axis. This observation may account for the higher occurrence of CIRCI during sepsis over other forms of critical illness (see Fig. 30.1).

Increased liberation of free hormone is also responsible for the observed effects of illness on glucocorticoid pathways. The cortisol's effect on tissue function is dependent on its "physiologic availability," a property contingent on circulating protein levels. Over 90 % of secreted cortisol is physiologically "inactive" because it is bound to corticosteroid-binding globulin (CBG) and albumin. CBG is best described as a high-affinity low-capacity binding protein. As CBG saturates, the role of albumin as a carrier becomes increasingly important. During states of illness, there may be a 50 % reduction in both CBG and albumin leading to altered free hormone concentrations, with clinical significance noted when albumin levels are less than 2.5 g/dL [10].

The most significant mechanism for the elevated glucocorticoid levels in critical illness, however, appears to be diminished cortisol breakdown. In a study of 158 ICU patients versus age-matched controls, Boonen et al. demonstrated that the half-life of cortisol was five times longer in the setting of critical illness. This decreased cortisol clearance appears to be the result of impaired cortisol reductase activity in the liver and adipose tissue and diminished expression of cortisol-metabolizing hormones [11, 12]. It has been hypothesized that the reduced clearance of stress hormone in times of illness may be energetically beneficial; that is, high cortisol levels are maintained while the energetic expenditure required to synthesize new hormone is minimized. This mechanism would also lead to increased negative feedback on the HPA axis and explain the decreased levels of ACTH in ICU patients.

Table 30.1 Medications that may affect the HPA axis [5, 9]

Effect on HPA axis	Medications
Binding proteins	Estrogen, OCPs
Interfere with glucocorticoid synthesis	Etomidate, ketoconazole, aminoglutethimide, metyrapone
Direct antiglucocorticoid activity	RU486
Mimic or cause glucocorticoid feedback and suppress HPA	Exogenous glucocorticoids, medroxyprogesterone, megestrol
Increase cortisol metabolism	Rifampin, phenytoin
Downregulate receptor	Antidepressants (clomipramine, amitriptyline, sertraline, paroxetine, and venlafaxine)

It is important, however, to realize that the increased level of plasma cortisol may not necessarily translate into enhanced target organ effects. Circulating levels of cortisol do not necessarily correlate with tissue concentrations. Furthermore, the regulation of tissue response can be modulated at the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) level [5, 13]. Animal and human models have shown evidence that the GR receptor is downregulated in protracted illness. Perhaps the best evidence is from ARDS patients showing markedly reduced nuclear density of the GR complex. This reduction in nuclear GR was observed in the setting of normal serum cortisol levels, thus supporting the concept that end-organ response to cortisol may be impaired despite adequate serum levels [13].

Aside from HPA dysfunction, a number of other factors may also contribute to insufficient adrenal function in states of severe illness. There is evidence that during prolonged illness the health of the adrenal gland is ultimately compromised in the ACTH depleted state. Autopsy findings of the adrenal gland of patients in the ICU for >7 days showed evidence of cholesterol depletion and loss architecture of the gland without the trophic stimulation of ACTH. This observation may have significant clinical implications during the protracted phases of critical illness [12].

Hemorrhage, trauma, primary or metastatic cancers, and infections can lead to adrenal insufficiency in the ICU patient through destruction of the adrenal or pituitary glands. Certain drugs commonly used in the ICU setting may also contribute to primary or secondary adrenal dysfunction; however this is beyond the scope of this chapter (see Table 30.1).

Diagnosing CIRCI

The underlying pathophysiology of CIRCI is a proinflammatory state. However the exact diagnostic criteria have yet to be defined. The best clinical indicator of potential CIRCI is the presence of severe hypotension refractory to vasopressor support and volume resuscitation. Patients with CIRCI are frequently hyperdynamic, with variable systemic vascular resistance depending on the underlying pathology (sepsis, cardiogenic shock).

Hypoglycemia and eosinophilia, however, are relatively common features; however hyponatremia and hyperkalemia are less prominent in CIRCI than in Addison's disease.

The use of serum cortisol levels and provocative testing to diagnose CIRCI is no longer recommended and represents a departure from the previous diagnostic recommendations [5, 14, 15].

Historically, three tests were used to diagnose adrenal dysfunction:

1. Random cortisol levels
2. ACTH provocative testing:
   (a) High-dose cosyntropin stimulation test
   (b) Low-dose cosyntropin stimulation test

Cortisol Levels

The use of random cortisol levels of <10 mg /dL had previously been granted a 2B recommendation [5]; however this is no longer advised by expert consensus [14, 15]. The retraction of the laboratory diagnostic criteria is due to several confounding factors in measuring cortisol for the diagnosis of CIRCI. For one, the *total* serum hormone is measured by the most available assays. Given that critical illness greatly alters the amount of *free* hormone due to reduced protein-binding capacity, the *total* hormone is a less useful measure of the adequacy of the patient's stress function. To minimize this limitation, some authors have suggested *free* cortisol levels and salivary cortisol levels be measured, thus representing a more accurate assessment of hormone levels in hypoproteinemic patients. To date there is insufficient evidence to fully support the use of free or salivary cortisol levels due to the lack of widespread availability and reproducibility of the tests [16, 17]. It is also important to account for the significant variation in the production of cortisol throughout an individual's circadian cycle. The timing of total, free, or salivary cortisol samples may lead to significantly different results in the same patient.

Secondly, the presence of antibodies and cortisol byproducts may interfere with the reliability of commercial cortisol levels [15]. An additional drawback to measuring cortisol levels is that the reproducibility of cortisol assays is unpredictable. The CORTICUS trial highlighted significant inter-assay variability with 27 % of patient samples changing class from hypofunctional to normal adrenal function depending on the location of where the specimen was tested [18, 19]. Lastly, it should be appreciated that the total serum cortisol level is not reflective of the tissue resistance to cortisol.

ACTH Stimulation Tests

ACTH provocative testing was also historically used to diagnose CIRCI.

High-dose ACTH testing was performed by administering cosyntropin (ACTH, 250 ug) and measuring the cortisol level 30–60 min later. A delta cortisol <9 after was considered diagnostic of relative adrenal insufficiency [20]. This method fell out of favor due to the concern that the supraphysiologic dose of 250 ug of cosyntropin could potentially mask ACTH resistance and thus an "appropriate" increase may not reliably reflect a clinical insufficiency. As such, a lower dose of cosyntropin (1ug) was suggested. This low stimulation test appeared to be more sensitive in identifying patients with suspected adrenal insufficiency [21, 22]. However, both provocative tests still fell prey to drawbacks of measuring cortisol levels detailed above.

Thus the adequacy of the patient's stress response cannot be accurately characterized with currently available diagnostics. Evidence to support the fact that laboratory testing is not predictive of treatment response is garnered from randomized trials showing response to steroid therapy is often independent of diagnostic testing [23, 24]. The differences in total and free cortisol levels and the confounders posed by hypoproteinemia and potential tissue resistance in combination with the poor reproducibility of cortisol levels make an absolute laboratory diagnosis nearly impossible. As such, clinical assessment of shock that is refractory to fluid and vasopressor support is the primary indication for therapy initiation (recommendation strength 2B [5, 14, 25, 26].

Evidence for Treatment

A number of studies have evaluated the role of steroid replacement in septic shock with varying results. Unfortunately, many of the inconsistencies in outcomes may be in part due to notable variations in study design with regard to:

1. The type of glucocorticoid administered and the use of additional mineralocorticoid replacement
2. The dosing of supplemental glucocorticoids – physiologic versus pharmacologic
3. The timing of enrollment, steroid initiation, and duration of treatment
4. Outcomes of interest – mortality, infection, and resolution of shock
5. Patient population treated – surgical versus medical, sepsis versus ARDS

Two landmark papers are critical to the discussion of treating CIRCI.

The first landmark paper from Annane et al. was a French randomized controlled trial demonstrating a 20 % mortality reduction in patients diagnosed with adrenal insufficiency compared to controls [20]. Patients with refractory septic shock of greater than an hour's duration were randomized to receive either placebo or a combination of glucocorticoid (hydrocortisone 50 mg q6hr) and mineralocorticoid replacement (fludrocortisone 50ug daily) for 7 days. Non-responders (defined as a delta cortisol of <9), who received supplemental steroids, showed a 20 % reduction in mortality when compared to those who received placebo [20]. This landmark greatly influenced clinical practice in favor of steroid therapy until the CORTICUS trial challenged its findings.

The CORTICUS trial represents the second notable study that questioned the use of glucocorticoids in sepsis [18]. This randomized, placebo-controlled multicenter European study failed to show a mortality benefit between treatment and control groups. A total of 499 patients underwent a cosyntropin stimulation test (250 mcg) and were randomized within 48 h to receive hydrocortisone (without additional mineralocorticoid) or placebo for 12 days [18]. In contrast to Annane's trial, the CORTICUS study found no statistically significant difference in 28-day all-cause mortality regardless of the patient's ACTH stimulation response (35 % versus 32 % mortality). Patients who received steroids, however, did display earlier resolution of shock and decreased need for vasopressors.

In evaluating the two trials, there are some important differences that deserve mention and may account for the differences in outcomes. First, the patient populations treated by the trials were heterogeneous. CORTICUS enrolled more surgical patients (65 %) as compared to the Annane study (40 %), and the enrollment period was more generous in the CORTICUS trial (72 h versus 8 h). Secondly, the treatment groups were managed with different steroid regimens and for different lengths of time. In the French study, fludrocortisone was given in addition to hydrocortisone for improved mineralocorticoid coverage versus hydrocortisone alone in CORTICUS. The addition of mineralocorticoid supplementation is unlikely to have contributed to the difference in mortality [18, 20]. This conclusion is drawn from the findings of the COIITSS trial (2010). This study specifically evaluated the impact of hydrocortisone alone versus hydrocortisone plus fludrocortisone in severe sepsis and found no added benefit [27].

Finally, the patient population was not quite as ill as the French study. This may be an important factor in explaining the different study conclusions as other trials have shown trends toward improved mortality in the severely ill. Specifically, these trends have been observed in patients with refractory shock. The Annane study focused on this patient group, whereas the CORTICUS trial enrolled patients regardless of fluid and vasopressor response. The difference in the severity of illness in the study populations is evident in higher SAPSII scores and higher mortality in the Annane study (61 % versus 32 %).

Nonetheless, many subsequent randomized controlled trials and meta-analyses have also supported the conclusion that steroids contribute to more rapid reversal of shock without a statistical difference in mortality [18, 20, 29–40].

Therapy

Adverse outcomes of steroid therapy are related to the dose and duration of therapy administered. While high-dose glucocorticoids are well known to increase the risk of infections, myopathy, wound complications, skeletal wasting, hyperglycemia, and psychosis, low stress dose steroids have been proven safe [20, 34]. Interestingly, the downregulation of sepsis-related inflammation over the short term may actually prove beneficial to a patient's resilience to infection [41]. In particular, treatment with hydrocortisone may enhance phagocytosis and neutrophil activity. Some studies have even noted a lower risk of hospital-acquired infections with low-dose steroid treatment [41, 42].

Current practice recommendations are to initiate hydrocortisone when patients have clinically severe septic shock that is refractory to volume replacement and vasopressor therapy. In critically ill patients without shock, or with hemodynamic restoration with vasopressors and fluids, there is no role for steroid therapy. The use of the cortisol levels and ACTH stimulation test to identify patients for treatment is discouraged (grade 2B [14]).

Therapy should be initiated with 200 g of hydrocortisone per day (Grade 2C [14, 28, 30, 31, 35, 36, 44, 45]. The dosing interval may be divided over 6 or 8 h dosing intervals or be given as a continuous infusion. A single prospective trial by Weber-Carstens showed less hyperglycemia and hypernatremia when hydrocortisone was given as a continuous infusion. This single study led to the 2D recommendation from the surviving sepsis campaign to consider this dosing strategy [14, 46]; however, further research is needed. The supplemental use of fludrocortisone is not necessary because hydrocortisone has both glucocorticoid and mineralocorticoid activity [14, 27].

Although consensus opinion suggests steroids should be tapered to avoid rebound hypotension and inflammation, to date the optimal duration of treatment has yet to be determined [47]. While 5–7 days of therapy is still endorsed by some authors [2, 5, 48], a recent study by Huh et al. showed no difference in outcomes when 3 days of therapy was compared to 7 days [49].

Perioperative "Stress Dose" Steroids

In as much as sepsis and acute illness may precipitate an adrenal crisis, the stress of a surgical procedure may also unmask adrenal insufficiency. For over 50 years, clinicians have administered supraphysiologic steroid doses to patients on long-term steroid therapy. More recently, steroid dosing has been based on the degree of the operative stress. For instance, minor surgery such as an inguinal hernia would be treated with a single dose of 25 mg hydrocortisone intraoperatively, whereas major operations such as a pancreaticoduodenectomy would be treated with 100–150 mg/24 h hydrocortisone for 3 days.

Recent systematic reviews have challenged the practice of given routine "stress dose" steroids at all. Both a 2008 review by Marik et al. and a 2009 Cochrane review concluded that a patient's baseline glucocorticoid dose should be continued without administering supraphysiologic doses of "stress" steroids. The caveat to this more relaxed approach, however, is that patients should be monitored and treated with rescue dose steroids should they display unresponsive hypotension in the postoperative period [50–52].

Steroids in Acute Respiratory Distress Syndrome (ARDS)

A second patient population that has been intensively evaluated for a potential role of steroid therapy is those with acute respiratory distress syndrome (ARDS). ARDS represents a potential complication of a group of heterogeneous disease processes. Theoretically, steroids may suppress the degree of fibroproliferative inflammation seen in some etiologies of respiratory dysfunction. However, steroids may be detrimental in ARDS stemming from an infectious process. Again, the available evidence is fraught with inconsistencies in the patient populations studied and the duration of outcome; thus there are conflicting conclusions and recommendations [53]. Aside from the Meduri trials in 1998 and 2007, most randomized controlled trials have failed to prove a clear mortality benefit, although secondary outcomes such as duration of mechanical ventilation and reduction of oxygen requirement have shown some promise [23, 54–58]. Taken together, the available evidence does not support the role of steroids in ARDS, and further investigation is needed.

Summary

In conclusion, CIRCI is a complex, proinflammatory state in which there is an inadequate cellular corticosteroid activity for the demand of the physiologic stress suffered by the patient. Despite decades of study, there are still many unanswered questions regarding the mechanisms, diagnosis, and treatment of CIRCI. At present the best evidence-based recommendations available include:

- A clinical diagnosis of CIRCI should be suspected in any critically ill patient who demonstrates hypotension, refractory shock, hypoglycemia, persistent systemic inflammation, and/or marked eosinophilia.
- ACTH stimulation and random cortisol levels are unreliable in the diagnosis of CIRCI.
- Hydrocortisone alone (200 mg/day in divided doses or as a continuous infusion) should be administered to patients with septic shock refractory to fluid resuscitation and vasopressor therapy.
- Patients without shock or with resolution of shock with vasopressor and fluid therapy should not receive steroids.
- Hydrocortisone should be tapered off after resolution of shock.
- Perioperatively, patients should remain on their pharmacologic steroid dose.
- "Stress dose steroids" should not be used unless a patient manifests unexplained hypotension in the perioperative period.
- There is no evidence to clearly support steroid therapy in ARDS.

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Thyroid Disorders

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Introduction

There are few thyroid conditions that are acutely life threatening, but the most notable are thyroid storm and myxedema coma, which result from thyroid hormone dysregulation. Thyroid storm is a severe manifestation of thyrotoxicosis (also known as thyrotoxic crisis). Thyroid storm was first described in an article in 1931 by Dr. Frank Lahey where he distinguished between the "activation type" of hyperthyroidism and what he dubbed "apathetic thyroidism" [5]. Many physiologic changes result from thyroid storm including dysfunction of the central nervous system, cardiovascular system, thermoregulatory system, and gastrointestinal and hepatic systems, with varying degrees of organ failure [1]. The most common cause of death in thyroid storm is multisystem organ failure, followed by congestive heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation, hypoxic brain syndrome, and sepsis [3, 6]. Burch and Wartofsky [2] developed a scoring system for thyroid storm in 1993 to aid in creating standardized diagnostic criteria. Akamizu et al. [3] tried to refine the diagnostic criteria based on a nationwide survey from the Japan Thyroid Association. Efforts at creating universal diagnostic criteria are important because early recognition can lead to lifesaving treatment. Diagnosis can be challenging because there are no laboratory abnormalities that are specific for thyroid storm [1].

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Epidemiology

According to the American Thyroid Association, more than 12 % of the United States population will develop a thyroid disorder in their life, and an estimated 20 million Americans have some form of thyroid disease [7]. More concerning is that up to 60 % of those with thyroid disorders are unaware of their disease [7].

Thyroid storm accounts for about 1–2 % of hospital admissions for thyrotoxicosis (or at least less than 10 %) [8, 9]. The incidence of thyroid storm in hospitalized patients in a nationwide survey in Japan was 0.2 per 100,000 per year or 0.22 % of all patients with thyrotoxicosis and 5.4 % of those patients admitted to the hospital with thyrotoxicosis [3, 6]. The current incidence is lower than previous estimates, perhaps for two reasons; first, maybe the increased screening for thyroid disorders has led to earlier diagnosis and more prompt treatment of hyperthyroidism which prevents the development of thyroid storm [10]; second, perhaps better preoperative management of hyperthyroidism prevents surgery from inducing thyroid storm [1]. Thyroid storm is more common in females than in males (10 % versus 2 %) [11, 12]. Thyroid storm occurs most commonly in those aged 20–49 years [12]. Thyroid storm is more common among patients with Graves' disease, and Graves' disease is the cause of hyperthyroidism 85 % of the time [11, 13]. Even with early diagnosis, the overall mortality of thyroid storm is high between 10 and 30 % and has been reported as high as 75 % in hospitalized patients [3, 8, 14].

The incidence of myxedema coma is estimated to be as low as 0.22 per million people per year [15, 16]. Myxedema coma occurs most commonly in hospitalized elderly women with long-standing hypothyroidism [15, 17]. Eighty percent of women affected by myxedema coma are older than 60 years, but it can occur in younger patients [15]. Since myxedema coma cases commonly occur in the winter, some have suggested that cold weather may lower the threshold in people at risk [15, 17, 18]. Mortality rates with myxedema

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coma have decreased from 60 to 70 % historically to 20–25 %, but mortality is highest in patients with severe hypothermia and hypotension [15, 19, 20].

Thyroid Storm

Pathophysiology

To understand the pathophysiology behind how uncomplicated hyperthyroidism can develop into thyroid storm, it is important to first understand normal thyroid hormone physiology. Thyroid hormones have widespread effects impacting the function of virtually every organ system [19]. There is a feedback loop between the hypothalamus, the anterior pituitary, and the thyroid gland that regulates thyroid function. The hypothalamus releases thyrotropin-releasing hormone (TRH) which causes the anterior pituitary to release thyroid-stimulating hormone (TSH), which then binds to a receptor on the surface of thyroid cells. Iodide is transported into the thyroid follicular cell with a sodium-iodide symporter and then iodide is oxidized by thyroid peroxidase (TPO). TPO catalyzes tyrosine residues on thyroglobulin to be iodinated, forming triiodothyronine (T3) and thyroxine (T4) [21]. The synthesis and secretion of T3 and T4 are stimulated by TSH. Thionamides inhibit TPO. Almost 90 % of the thyroid hormones released from the thyroid are T4, whereas only about 10 % is T3 [22]. About 10–20 % of circulating T3 was directly secreted by the thyroid, whereas the other 80–90 % was peripherally converted from T4 to T3 by the removal of one of the four iodine atoms in T4 [1, 22]. The liver and kidney 5′-deiodinases convert T4 to T3. Deiodinase D2 is the main active enzyme in the euthyroid state and deiodinase D1 is the main active enzyme in the hyperthyroid state. Deiodinase D1 can be inhibited by thionamides and propylthiouracil (PTU). T3 is more physiologically active than T4 and T3 is about four times more potent than T4 [22]. Peripherally circulating thyroid hormone (T3 and T4) inhibits the release and synthesis of TSH and TRH in a negative feedback loop. Glucocorticoids and propranolol inhibit the peripheral conversion of T4 to T3.

More than 99 % of T3 and T4 are bound to thyroid-binding globulin (TBG), albumin, and transthyretin [23]. The unbound (free) hormone is available to be taken up by peripheral tissues (and enter cells and carry out thyroid functions), whereas the bound hormone serves as a storage capacity in the circulation [22]. TBG has a higher affinity for T3 and T4 than albumin and transthyretin, so most of the thyroid hormone delivered to peripheral tissues is delivered by albumin and transthyretin.

Although the mechanism behind progression from uncomplicated hyperthyroidism to thyroid storm remains controversial, a heightened response to thyroid hormone is often implicated [2, 8, 24]. Additionally, increased or abruptly available free (unbound) thyroid hormone and enhanced binding of thyroid hormone to receptors are other often suggested mechanisms behind the development of thyroid storm [2, 8, 24]. As mentioned earlier, there are no diagnostic laboratory abnormalities for thyroid storm, and thus total T3 and T4 concentrations are not necessarily higher in patients in thyroid storm than in patients with uncomplicated hyperthyroidism. However, the mean dialyzable fraction of T4 and mean free T4 concentrations are higher in patients with storm compared to those with uncomplicated thyrotoxicosis who have similar total T4 levels [25]. It has been suggested that the mean free T4 concentrations are higher because the thyroid hormone binding affinity of TBG, albumin, and transthyretin is decreased due to various stressors [25, 26]. The rate at which free thyroid hormone levels increase is potentially more important than the absolute concentration of free thyroid hormone in determining whether the presentation is uncomplicated thyrotoxicosis or thyroid storm [24].

Activation of the adrenergic system has a significant role in the clinical manifestations of thyroid storm. There is no evidence that there is increased plasma concentrations or increased secretion of epinephrine or norepinephrine in patients with hyperthyroidism compared to patients who are euthyroid or hypothyroid [27, 28]. Instead, patients who are hyperthyroid are more responsive to catecholamines perhaps because of an increase in the density of beta-adrenergic receptors or downstream signaling from the receptors [2, 29, 30]. This is important because nonselective beta-adrenergic antagonists like propranolol can be used to dampen these adrenergic effects [24, 30].

Patients in thyroid storm have several hematologic changes. They have a leukocytosis even without an infection and an increased red blood cell mass from erythropoietin upregulation [15]. Thyroid storm patients may become hypercoagulable, with 18 % of thyroid deaths attributed to thromboembolic complications [15]. Fibrinogen, factor VIII, factor IX, and von Willebrand factor can increase in thyroid storm [15, 19].

Precipitating Causes

The change from uncomplicated thyrotoxicosis to thyroid storm usually requires a precipitating cause or insult. Historically thyroid surgery was the most common precipitating cause of thyroid storm, but better preoperative preparation and the increased use of radioactive iodine instead of surgery have rendered thyroid surgery a rare precipitating cause [1]. Incomplete or inadequate treatment of hyperthyroidism or interruptions in the drug regimen for hyperthyroidism are a risk factor for progression to thyroid storm [1].

Anything that causes hyperthyroidism can lead to thyroid storm, but Graves' disease is the most common etiology (60–80 % of cases), with toxic multinodular goiter or a toxic adenoma being other primary hyperthyroidism etiologies [1, 19]. A pituitary adenoma can be another cause of thyrotoxicosis and secondary hyperthyroidism [31, 32]. Infection is the most common precipitating cause of thyroid storm in hospitalized patients [2, 3, 8]. The list of precipitating causes is extensive and in addition to the causes listed above includes (in alphabetical order) alcohol abuse, antithyroid treatment withdrawal, burns, cardiac failure, cerebrovascular accidents, diabetic ketoacidosis, emotional stress, exercise, H1N1 infection, hypoglycemia, interferon treatment, iodine exposure from radiocontrast dyes or amiodarone, medications (amiodarone, anesthetics, fludrocortisone, insulin, nonsteroidal anti-inflammatory drugs, pseudoephedrine, salicylates, steroids, thiazide diuretics, tricyclic antidepressants), molar pregnancy, myocardial infarction, non-thyroid surgery, parturition, pulmonary embolism, radioactive iodine treatment, thyroid cancer, thyroid gland manipulation, thyroid hormone ingestion (especially when large doses are ingested acutely), thyroiditis, and trauma [1, 8, 9, 12, 31, 33–40]. Despite the long list of known precipitating causes, between 25 and 43 % or patients with thyroid storm present without a clearly identifiable precipitating cause [41].

Clinical Features and Diagnosis

The diagnosis of thyroid storm is a clinical diagnosis, and a low index of suspicion is important so that treatment is not delayed given the high mortality. The patient will have an exaggerated presentation of hyperthyroidism as well as multi-organ dysfunction [42]. High fever (as high as 104–106 °F) and heat intolerance are very common and often accompanied by profuse sweating and significant insensible fluid losses, as well as tachycardia out of proportion to the underlying disease process [1, 24, 31, 32]. Fatigue, loss of libido, oligomenorrhea and polyuria, weakness, and weight loss despite increased appetite are common constitutional symptoms [31, 32]. Cardiovascular manifestations of thyroid storm have been well described and may include atrial fibrillation, cardiac ischemia, dyspnea on exertion, exercise intolerance, heart failure, palpitations, tachycardia (sinus or supraventricular), and/or widened pulse pressure [22, 31, 32, 43–45]. The arrhythmias, tachycardia, and increased cardiac output can lead to heart failure and cardiogenic shock [31, 32, 45, 46]. Central nervous system and psychiatric manifestations are very common including agitation, apathy, coma, confusion, delirium, dysphoria, hyperactivity, irritability, obtundation, restlessness, seizures, stupor, or tremor [3, 22, 31, 32]. Gastrointestinal symptoms may be present including abdominal pain, diarrhea, nausea, and vomiting which lead to hypovolemia and electrolyte imbalances [1, 22, 31, 32]. Hepatic manifestations including liver dysfunction with elevated aspartate aminotransferase and alkaline phosphatase, hepatomegaly from hepatic congestion, and inadequate perfusion may be present; jaundice portends a poor prognosis [15, 22, 47, 48]. Other atypical presentations of thyroid storm have been published in case reports, including acute abdomen, disseminated intravascular coagulation, hypoglycemia, lactic acidosis, rhabdomyolysis, status epilepticus, and stroke [49–52].

Burch and Wartofsky [2] developed a scoring system for thyroid storm in 1993 to aid in creating standardized diagnostic criteria, which has been widely accepted, but should not replace clinical judgment. The scoring system assigns points based on temperature (0–30), heart rate (0–25), central nervous system dysfunction (0–30), heart failure (0–15), gastrointestinal and hepatic dysfunction (0–20), atrial fibrillation (0–10), and precipitant history (0–10), with a score of 45 or greater highly suggestive of thyroid storm, a score of 25–44 suggestive of impending storm, and a score below 25 unlikely to suggest thyroid storm [2].

Akamizu et al. [3] tried to refine the diagnostic criteria put forth by Burch and Wartofsky [2] based on a nationwide survey from the Japan Thyroid Association for cases of thyroid storm in Japanese hospitals from 2004 to 2008. Akamizu et al.'s [3] study is the largest single case series of thyroid storm [1, 3]. Similar to Burch and Wartofsky [2], the diagnostic criteria included temperature/fever, heart rate/tachycardia, central nervous system dysfunction, heart failure, and gastrointestinal and hepatic dysfunction, but the Akamizu et al. [3] criteria are based on combinations of symptoms rather than an absolute score. More than 75 % of patients had a pulse greater than 130 beats per minute, and 84 % of patients had central nervous system manifestations [3]. Forty percent of patients had heart failure and 69 % had gastrointestinal symptoms [3], while 76 % of patients had more than three organ system manifestations (multisystem organ dysfunction/failure) [3]. One caveat to this study is that it may not be generalizable outside of Japan given the specific population surveyed and the somewhat unique high iodine diet customary in Japan [6].

Although the diagnosis of thyroid storm is clinical, laboratory values can still be useful. Although there is no absolute cutoff for serum T3 or T4 that distinguishes uncomplicated thyrotoxicosis from thyroid storm, checking TSH, free T3, free T4, blood urea nitrogen, liver function tests, calcium, and glucose levels is important. Patients can have a leukocytosis in the presence or absence of infection, and elevated blood urea nitrogen is correlated with irreversible complications [3]. Patients with thyroid storm can be hyperglycemic from catecholamines inhibiting insulin release and increasing gluconeogenesis or rarely can be hypoglycemic [10, 49]. Systemically ill

patients are less able to convert T4 to T3 so a minimally elevated or free T3 that is in the "normal" range may be inappropriately elevated [8].

Medical Treatment

Treatment of thyroid storm should begin as soon as possible with a low index of suspicion given the high mortality, and patients should be transferred to an intensive care unit for close monitoring. There are three main goals in thyroid storm treatment: (1) create a euthyroid state, (2) prevent cardiovascular collapse, and (3) control hyperthermia [22]. A multidisciplinary approach is important, and treatment should be both supportive as well as targeting the synthesis, release, peripheral effect, and enterohepatic circulation of thyroid hormone.

The first-line therapy for thyroid storm is thioamides/thionamides, which inhibit new thyroid hormone production [1]. The most common agents are propylthiouracil (PTU) and the imidazoles (methimazole and carbimazole) [1]. As mentioned above, thionamides inhibit thyroid peroxidase (TPO, which helps form T3 and T4) [21]. Although both PTU and methimazole are used to treat hyperthyroidism, PTU is preferred in the treatment of thyroid storm because it also decreases conversion of T4 to T3 in the periphery [1]. When treating thyroid storm, the dose of PTU or methimazole should be much higher than the doses used to treat hyperthyroidism, with 600–1,500 mg per day of PTU divided into doses every 4–6 hours (possible loading dose of 600 mg) and 80–120 mg per day of methimazole divided into doses every 4–6 hours [2, 8, 53]. The American Association of Clinical Endocrinologists/American Thyroid Association guidelines recommend a PTU loading dose of 500–1,000 mg and then 250 mg every 4 hours and for methimazole 60–80 mg per day in divided doses [54]. Side effects of propylthiouracil and methimazole include arthralgias, benign transient leukopenia, fevers, hepatotoxicity (less hepatotoxicity with methimazole than with PTU), and rashes [19].

For patients without enteral access, rectal formulations of PTU and methimazole have been developed, but have lower bioavailability [55–57]. Rectal suppositories have a lower bioavailability than retention enemas, but the suppositories are preferred since they are easier for nurses to administer and less uncomfortable for patients [55–58]. PTU is relatively insoluble at a physiologic pH, and so compounding for intravenous administration is difficult, but intravenous methimazole is commercially available in Europe and can be compounded in the United States by dissolving methimazole powder in normal saline [1, 59]. Treatment can also be given via nasogastric tube [19].

Iodine administration can also decrease new thyroid hormone synthesis by inhibiting binding of iodide to thyroglobulin via the Wolff-Chaikoff effect [1]. This mechanism prevents binding once a critical threshold of iodide is reached in the plasma, but only lasts 26–50 hours, as the thyroid will adapt to the excessive iodide over time [60]. Iodine can be administered as potassium iodine 250 mg (0.25 mL or five drops) every 6 hours or as Lugol's solution with eight drops given orally every 6 hours (iopanoic acid and sodium ipodate are not commercially available in the United States) [2, 54]. Side effects of potassium iodide include hypersensitivity reactions, metallic taste, and salivary gland swelling [19]. Iodine can also be administered rectally or intravenously. Potassium iodide can be compounded for rectal administration by placing 1 g of iodide in 60 mL of water and giving 2 g per day in divided doses [61]. Lugol's solution can be administered rectally in doses of 4 mL (80 drops) per day [62]. Iodine should be given at least 30–60 minutes after giving thionamides to prevent it serving as material for further thyroid hormone synthesis, and thionamides must be continued during the time that iodine is used for therapy [1]. Additionally, giving iodine may delay treatment of hyperthyroidism with radioactive iodine and thus is often utilized when the plan is for thyroidectomy [1, 2, 8]. Finally, lithium (carbonate) inhibits T3 and T4 synthesis by inhibiting the coupling of iodotyrosine residues and can be used as an alternative to iodine; 300 mg should be given every 6–8 hours with repeated monitoring of serum drug levels because of the narrow therapeutic window (goal range is 0.6–1 mEq/L) [2, 8, 15].

Once new thyroid hormone synthesis is stopped, another agent of thyroid storm treatment is preventing release of thyroid hormone that has already been formed into systemic circulation [1]. Iodine also inhibits release of already formed thyroid hormone by inhibiting the proteolytic release of T3 and T4 from thyroglobulin [2, 63]. This action gives iodine treatment a faster onset than PTU [41]. The combination of thionamides and iodine treatment can decrease serum T4 levels to close to the normal range within 4–5 days [64]. Lithium can also be used to decrease thyroid hormone release [1].

Oral iodinated contrast agents inhibit deiodinases D1 and D2 and profoundly decrease T3 levels, and because of their iodine content, both decrease new thyroid hormone synthesis and preformed thyroid hormone release [1]. These contrast agents should be given as a 2 g loading dose then 1 g daily to treat thyroid storm, or in lower doses to rapidly prepare for thyroid surgery, or in addition to thionamides when treating Graves' disease [65–67].

An additional treatment modality is aimed at preventing the recirculation of thyroid hormone metabolites after being processed by the liver [1]. Thyroid hormone is conjugated to glucuronides and sulfates in the liver, and these metabolites are excreted in bile into the intestine where they are reabsorbed and then recirculated in a process known as enterohepatic circulation of thyroid hormone [1]. Cholestyramine

when dosed at 1–4 g twice a day will bind the metabolites, promote their excretion, and thus decrease enterohepatic circulation of thyroid hormones [15, 68–70].

Thyroid storm treatment should also focus on mitigating the downstream effects of thyroid hormone via adrenergic blockade. Hughes was the first to report using a beta-blocker (pronethalol) along with carbimazole to treat thyrotoxicosis in 1966 [71]. Propranolol has become the most commonly used beta-blocker in thyroid storm because it is nonselective and decreases conversion of T4 to T3 in the periphery [1]. Propranolol ameliorates symptoms by decreasing pulse and oxygen demand, reducing convulsive symptoms and tremor, psychotic behavior, agitation, and fever [15, 19, 22]. Propranolol dosing can be as high as 60–120 mg orally every 6 hours (or 40–80 mg orally every 4 hours) since it is metabolized more rapidly in thyroid storm [10, 19]. Beta-blockade can also be accomplished intravenously for a faster effect with IV propranolol or esmolol; IV propranolol dosing is 0.5–1.0 mg slow IV push then 1–2 mg every 15 minutes (or just 2 mg IV every 4 hours) with telemetry monitoring of the pulse, whereas esmolol is 0.25–0.5 mg/kg initial bolus then a continuous infusion at 0.05–0.1 mg/kg per minute [19, 41, 72]. Side effects of propranolol include bradycardia, nausea, and vomiting and should be avoided in patients with decompensated heart failure [19]. Calcium channel blockers can be utilized to treat thyroid storm in patients with pulmonary conditions like asthma or chronic obstructive pulmonary disease (COPD), but may not be as effective as beta-blockers [22].

Supportive resuscitative treatment is also important, including temperature regulation with cooling and antipyretics, intravenous fluid resuscitation for dehydration, monitoring hemodynamic status and fluid status in patients with congestive heart failure, oxygen, treatment of dysrhythmias as they arise, and prevention of adrenal insufficiency. In managing fever, acetaminophen is preferred to salicylates because salicylates can increase free thyroid hormone levels by limiting the binding to T4-binding globulin [15, 73]. Peripheral cooling can be achieved with cooling blankets and/or ice packs. Shivering should be avoided since it can increase temperature and cardiac demands by increasing the metabolic rate [22]. Intravenous fluid resuscitation is important to support insensible losses from fever and fluid losses for diarrhea and vomiting. A central venous line for central venous pressure monitoring and pulmonary wedge pressure monitoring with a Swan-Ganz catheter can also be useful adjuncts. Vasopressors may be needed to treat hypotension that does not resolve with intravenous fluids. The hypothalamic-pituitary-adrenal axis is impaired in thyrotoxicosis, and despite increased cortisol production by the adrenal gland which compensates for the increased glucocorticosteroid metabolism in hyperthyroidism, an inadequate response to adrenocorticotropic hormone (ACTH) occurs. Stress dose steroids are recommended with a loading dose of 300 mg of hydrocortisone intravenously and then 100 mg every 8 hours to prevent adrenal insufficiency and decrease the peripheral conversion of T4 to T3 [74]. Hyperglycemia is a notable side effect of hydrocortisone [19].

Finally, medical treatment of thyroid storm includes correcting the precipitating cause if possible. Sometimes the precipitating cause is obvious like trauma or surgery, but sometimes it is more subtle, and fever and/or leukocytosis should prompt a search for an infectious source. Evaluate for exposure to iodine or iodinated contrast or withdrawal of thionamides, and treat other precipitating causes like burns, diabetic ketoacidosis, myocardial infarction, stroke, or pulmonary emboli in the standard fashion.

Therapeutic Plasma Exchange

For refractory cases of thyroid storm, therapeutic plasma exchange (TPE) is an additional option which rapidly reduces circulating thyroid hormone levels and can effectively yield clinical improvement. During TPE, the patient's plasma is extracted and a colloid replacement like albumin and/or plasma is infused [75, 76]. Ashkar et al. [77] described the first use of plasmapheresis in thyroid storm in a case series of three patients who failed conventional therapy published in 1970. In thyroid storm, thyroid-binding globulin (TBG) is removed from the circulation along with the thyroid hormone bound to TBG, and the colloid replacement, which is most often albumin, provides available binding sites for circulating free thyroid hormone to bind too, thus decreasing free thyroid hormone concentrations [26].

Most case series show a reduction in free T3 and free T4 with TPE, and Ezer et al. [76] published the largest plasma exchange series in thyrotoxicosis with 11 patients who underwent preoperative TPE before thyroid or non-thyroid surgery. Free T3 decreased among patients 22.2–89.9 % and free T4 decreased 8.3–64.8 %, but these declines were not statistically significant, although all patients improved in signs and symptoms of thyrotoxicosis [76]. Clinical improvement often occurs within a few hours of the first TPE session, especially cardiac signs and symptoms of thyroid storm [78]. Plasmapheresis and therapeutic plasma exchange provide only temporary reductions in T3 and T4 (for up to 36 hours), and so they must be continued or definitive therapy instituted [15]. Despite this the American Society of Apheresis 2010 guidelines only recommended TPE as a grade IIc (weak recommendation, low-quality evidence based on observational studies or case series) and a category III (optimal role of apheresis therapy is not established; decision-making should be individualized) recommendation, suggesting that further

more rigorous research needs to be performed to clarify the role of TPE in thyroid storm, especially regarding the timing or triggers for initiation.

Muller et al. [78], in contrast, recommended initiating TPE early for the following indications: severe symptoms (cardiac or neurologic manifestations, severe myopathy, etc.), rapid clinical deterioration, contraindications to other therapies, and refractory cases. The American Society of Apheresis recommends performing TPE daily to once every 2 or 3 days until clinical improvement and monitoring free T3 and T4 before and after each session, but continuing TPE regardless of hormone levels if clinical stabilization occurs with TPE therapy [75]. The complication rate of TPE is about 5 %, and complications include allergic reactions, coagulopathy, hemolysis, hypotension, infection, and vascular injury [76, 78, 79].

Thyroid Surgery

While thyroid surgery is a definitive therapy for thyroid storm producing rapid resolution of hyperthyroidism, it is only rarely needed emergently in the modern era given recent advances in medical treatment and critical care to treat thyroid storm patients [1]. A multidisciplinary approach to thyroid storm is critical, and the surgical team should be consulted within the first 12–72 hours [1]. However, medical management should be attempted first, and there are only three types of patients who qualify for emergent surgery: (1) patients who clinically deteriorate or are refractory to medical treatment within 24–48 hours; (2) patients with side effects from medical management, such as agranulocytosis or hepatitis or severe thrombocytopenia from thionamides; or (3) patients with severe cardiac or pulmonary comorbidities who lack the reserve to tolerate prolonged thyroid storm [1, 80]. There are several treatment plans to quickly prepare patients for surgery with most utilizing iopanoic acid (an oral cholecystographic agent) which is unavailable commercially in the United States [22, 65, 66, 81]. Therapeutic plasma exchange (TPE)/plasmapheresis is an alternative to iopanoic acid to quickly prepare a patient for thyroid surgery by controlling thyroid storm [1, 75–78]. However, for hyperthyroidism in general, it is customary to achieve euthyroidism prior to surgery via medical management [8].

The recommended surgery for thyroid storm is a subtotal or near-total thyroidectomy, just like for Graves' disease [41]. For the patient on steroids or beta-blockers preoperatively, they should be continued perioperatively and slowly weaned over the following weeks [8]. Given that medical and critical care management have rendered emergency surgery for thyroid storm so rare, there is limited surgical outcome data available. Scholz et al. [80] reported their own series of ten patients and summarized the literature of early thyroidectomy for thyroid storm, noting a long-term overall mortality of 10 % (5 of 49 patients).

Thyroid Storm in Pregnancy

Hyperthyroidism occurs in 1 in 500 pregnancies [13]. Women with thyrotoxicosis with limited access to prenatal care or with medical or obstetrical complications have an increased risk of developing thyroid storm [13]. The signs and symptoms of thyroid storm are the same in pregnant women but are more likely to be mistaken for the normal hypermetabolic state of pregnancy [13]. Both propylthiouracil and methimazole cross the placenta, with PTU recommended for the first trimester and methimazole recommended for the remainder of the pregnancy [13, 19]. Delivery of the fetus during thyroid storm is not recommended, unless the fetal condition demands it [19]. Radioactive iodine is contraindicated during pregnancy and breastfeeding since it may also ablate the thyroid gland of the fetus or neonate [13, 22]. Thyroidectomy should be avoided during pregnancy because of an increased risk of preterm delivery or of spontaneous abortion [13]. A full review of thyroid storm during pregnancy is beyond the scope of this chapter, and additional information can be found in the cited article by Waltman et al. [13].

Long-Term Management of Hyperthyroidism

After the acute thyroid storm episode is over, definitive treatment of hyperthyroidism should be offered. Given the long half-life of T4 (about 1 week), treatment should be slowly weaned to prevent a recurrent episode of thyroid storm [1]. If nonadherence to thionamides is suspected as the precipitating cause for the thyroid storm, definitive treatment with surgery or radioactive iodine should be initiated as soon as possible. If the patient received iodine treatment for their thyroid storm episode, radioactive iodine ablation would need to be postponed until the intrathyroidal iodine stores are eliminated [1]. While waiting for the intrathyroidal iodine stores to clear, thionamide treatment should continue and thyroid function studies should be monitored for stability [1]. If the patient is compliant, continued thionamide treatment is acceptable [1]. Improvement from thyroid storm can occur rapidly within as little as 24 hours [15]. Once a patient has stabilized from thyroid storm and the precipitating cause(s) has been addressed, iodide therapy and glucocorticoids can be withdrawn [19]. Beta-blockers should be continued until thyroid function tests return to normal [19].

Outcomes of Thyroid Storm

A high index of suspicion, early diagnosis, and rapid treatment result in the best outcomes and can significantly impact the outcomes for thyroid storm. While early case series reported mortality rates as high as 37.5 %, more recent stud-

ies report a 10.7 % mortality rate for thyroid storm [3, 82]. The most common causes of death in Akamizu et al.'s [3] study with the Japan Thyroid Association were multisystem organ failure and congestive heart failure. Even if the patient survives, there was often significant morbidity, including brain injury, cerebrovascular disease, muscular disuse atrophy, psychosis, and/or renal function impairment [1].

Myxedema Coma

Myxedema coma is the life-threatening end stage of inadequately treated or untreated hypothyroidism and is often triggered by a precipitating cause [19]. Precipitating causes include cerebrovascular accident, diuretics, excessive hydration, exposure to cold, gastrointestinal bleeding, heart failure, infection, medications (amiodarone, lithium, phenytoin, lack of compliance with thyroid replacement), myocardial infarction, narcotics, sedatives, surgical procedures, or trauma [12, 17, 19, 20, 83–85]. Although usually it is primary hypothyroidism that leads to myxedema coma, in 5–15 % of cases, a pituitary or hypothalamic source of hypothyroidism is identified [86].

Clinical Features and Diagnosis

Myxedema coma typically begins with lethargy and worsening mental status that progresses to coma, then respiratory decompensation and hypothermia [17]. Hypothermia may be profound (temperature as low as 74 °F and often 91–95 °F) [19, 22, 31]. Those patients with myxedema without coma can have central nervous system and psychiatric manifestations including adiadochokinesia, ataxia, cerebellar signs (poorly controlled purposeful movements of the hands and feet), delayed deep tendon reflexes, depression, disorientation, hallucinations (myxedema madness), mental status changes, paranoia, poor memory and recall, or seizures [15, 17, 20, 22]. Up to 25 % of patients with myxedema coma may experience seizures, possibly secondary to hypoglycemia, hyponatremia, and hypoxemia [15]. Cardiovascular manifestations of myxedema coma can include arrhythmias (especially bradycardia, varying types of heart block, prolonged QT intervals, torsades de pointes), cardiac contractility impairment, cardiac tamponade (from an accumulation of mucopolysaccharide fluid in the pericardial sac), hypotension from low intravascular volumes, and shock from cardiac dysfunction [15, 17]. Respiratory manifestations include airway obstruction from edema of the tongue and vocal cords, decompensation requiring mechanical ventilation because of decreased hypoxic respiratory drive and decreased ventilator response to hypercapnia, pleural effusions, and prolonged need for mechanical ventilation from slow respiratory recovery [15, 17, 20, 87].

Myxedema coma also affects the gastrointestinal, hematologic, and renal systems. Renal and genitourinary manifestations include atonic bladder with urinary retention, decreased glomerular filtration rate, hyponatremia (from increased serum antidiuretic hormone and impaired diuresis because less water gets to the distal nephron), increased total body water, and rhabdomyolysis with increased creatine kinase levels and increased risk of kidney failure [15, 17, 20]. Critically ill patients with symptomatic hyponatremia have a higher mortality rate than patients who do not [15]. Hematologic manifestations include anemia (microcytic from hemorrhage or macrocytic from vitamin B12 deficiency), bleeding and coagulopathy (secondary to decreased factors V, VII, VIII, IX, and X and acquired von Willebrand syndrome type 1), disseminated intravascular coagulation (if patients become septic), and granulocytopenia (increasing infection risk and decreasing cell-mediated immune response) [15, 88]. The von Willebrand syndrome is reversible with T4 treatment [15]. Gastrointestinal manifestations include ascites, decreased motility (secondary to mucopolysaccharide infiltration and gut edema and ranging from gastric atony and impaired peristalsis to paralytic ileus), and gastrointestinal bleeding (from coagulopathy) [15, 17]. Other manifestations can include dry skin and hoarseness [15].

Laboratory studies, imaging, and other testing are useful in the diagnosis of myxedema coma. Thyroid function tests will reveal a decreased free T4 and increased TSH [22]. Hyponatremia, respiratory acidosis, hypercapnia, hypoxemia, hypoglycemia, and hyperlipidemia are all common in myxedema coma [22]. An EKG may show bradycardia, varying types of heart block, low voltage, flattened or inverted T waves, prolonged QT intervals, or torsades de pointes [15, 22]. A chest X-ray may reveal cardiac and/or pleural effusions [22].

Popoveniuc et al. [4] described a scoring system for myxedema coma diagnosis. The scoring system assigns points based on temperature (0–20), heart rate (0–30), central nervous system effects (0–30), cardiovascular dysfunction (10 for other EKG changes besides bradycardia, 10 for pericardial/pleural effusions, 15 for pulmonary edema, 15 for cardiomegaly, 20 for hypotension), gastrointestinal findings (0–20), metabolic disturbances (10 each for hyponatremia, hypoglycemia, hypoxemia, hypercarbia, decrease in glomerular filtration rate), and precipitant history (0–10), with a score of 60 or greater highly suggestive/diagnostic of myxedema coma, a score of 25–59 suggestive of risk for myxedema coma, and a score below 25 unlikely to indicate myxedema coma [4].

Treatment

The treatment of myxedema coma involves thyroid hormone replacement, supportive care, and addressing the underlying

precipitating cause [20]. Additional treatment goals include (1) thermoregulation, (2) stabilization of cardiac status, and (3) improved ventilation [22]. Optimal thyroid hormone replacement dosing is lacking because there are few well-controlled trials given the rarity of cases [15, 20]. Replacement can be with T3 or T4 or both and some advocate replacing both since T4 to T3 conversion is impaired in myxedema coma [15, 19]. If treating with levothyroxine (T4) only, a loading dose of 300–600 mcg IV then 50–100 mcg IV daily is recommended [15]. If treating with liothyronine (T3), only a 10–25 mcg IV bolus loading dose followed by 10 mcg every 4 hours for the first 24 hours then 10 mcg every 6 hours for days 2 and 3 is recommended [15, 19]. In the combined approach, an initial bolus loading dose of 4 mcg/kg lean body weight (or about 200–300 mcg) of T4 is given IV, followed by 100 mcg 24 hours later and then a daily maintenance dose of 50 mcg by the third day, which can be given orally when the patient is conscious and extubated; simultaneously, a bolus loading dose of 10 mcg of T3 is given IV and then 10 mcg every 8–12 hours is given until the patient is conscious [15]. Overly aggressive replacement of T4 is undesirable as it can cause myocardial infarction [19]. Antacids and iron interfere with the absorption of levothyroxine so it should be taken on an empty stomach [22].

Supportive care includes intravenous fluid resuscitation with 0.9% sodium chloride and possibly sodium replacement for hyponatremia with hypertonic saline (50–100 mL of 3% sodium chloride followed by 40–120 mg furosemide) [15, 19]. Sodium levels should be corrected slowly to prevent central pontine myelinolysis. Hypothermia will resolve with T3 and T4 treatment, but a warm ambient temperature and warming blankets can be used; however, aggressive rewarming should be avoided to prevent vasodilation [15, 20]. Ventilation is improved with oxygen, but may require either continuous positive airway pressure (CPAP) or Bi-PAP or even endotracheal intubation with mechanical ventilation [22]. Hydrocortisone 100 mg IV every 8 hours is recommended for patients with hypotension for at least 48 hours and up to the first 7 or 10 days or until adrenal suppression is ruled out, as the patient may have relative adrenal insufficiency [15, 19]. If the patient has a seizure, phenytoin should be avoided in the treatment, since phenytoin decreases thyroid hormone levels via breakdown of thyroid hormone [22]. Drugs including anesthetics, antidepressants, narcotics, sedatives, and tranquilizers may depress the respiratory drive and thus exacerbate the hypothyroid patient into a coma and thus should be minimized or avoided [15, 20]. Additionally, all patients should have continuous telemetry monitoring given the risk for arrhythmias and bradycardia.

Myxedema Coma in Pregnancy

There have been at least 36 documented cases of myxedema coma in pregnant women [15, 89, 90]. A full review of myxedema coma during pregnancy is beyond the scope of this chapter, and additional information can be found in the cited articles by Blignault and Patel et al. [89, 90].

Conclusion

Thyroid storm and myxedema coma are endocrine emergencies with high morbidity and mortality, where early recognition with a low index of suspicion and prompt treatment can significantly impact outcomes [1]. The diagnosis of thyroid storm is made clinically and cannot be based on laboratory abnormalities, and diagnostic criteria have been put forth by Burch and Wartofsky and by Akamizu et al. [2, 3]. Multidisciplinary care in a critical care setting is recommended, and identification of the precipitating cause and reversal or treatment of that cause should be sought if possible [1]. Medical treatment of thyroid storm involves understanding the pathophysiology underlying its development and then targeting all steps of thyroid hormone synthesis, release, and action in a specified order, along with supportive care [1]. Treatment should begin with thionamides (propylthiouracil/PTU preferred over methimazole), then iodine administration (potassium iodine or Lugol's solution) or alternatively lithium, then cholestyramine to block the enterohepatic circulation of thyroid hormone, and beta-blockers (propranolol or esmolol), temperature regulation with cooling and antipyretics (Tylenol preferred over salicylates), intravenous fluid resuscitation for dehydration, and stress dose steroids (hydrocortisone) with vasopressors as needed. Therapeutic plasma exchange (TPE) or plasmapheresis can also be utilized. Finally, definitive therapy is surgery (subtotal or near-total thyroidectomy) or radioactive iodine ablation.

Myxedema coma is severe hypothyroidism, often with significant hypothermia, bradycardia, and mental status changes as substantial as a coma, often with a precipitating cause. Popoveniuc et al. [4] have proposed a diagnostic scoring system for myxedema coma. Medical treatment for myxedema coma involves thyroid hormone replacement (with T3 and/or T4), supportive care (warm ambient temperature and warming blankets, IV fluids including potentially hypertonic saline for hyponatremia, mechanical ventilation or other ventilation support, and hydrocortisone), and treatment of the precipitating cause and any other sequelae of myxedema coma including seizures. The mortality of both thyroid storm and myxedema coma has improved over the years with improvements in critical care.

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Hyperadrenergic Crisis

32

Lindsay E. Kuo and Douglas L. Fraker

Case Report

The patient is a 40-year-old nurse who presented with a hypertensive crisis due to an unrecognized pheochromocytoma. The patient had no significant past medical history or family history and developed hypertension 2 years prior to her event at age 38. In the 6 months prior to her event, her blood pressure was more difficult to control. She also developed diabetes with highly variable glucose levels also difficult to control. She had had a 1-year history of headaches, diaphoresis, and palpitations. She presented to the emergency room after a witnessed collapse at home. Her initial blood pressure was 210/125, heart rate 135, and very short of breath. She was intubated and was difficult to ventilate. Her echocardiogram showed a moderately dilated left ventricle with an LVEF of 15 % and moderate to severe mitral regurgitation. She underwent cardiac catheterization that showed normal coronary arteries. She was transferred by helicopter to our institution to be placed on ECMO. At our institution she was treated with intravenous nicardipine, phenoxybenzamine, and metyrosine. A repeat cardiac echo showed an LVEF of 30 % and her blood pressure was 180/110. Imaging demonstrated 7 cm left adrenal mass. Laboratory testing showed a plasma epinephrine of >30,000 pg/ml (ULN 200) and plasma norepinephrine of 35,556 pg/ml (ULN 520). She remained intubated in the ICU during blood pressure control. On hospital day 6, she underwent an uneventful laparoscopic left adrenalectomy. Final pathology showed a relatively benign pheochromocytoma (PASS score of 4). She was extubated on postoperative day #1 and was discharged to home on postoperative day #3.

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This case demonstrated the potential for unrecognized pheochromocytoma to have lethal consequences. This healthy 40-year-old nurse almost died due to cardiogenic shock and pulmonary edema associated with incredibly high catecholamine levels despite having a benign neoplasm cured by a minimally invasive procedure. She had every classic symptom of catecholamine excess yet was not tested until she presented in shock.

Introduction

Pheochromocytomas and paragangliomas are tumors arising from the catecholamine-producing chromaffin cells originating from the neural crest. The sympathetic paraganglia are located from the skull base to the pelvis along the para-aortic and paravertebral axes, with the largest concentration in the adrenal medulla [1]. Tumors arising from the adrenal medulla are known as pheochromocytomas, while tumors located outside the adrenal gland are known as extra-adrenal pheochromocytomas or paragangliomas. Although they have distinct locations, pheochromocytomas and sympathetic paragangliomas are clinically and pathologically identical: both produce catecholamines and result in similar signs and symptoms [2]. For the purpose of this text, we will refer solely to pheochromocytomas. All content also applies to paragangliomas unless stated otherwise.

Pheochromocytomas are rare and have an estimated prevalence of approximately 1 in 2,500–6,000 patients [3]. The majority of pheochromocytomas are benign. Malignant tumors are defined by the presence of metastases or local invasion. However, the signs and symptoms of benign and malignant tumors are similar.

The clinical presentation of pheochromocytomas is highly variable. The classic scenario is the triad of headaches, palpitations, and sweating, in addition to paroxysmal or sustained hypertension. The most extreme and rare presentation is known as pheochromocytoma crisis (PCC), in which catecholamine-induced hemodynamic instability results in

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acute end-organ dysfunction or damage and a critically ill patient [4, 5]. Patients with PCC may have had previous symptoms related to pheochromocytoma, or PCC may be the first manifestation of the disease. This crisis syndrome, which we will refer to as PCC throughout, is estimated to occur in 7–20 % of pheochromocytoma patients [4, 6]. While mortality from this clinical spectrum was once estimated to be as high as 85 % [7], a more recent study reports a 15 % mortality rate [4].

Because PCC is rare, there is little randomized evidence on optimal diagnosis and management to guide physicians, and much of the recommendations are based upon expert consensus opinion. Regardless, an understanding of PCC by the critical care physician and surgeon is paramount because timely diagnosis and management are crucial to reducing mortality and restoring of normal organ function. An individualized approach to diagnosis and management is necessary given the wide spectrum of clinical presentations, particularly in the acutely ill patient [8].

Clinical Presentation

Critical to the effective treatment of pheochromocytoma crisis is a prompt diagnosis. Making this diagnosis, however, can be difficult because of variable presentations. Furthermore, the associated signs and symptoms are nonspecific and are more frequently encountered in non-PCC patients. Just as pheochromocytomas are known informally as "the great mimic," so too is PCC frequently mistaken for other critical illnesses.

Classification System

Pheochromocytoma crisis encompasses a wide range of disease severity. In 1988, Newell et al. named the clinical spectrum of severe hypertension and/or hypotension, multi-organ system failure, high fever, and encephalopathy "pheochromocytoma multisystem crisis" (PMC) [5]. Both PMC and PCC have been used in the literature, although PCC is a somewhat broader term because it does not require the presence of fever or encephalopathy. In 2014, Whitelaw et al. proposed a two-tiered classification system for PCC: type A crises include those with hemodynamic instability and single organ damage or dysfunction but are limited in duration, while type B crises include those with prolonged hypotension (shock) and multi-organ dysfunction. Patients may progress from type A to type B during a crisis episode [4]. This classification system has not been widely adopted in the literature, but this may be due to the recency of its introduction. For the purposes of this text, we will not differentiate types A and B.

Signs and Symptoms by Organ System

PCC can affect every organ system. Below is a systemic review of the organ-specific signs and symptoms of PCC.

Hypertension, Hypotension, and Shock

Hypertension, paroxysmal or sustained, is the most common symptom of a pheochromocytoma. Hypertensive crises, which occur when hypertension reaches such high levels that normal bodily functions are threatened, are the most common presentation of patients in PCC. Common associated symptoms of hypertensive crises include headaches, vision changes, palpitations, and diaphoresis [2].

Hypotension and shock are also commonly seen in PCC, although this is rarely the reason for presentation [9]. Patients presenting in shock may have a history of syncope and may also report abdominal pain, weakness, diaphoresis, and cyanosis [2].

Cardiac

PCC is associated with a broad range of cardiac effects. Sinus tachycardia and other tachyarrhythmias, including supraventricular, nodal, and ventricular tachycardia, as well as torsades de pointes, Wolff-Parkinson-White syndrome, and atrial and ventricular fibrillation have all been described in the literature. Unlike patients with primary cardiac disease, PCC patients may present with simultaneous tachyarrhythmias and hypertension. Bradyarrhythmias and asystolic arrest are also possible in PCC patients [2]. Treatment of these arrhythmias is the same as treatment of arrhythmias in non-PCC patients, although caution must be taken when administering beta-blockers.

Myocardial ischemia and infarction (MI) can result from PCC, and the presentation is similar to the presentation of acute coronary syndrome due to cardiac pathology: chest pain and shortness of breath. Electrocardiographic abnormalities and elevated troponins are also similar to ischemic events secondary to cardiac disease. Indeed, many patients who present with signs and symptoms of an MI undergo cardiac catheterization, and only after normal coronary arteries are visualized is an alternate diagnosis considered [10–13]. Myocarditis and several cardiomyopathies have also been described in several PCC patients [14]. Acute heart failure, cardiogenic shock, and cardiogenic pulmonary edema may be the presenting signs [12, 15–17].

Pulmonary

Both cardiogenic and noncardiogenic pulmonary edemas have been reported in PCC patients. While neither symptom is often the predominant symptom, both have been reported as such [18–24]. Massive hemoptysis resulting in acute respiratory failure has also been described [25]. Ventilatory support is often needed in patients with pulmonary complications.

Peripheral Vasculature

Catecholamine-induced peripheral vasoconstriction and vasospasm can lead to the acute onset of peripheral ischemia, manifesting as necrosis or gangrene [26, 27]. Rarely, patients with pheochromocytoma-induced tachyarrhythmias can experience embolism to the peripheral vasculature [2].

Gastrointestinal

The acute onset of abdominal pain is the predominant abdominal symptom of PCC. Tumor hemorrhage in particular is associated with acute, severe abdominal pain and may also present with intraperitoneal and/or retroperitoneal bleeding [28, 29]. In these cases, emergent angiographic embolization may be needed to stabilize the patient prior to diagnosis and definitive management of the tumor [29]. Mesenteric vasoconstriction or vasospasm can cause mesenteric ischemia, which may require surgical intervention. Nonspecific symptoms such as nausea and vomiting, constipation or diarrhea, and diagnoses of ileus, pseudo-obstruction, and megacolon have been reported in PCC patients [2, 23, 30].

Renal

Both acute renal failure and pyelonephritis have resulted from PCC [31]. Excess vasoconstriction secondary to catecholamines can directly result in renal ischemia and subsequent renal failure. Rhabdomyolysis may occur as well because of reduced blood flow to the musculature and cause myoglobinuric renal failure [32]. Hemodialysis, ultrafiltration, or continuous renal replacement therapy may all be needed.

Neurologic

Ischemic or hemorrhagic cerebrovascular accidents (CVAs) secondary to severe hypertension are the most common neurologic consequence of PCC [14, 33]. Subarachnoid hemorrhage may also result, and hemiparesis and seizures can be the presenting symptoms [34, 35]. Encephalopathy was first reported by Newell et al. [5]. Vision changes or vision loss have also been reported [21].

Multiple Organ System Failure

As noted above, Newell et al. reported three patients with hypertension or hypotension, fever, multiple organ system failure, and encephalopathy, coining the term "pheochromocytoma multisystem crisis" [5]. Since this report in 1989, a multitude of additional case reports have been published, each reporting a unique constellation of signs and symptoms of organ failure from several organ systems [36–38]. For example, in one case a patient presented with acute myocarditis, pancreatitis, and pneumonia; her condition progressed to include shock, rhabdomyolysis, hepatic cytolysis, anuric renal failure, respiratory failure, and DIC, all despite normotension [36]. Fevers may also be present [10, 38].

Misdiagnosis

Because of the wide range of clinical presentations and nonspecific signs and symptoms, and because many PCC patients present without paroxysmal symptoms or hypertension, PCC is frequently misdiagnosed [4]. In some cases, PCC patients were not diagnosed with a pheochromocytoma until autopsy after succumbing to the crisis, and PCC was not on the differential diagnosis at all [36, 39].

Patients with multisystem organ failure are diagnosed with septic shock, especially if also presenting with a fever [2, 10, 36]. If a patient with potential septic shock is unresponsive to fluid administration and inotropic agents, pheochromocytoma should be considered [2]. In patients presenting with cardiac abnormalities or signs and symptoms of an MI, clues that suggest a noncardiac etiology include episodic symptomatology or associated hypertension, headache, diaphoresis, or pallor [2]. Normal coronary arteries in a patient presenting with acute coronary syndrome, acute cardiogenic shock, or cardiomyopathy should also trigger suspicion for a pheochromocytoma.

PCC should be considered in the differential diagnosis of a critically ill patient in the setting of unexplained shock, left ventricular failure, multi-organ system failure, fever, and hypertensive crisis or hypotension [4]. Other potential clues include a family or personal history of pheochromocytoma or hereditary syndromes associated with pheochromocytomas, history of signs and symptoms associated with pheochromocytomas, and a history of hemodynamic instability during surgical procedures [6].

In pregnant women, the hypertensive symptoms of PCC are often attributed to preeclampsia or gestational hypertension [21]. However, preeclampsia most commonly occurs after 20 weeks of gestation and is associated with proteinuria and edema. Gestational hypertension, which also develops after 20 weeks, is unlikely to be paroxysmal [40]. Extreme hypertension in a pregnant woman before 20 weeks of gestation or without proteinuria or edema should trigger suspicion for PCC, as should paroxysmal hypertension, which is the most common symptom in this patient population [2, 41]. Early recognition is important because of high associated maternal and fetal mortality rates: maternal mortality is as high as 17 % and fetal mortality ranges from 15 to 26 %. Concerningly, pheochromocytomas go undiagnosed in 47–65 % of pregnant women [40, 42, 43].

Pathogenesis

Pathophysiology

Pheochromocytomas primarily secrete catecholamines, which act predominantly on alpha-adrenergic receptors to cause arterial vasoconstriction. In turn, arterial vasoconstriction results

in hypertension and compensatory decreased intravascular volume. End-organ perfusion may decrease as a result, causing tissue ischemia and the signs and symptoms that define PCC. Differences in alpha- and beta-adrenergic signaling pathways and different amounts and proportions of secreted catecholamines may also contribute to the variety of presentations seen in pheochromocytoma and PCC patients [6, 44].

Hypotension and shock result, paradoxically, from chronically elevated catecholamine levels. Downregulation of catecholamine receptors on vasculature structures desensitizes these structures to catecholamines. Intermittent release of catecholamines therefore may cause hypotension during periods of decreased catecholamine release [44]. Vasodilation due to epinephrine and myocardial dysfunction may also contribute. While hypotension was once hypothesized to occur in patients with tumors that secrete predominantly epinephrine, hypotension has been described in norepinephrine-secreting tumors as well [2, 45]. Hyperglycemia may develop secondary to altered glucose metabolism and may exacerbate decreased intravascular volume.

The cardiac pathology associated with PCC is due to elevated catecholamine levels through a multitude of pathways. Excessive catecholamines stimulate cardiac beta-receptors, causing tachyarrhythmias. Bradyarrhythmias occur secondary to reflexive sinus slowing in response to hypertension [2]. Similar to the vasoconstrictive effects of high catecholamine levels on the systemic circulation, the coronary arteries undergo vasoconstriction and vasospasm in response to catecholamines. Elevated catecholamines also increase myocardial contractility and heart rate which, in conjunction with decreased arterial flow, cause myocardial ischemia, infarction, and cardiomyopathy [46]. Catecholamine-induced cardiomyopathy also results from direct catecholamine-mediated injury of myocardial fibers [12]. Takotsubo cardiomyopathy (apical hyperkinesis with basilar akinesis), inverted takotsubo cardiomyopathy (with apical sparing), dilated cardiomyopathy, obstructive cardiomyopathy, and nonobstructive hypertrophic cardiomyopathy have all been described in PCC [14, 17, 46–48]. Furthermore, chronic exposure to elevated catecholamine levels leads to a downregulation of cardiac catecholamine receptors, reducing the number of myocardial contracting units and decreasing myocardial functionality. Alterations in myocardial membrane calcium permeability and myocyte necrosis with inflammatory infiltration can result in acute adrenergic myocarditis, myocardial necrosis, and, subsequently, decreased cardiac output [49]. In the setting of systemic vasoconstriction and intravascular hypovolemia, decreased cardiac output can lead to cardiogenic shock [46]. Reassuringly, both medical and surgical treatments reverse the cardiomyopathy [27].

A recent investigation by Mobine et al. found that catecholamines secreted in the context of a pheochromocytoma led to more severe cardiac pathology than catecholamine administration without concurrent pheochromocytoma. These findings suggest that tumor cells secrete additional substances that work in conjunction with or exacerbate the effects of catecholamines [50]. Further investigation into the nature of these substances and their role in the cardiac symptomatology of PCC is needed.

Cardiogenic pulmonary edema develops secondary to cardiac sequelae of PCC. Vasoconstriction of pulmonary vessels and increased pulmonary capillary permeability due to catecholamines are hypothesized to be the source of non-cardiogenic pulmonary edema [45]. Cerebrovascular accidents develop due to cerebrovascular vasoconstriction or vasospasm or are secondary to cardiac emboli [14]. Paroxysmal vision changes, predominantly blindness, have been reported in pheochromocytoma patients and are thought to be secondary to peripheral vasoconstriction [27]. Fevers in the absence of systemic infection are likely secondary to interleukin-6 (IL-6) production by the pheochromocytoma [51, 52].

Precipitants

What causes an episode of pheochromocytoma crisis instead of the traditional pheochromocytoma symptoms? One hypothesis is that in PCC, a surge of catecholamines are released, causing acutely reduced end-organ perfusion that results in an acutely ill presentation [4].

Tumor hemorrhage can be the inciting event and may go clinically unapparent, cause abdominal pain, or result in further hemodynamic instability due to blood loss [23, 28, 38, 47, 53]. Tumor necrosis, due to vasoconstriction and poor end-organ perfusion, can also bring on a crisis [36, 38, 46]. In both tumor hemorrhage and necrosis, large quantities of catecholamines are spilled into the systemic circulation [29]. Biopsy, which is not recommended for pheochromocytoma diagnosis under any circumstance, may also precipitate a crisis episode [54]. Undergoing a trauma, surgery, or general anesthesia can stimulate a crisis, as can systemic infection [23, 53, 55, 56]. While ionic contrast dye was historically reported to cause PCC, it is no longer used. Nonionic contrast dye, which is commonly administered in current practice, is not associated with PCC [57].

Anecdotally, some medications have been reported to precipitate an episode of PCC. Classes of medications, including dopamine type-2 receptor antagonists and beta-blockers, have a high associated risk of precipitating symptomatology [58]. When stimulated, dopamine type-2 receptors such as metoclopramide inhibit catecholamine release; blocking these receptors can initiate catecholamine release [59, 60]. When given without preexisting alpha-adrenergic blockade, beta-blockers result in unopposed alpha-adrenergic stimulation [58]. Glucagon directly stimulates catecholamine

secretion and can incite a crisis [61]. Other medication groups, including opioid analgesics, tricyclic antidepressants, monoamine oxidase inhibitors, corticosteroid medications, sympathomimetics, and neuromuscular blocking agents have also been reported to cause symptoms but with less consistency [8, 62–66]. Stimulation of PCC with dobutamine for a stress echocardiogram has also been reported [39].

In pregnant women, PCC can be induced by fetal movements, increased intra-abdominal pressure due to an enlarging uterus, postural changes, contractions, or vaginal delivery [2].

Diagnosis

Because of the wide variety of clinical presentations and the rarity of pheochromocytomas, clinical suspicion for pheochromocytoma crisis may be low. However, the most important factor in a timely diagnosis of PCC is recognition that a pheochromocytoma may be the cause of the disease [8]. Only then can an appropriate workup be initiated.

Biochemical Diagnosis

The initial testing for pheochromocytoma is biochemical, through plasma-free or urinary fractionated metanephrines [8, 67]. Metanephrines are the product of catecholamine metabolism: norepinephrine becomes normetanephrine, and epinephrine becomes metanephrine. Catecholamines are converted to metanephrines by chromaffin cells in a process independent of catecholamine excretion, which can be intermittent (in response to stress) or constant [68]. Measurements of metanephrines in urine or plasma are therefore more sensitive than measurements of catecholamines [67].

Metanephrines can be measured in their free state in plasma, while urinary metanephrines are measured after a deconjugation step. As a result, plasma-free metanephrines are a more accurate way to assess for a pheochromocytoma than urinary testing [8, 67]. However, there is no consensus on whether urine or plasma measurements are the gold standard. If blood testing is performed, the patient should be supine during the sampling process in order to minimize the likelihood of false positivity [67].

There is no defined level of plasma or urine metanephrines that is sufficient to make a diagnosis of a pheochromocytoma. Pheochromocytoma can be ruled out with some certainty if both normetanephrine and metanephrine levels are within a normal range [67]. The degree to which a metanephrine level is heightened may also help guide decision-making: elevation of plasma metanephrines at least fourfold above the upper limit of normal is associated with 100% probability of a pheochromocytoma [69]. Furthermore, because catecholamines are produced in times of stress or in response to certain medications, false-positive results are likely in times of acute illness [6]. Consequently, elevated levels of metanephrines in a critically ill patient may not be sufficient to diagnose a pheochromocytoma. Further complicating this issue is that there is no range of "normal" metanephrines in acutely ill patients – all ranges currently reported relate to a normal, well, nonstressed subject [4]. Lastly, elevated catecholamines may only be intermittently present. If all levels are normal on biochemical testing, repeat testing may be needed [23, 27].

Table 32.1 Urinary vs. plasma metanephrine testing

Urinary fractionated metanephrines	Plasma-free metanephrines
Urinary metanephrines are created after free metanephrines undergo deconjugation step	Measurements reflect free metabolites produced within chromaffin cells
Widely established, widely available test	Newer test but increasing availability
Urinary concentrations of 200–2,000 nmol/L make analysis easy	Plasma concentrations of 0.1–0.5 nmol/L make analysis difficult
24 h collection difficult for patients	Blood sampling more convenient
Problems with reliability of incompletely timed collections	Easy to collect
Difficult to control for influences of daily life on sympathoadrenal function	Easy to control for influences, sympathoadrenal function
Not useful in patients with renal failure	Can be used in patients with renal failure

Adapted from Kohle et al. [37]

Both urine and plasma testing are complicated in a critically ill patient, as seen in Table 32.1. Urinary testing requires a 24-h sample to be collected, which may result in a delay in diagnosis. Urine collection may not be feasible in a patient in shock or with renal failure. Not all institutions are capable of performing the blood test, and the sample may need to be transported to an off-site location for testing, and this too may lead to a delay in diagnosis [6].

There is no consensus on which biochemical test should be performed to diagnose a pheochromocytoma in an acutely ill patient. In a critically ill patient, biochemical testing should be performed expeditiously in whatever modality is possible for the institution. In stable patients, a biochemical diagnosis of a pheochromocytoma must be established prior to performing imaging [8]. In PCC patients, the results of urine or plasma testing should be incorporated with the patient's clinical picture to determine if there is high enough suspicion for pheochromocytoma, and localization with imaging can then be performed. If biochemical testing is not readily or reliably available, or if the patient's clinical presentation demands quicker intervention than laboratory testing allows, the clinical picture alone can warrant imaging [6, 70].

Imaging

When imaging is indicated, computed tomography (CT) scanning is the modality of choice in the critically ill patient [4, 6]. CT scan has a sensitivity of 88–100 % for detecting pheochromocytomas. The CT scan can be performed without IV contrast if the patient is in renal failure or is allergic to contrast dye; unenhanced imaging has approximately 90 % sensitivity [57]. While some historic studies had reported the precipitation of hyperadrenergic symptoms following the administration of IV contrast dye, more recent studies have found no association between the administration of nonionic IV contrast dye and adverse events [57]. Use of nonionic contrast dye can assist in locating extra-abdominal lesions or metastases and may aid surgical planning.

If the patient is too ill to travel to a CT scanner, bedside ultrasound may diagnose an adrenal lesion but may not be sufficient to locate a paraganglioma, given the range of possible locations along the sympathetic chain [4]. Magnetic resonance imaging (MRI) can be performed in noncritically ill patients to diagnose pheochromocytoma (Fig. 32.1) and is the preferred imaging modality in children and pregnant or lactating women [3, 71]. However, it is not practical in an unstable patient.

CT, MRI, and ultrasound all lack the diagnostic specificity needed to diagnose a pheochromocytoma independent of biochemical findings [3]. ^{123}I-labeled meta-iodobenzylguanidine scintigraphy (MIBG) has a specificity of 95 % for catecholamine-producing lesions but a sensitivity of only 77–90 % [72]. Because of the low sensitivity, MIBG cannot be used to localize pheochromocytomas and should be performed to confirm localization. However, some studies have shown that it does not change operative management and therefore does not warrant regular performance [72]. It is primarily of use in patients with a high risk of recurrent, multifocal, or malignant disease or if CT or MRI has failed to locate a tumor despite high metanephrine levels [8, 72]. More recently, radiolabeled positron-emission tomography (PET) has demonstrated superiority over MIBG, particularly in localizing small extra-adrenal lesions [3]. In the critically ill patient in whom an expedited diagnosis is necessary, however, these techniques have no role; when surgery is performed on an elective basis on a stable patient, they may be useful in selected patient populations [8].

Management

No randomized controlled trials have been performed to address management of PCC patients. All recommendations are based upon expert consensus and retrospective series. Individualized treatment decisions should be made depending on the circumstances and the resources available. Patients may require transfer to an institution able to appropriately manage the crisis and perform the operation [73].

Immediate Management

All patients presenting with PCC are by definition hemodynamically unstable and require immediate stabilization. All patients should be placed in an intensive care unit able to provide continuous noninvasive monitoring and circulatory and ventilatory support. Patients with significant cardiac involvement may also require invasive monitoring, including pulmonary artery catheters, or frequent echocardiograms [4, 74].

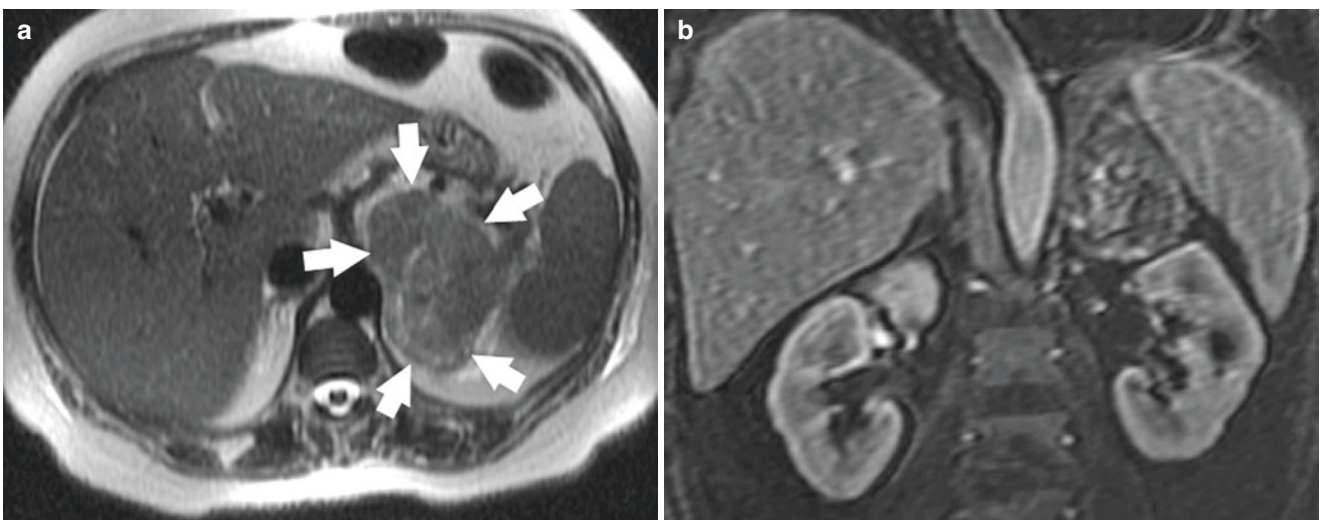

Fig. 32.1 Selected images from the MRI of the patient discussed in the initial case report: (**a**) axial image; (**b**) coronal image of the 7 cm left adrenal pheochromocytoma (boarders of which are denoted by *arrows*), which caused a hypertensive crisis

Catecholamine release during PCC results in sympathetic vasoconstriction, which in turn leads to intravascular hypovolemia. While patients continue to be hypertensive despite this hypovolemia, administration of antihypertensive medications can result in severe hypotension. Aggressive fluid resuscitation with crystalloid is therefore recommended, either simultaneously with or prior to alpha-blockade [4, 74]. Fluid resuscitation also helps prevent hypovolemia following catecholamine withdrawal due to surgical resection [75]. The success of fluid resuscitation can be monitored through biochemical testing, such as lactic acid levels, or through more invasive measures, including a cardiac index or central venous pressure.

Medications

Medical treatment to stabilize the patient by blocking the effect of catecholamines is widely accepted as first-line therapy. There are no evidenced-based recommendations supporting the use of a specific medication or class of medications, and in hemodynamically ill patients, medications likely need to be used in conjunction with fluid resuscitation and even circulatory support. A variety of medications have been successfully implemented in the literature, including alpha-blockers and calcium channel blockers [67]. A full listing, with dosages, can be seen in Table 32.2.

The most widely accepted first-line medication is alpha-blockers, which are strongly associated with survival [4]. Alpha-blockers act by reversing vasoconstriction that causes hypertension. Alpha-blockers also decrease cardiac arrhythmias [76]. Phenoxybenzamine is the most commonly used alpha-blocker [4]. It is nonselective, noncompetitive, and long acting, allowing for intravascular volume repletion [2, 74]. It may be given in intravenous (IV) or oral (by mouth or through a nasoenteric tube) formats; in unstable patients, IV administration is preferred [13]. While protocols exist for dosing phenoxybenzamine in stable patients, no guidelines for the drug dosing or frequency in the critically ill patient have been published [4]. Phenoxybenzamine is long acting and may result in postoperative hypotension because of ongoing alpha-blockade [74].

Alternative alpha-blockers include phentolamine, prazosin, terazosin, and doxazosin. Phentolamine is nonselective, competitive, and short acting and can be given intravenously [4]. Competitive, selective alpha-1 blockers such as doxazosin, terazosin, and prazosin have been used because there is no activation of presynaptic alpha-2 receptors to release norepinephrine, causing reflex tachycardia. Additionally, these medications are shorter acting than phenoxybenzamine, so dosing can be adjusted with more frequency and there is less postoperative hypotension [74]. Unfortunately, the competitive nature of these medications means that their actions can be superseded by large amounts of catecholamines [77]. All three medications are only available for oral administration and so should only be given in critically ill patients if clinically appropriate. Doxazosin can be administered daily. The simplicity of doxazosin dosing in controlled-release tablets is an advantage over phenoxybenzamine in the outpatient setting [78] but limits its usefulness in critically ill patients. Prazosin and terazosin have shorter half-lives than doxazosin and so must be given several times each day [74]. Prazosin, terazosin, and doxazosin are inferior to phenoxybenzamine in preventing intraoperative hemodynamic fluctuations but have no differences in postoperative outcomes [77, 79].

A few case reports describe the use of a calcium channel blocker, primarily nicardipine, as a single agent to treat hypertension associated with PCC [80–82]. Calcium channel blockers inhibit the effects of norepinephrine on peripheral

Table 32.2 Medications used in treatment of pheochromocytoma crisis

Medication	IV dosing	PO dosing
Phenoxybenzamine	Bolus: 0.5 mg/kg over 5 h, up to 1–2 mg/kg/day	10 mg BID, titrate up to total of 60–80 mg/day in 2–3 doses
Phentolamine	Bolus: 2.5–5 mg at 1 mg/min rate, repeat q3–5 min Infusion: 100 mg in 500 ml 5 % D5W, begin at 1 mg/min, titrate as needed	n/a
Doxazosin	n/a	4–12 mg/day, increase up to 24 mg/day
Prazosin	n/a	1.0 mg q6–8 h, increase frequency as needed [74]
Terazosin	n/a	1.0 mg qD, increase frequency as needed [74]
Sodium nitroprusside	Infusion: 50–100 mg in 500 ml 5 % D%W, begin at 0.5–10.0 mcg/kg/min, titrate as needed	n/a
Hydralazine	Bolus: 10–50 mg IV, q4–6 h	n/a
Magnesium	Bolus: 4 g over 5 min Infusion: 1 g/h, up to 4 g/h	n/a
Nicardipine	Bolus: 5 mg/h Infusion: 20 mg in 200 ml dextrose or NS, begin at 5 mg/h, titrate by 2.5 mg/h q 5 min, up to 15 mg/h [74]	n/a
Metyrosine	n/a	250 mg qD, up to 4 g qD [74]

Adapted from Brouwers et al. [2] and Whitelaw et al. [4] with additional references as noted

arteries without causing venous vasodilation and prevent coronary artery vasospasm and myocarditis. In addition to IV nicardipine, oral dosing of nifedipine and diltiazem has been described [74]. Recently, Brunnaud et al. found no differences in intraoperative hemodynamic stability in patients treated with either alpha-blockers or calcium channel blockers, indicating that calcium channel blockers may be a useful alternative to alpha-blockers in managing pheochromocytomas, particularly if alpha-blockers are not readily available [83]. However, this study was performed on pheochromocytoma outpatients, not PCC patients, and there is currently no evidence to support the use of calcium channel blockers as a single agent in the treatment of PCC. Magnesium sulfate also acts as a calcium channel antagonist to affect arterial vasodilation. Additionally, magnesium sulfate inhibits catecholamine release, blocks catecholamine receptors, and acts as an antiarrhythmic [84, 85]. Its use has also been reported to assist in hemodynamic stabilization, in conjunction with other antihypertensive medications or in situations in which traditional medications were unsuccessful in stabilizing a PCC patient [86]. It too is administered intravenously.

Additional antihypertensive medications may be required to stabilize the patient. The most commonly used are sodium nitroprusside and hydralazine, both of which can be given through an IV [4]. Beta-blockers such as atenolol, labetalol, and metoprolol can also be given to reduce hypertension and tachyarrhythmias. However, beta-blockers should not be used until after alpha-blockade has been achieved, as beta-blockade without alpha-blockade will lead to unopposed alpha-receptor activity, worsening hypertension and other effects of PCC. These antihypertensives can be given in combination as needed, in concert with alpha-blockade, to stabilize the patient.

Metyrosine, a tyrosine hydroxylase inhibitor that reduces catecholamine synthesis, can be used in combination with phenoxybenzamine to treat pheochromocytoma or in patient's refractory to alpha-blockade [87, 88]. However, crisis episodes have occurred even in patients receiving metyrosine because of preexisting catecholamine stores [88]. There is no randomized evidence or expert opinion to encourage its use in PCC patients, but it may be a useful adjunct in patients with labile hypertension despite medical management.

Pregnant women presenting with hypertension from PCC should receive immediate alpha-blockade because of the poor consequences of severe maternal hypertension, including uteroplacental insufficiency, placental abruption, fetal hypoxia, and fetal death [40, 41]. Phenoxybenzamine, prazosin, and phentolamine can be used in the pregnant patient; there is no consensus on the best choice of medication [40]. If phenoxybenzamine is used, there is a small risk of neonatal respiratory depression, and infants should be monitored for a few days after birth [40]. Sodium nitroprusside may be used but only at doses less than 1 μg/kg/min because of potential cyanide toxicity in the fetus [2]. Magnesium sulfate is also a treatment option and has additional fetal neuroprotective properties. As a result, some have proposed magnesium as the first-line treatment in pregnant patients with pheochromocytoma [85]. Only selective beta-blockers such as metoprolol or atenolol should be used, as nonselective beta-blockers can lead to fetal growth retardation [41].

Hypotension and Circulatory Support

Patients may also present with hypotension. There is no evidence beyond case reports that indicates the best vasopressors to use in hypotensive PCC patients, and a wide range of vasopressors have been utilized in the literature. Because patients may be insensitive to catecholamine-based vasopressors, nonadrenergic medications, such as vasopressin, may prove useful.

In several cases, additional circulatory support has proven useful to help stabilize a hypotensive patient. An intra-aortic balloon pump (IABP), cardiopulmonary bypass (CPB), and extracorporeal membrane oxygenation (ECMO) have all been described in this setting [12, 13, 89–91] and are particularly useful in patients presenting in acute cardiogenic shock. These methods of circulatory support can stabilize the patient, allowing for the administration of alpha-blockers or other medications described above, which would not have been feasible in a hypotensive patient. ECMO and CPB can provide intraoperative support as well.

Timing of Surgery

Controversy exists over the optimal timing of surgical intervention in PCC patients. In noncrisis pheochromocytoma patients, surgical resection after 2 weeks of alpha-blockade is recommended. Alpha blockade must be successfully achieved, as patients who are not fully blocked experience higher postoperative morbidity and mortality rates [92]. There is no consensus, however, on the best timing for surgery in PCC patients.

In patients with PCC, emergent surgical resection is one option. In 1988, Newell et al. recommended urgent surgical intervention, even if alpha-blockade has not yet been established, because removal of the source of catecholamines was thought to be the only way to stop disease progression [5]. Several case reports describe death in patients treated with medical management alone [23, 30, 38, 93] and advocate for emergent resection if medical management fails [38, 70, 73, 89].

In contrast, in the largest case series of PCC patients published, Scholten et al. reported that none of the 25 PCC patients operated on at their institution required emergent intervention, and all were adequately alpha-blocked prior to

surgery. Ten patients received surgery during the index hospitalization, but 15 were discharged from the hospital and received an elective resection at a later date. There were no patient deaths, demonstrating that surgical resection following complete medical stabilization is a safe and feasible approach [94]. However, the study may suffer from selection bias and may not be generalizable to all institutions. In an extensive literature review, Scholten et al. also found that emergent operations were associated with higher rates of intraoperative and postoperative complications and concluded that pheochromocytoma crisis should not be treated with emergent surgery if avoidable [89, 94].

Once the patient is stabilized, resection should be performed in a timely fashion. Scholten et al. recommend surgery within 1 month of discharge [94]. However, this window of time provides an opportunity for another crisis episode [4]. There are no studies on the optimal timing of surgery after stabilization. However, an attempt at stabilization is warranted and should be achieved prior to surgery except in the most desperate of circumstances.

In pregnant women, surgery should be performed if the pheochromocytoma is discovered between 12 and 24 weeks of gestation and the pregnancy carried to maturity. Notably, resection prior to 24 weeks' gestational age is associated with a fetal mortality risk as high as 44 % [95]. Before 12 weeks of gestation, pregnant women should receive medical treatment alone and undergo surgical resection during the second trimester when the risk of spontaneous abortion has decreased [41]. After 24 weeks of gestation, it is unlikely that the pheochromocytoma will be surgically accessible because of the gravid uterus. Instead, the pregnancy should be carried to term and the pheochromocytoma managed medically; if fetal distress occurs, earlier surgical intervention may be needed [21]. In these patients, cesarean section should be performed rather than attempting a vaginal delivery because of the potential for vaginal delivery to stimulate catecholamine release [43, 60, 71, 96]. Resection of the pheochromocytoma can be performed simultaneously with cesarean section or after an appropriate recovery period, although this timeframe is not defined [41, 97].

Operative Management

For resection of a pheochromocytoma or paraganglioma, the patient may need to be transferred to an institution with an experienced surgeon. Resection of a pheochromocytoma requires careful surgical dissection and constant communication between the operative and anesthesia teams. General anesthesia is commonly used, and anesthetic agents that can stimulate PCC should be avoided [74].

A laparoscopic adrenalectomy should be performed instead of an open procedure if the patient is stable [94]. The laparoscopic approach is commonly accepted as the surgical gold standard for pheochromocytomas less than 6 cm in greatest dimension because of shorter intraoperative duration, less intraoperative blood loss [98], reduced postoperative complications, a shorter postoperative length of stay, and decreased expense when compared to the open approach [99–101]. In the case series presented by Scholten et al., laparoscopic resection was feasible in PCC patients with a conversion-to-open rate equivalent to that of non-PCC patients [94].

In unstable patients, an open approach may be needed because patients may not tolerate hemodynamic changes associated with insufflation [89, 98, 99, 102]. For pheochromocytomas greater than 6 cm in size or invading adjacent organs, an open procedure is recommended to achieve complete resection and prevent future recurrence [8]. In open adrenalectomies, a mid- to low-thoracic epidural will assist in both stabilizing the patient and in postoperative analgesia. However, open adrenalectomies are associated with perioperative hemodynamic instability and a larger postoperative vasopressor requirement than laparoscopic resections [103]. Paragangliomas should also be resected through an open approach unless they are small, noninvasive, or in locations amenable to laparoscopic resection [8].

Vasopressors or antihypertensives may be needed throughout the case, depending on the clinical scenario. In patients receiving antihypertensives or catecholamine antagonists intraoperatively, these medications must be discontinued prior to adrenal vein ligation in anticipation of an abrupt drop in catecholamine release [73]. Intravenous fluids and vasopressors may be required after adrenal vein ligation as well [104].

Postoperative Care

Postoperatively, patients require continued intensive care until hemodynamically stable. Hypotension is the most common postoperative complication, and intravenous fluid and vasopressors may be required to ensure stability. The degree of preoperative catecholamine secretion is the greatest risk factor for postoperative hypotension [85]. There is often some catecholamine resistance after pheochromocytoma resection, and vasopressin is the treatment of choice in this scenario [73]. Patients may also have new-onset hypoglycemia, as insulin is no longer suppressed by catecholamines and should receive blood sugar monitoring postoperatively [104].

Although the majority of pheochromocytomas are sporadic, approximately 24–28 % of pheochromocytomas are caused by a hereditary mutation associated with a familial syndrome [1, 105]. Pheochromocytoma is a component of the MEN 2A, MEN 2B, von Hippel-Lindau, neurofibromatosis, and familial paraganglioma syndromes 1 and 4, all of

Table 32.3 Common genetic syndromes associated with pheochromocytomas or paragangliomas

Syndrome	Gene	Location	Pheochromocytoma or paraganglioma	Associated symptoms or diagnoses
Multiple endocrine neoplasia, type 2A (MEN 2A)	RET	10q11.2	Pheochromocytoma	Medullary thyroid carcinoma
				Primary hyperparathyroidism
Multiple endocrine neoplasia, type 2B (MEN 2B)	RET	10q11.2	Pheochromocytoma	Medullary thyroid carcinoma
				Ganglioneuroma
				Marfanoid habitus
Von Hippel-Lindau disease (VHL)	VHL	3p26-25	Pheochromocytoma	Renal cell carcinoma
				Hemangioblastoma
				Pancreatic islet cell tumors
Neurofibromatosis type 1 disease (NF1)	NF1	17q11.2	Pheochromocytoma	Neurofibromatosis
				Café au lait spots
				Axillary or inguinal freckling
				Optic nerve glioma
Familial paraganglioma 1	SDHD	11q23	Both	
Familial paraganglioma 4	SDHB	1p36.1–35	Both	

Adapted from Elder et al. [1]

which have other manifestations (see Table 32.3). However, familial pheochromocytomas may also exist outside of these well-defined syndromes [106]. These syndromes may affect the PCC patient, necessitating further treatment, or may affect a family member. Genetic testing should only be performed on PCC patients at high risk for a genetic mutation to better inform treatment decisions; "high risk" is defined as patients with a family history of pheochromocytoma or another genetic syndrome component, patients with multifocal, metastatic or extra-adrenal disease, or patients younger than 50 years of age [1, 106].

There is no evidence on the optimal timing of genetic testing: some syndromes are associated with multifocal or bilateral pheochromocytomas, which all may contribute to the episode of PCC. Genetic testing prior to surgical intervention may therefore be helpful in guiding surgical management. However, genetic testing in a timely fashion may not be feasible in all situations, and delaying surgery due to genetic testing may not be possible or may provide an opportunity for further crisis episodes. PCC in a patient with a genetic syndrome has not been described in the literature, and there is no evidence or expert opinion to guide the timing.

Conclusion

Pheochromocytoma crisis is a rare event but should be considered in critically ill patients presenting with multiple organ system failure. Timely diagnosis and individualized management are essential to patient survival.

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Trauma

33

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General Approach

The care of the trauma patient in the intensive care unit (ICU) follows the same principles as the care of the patient in the trauma bay. An initial focus on airway, breathing, circulation, and disability allows for an expedited initial assessment of the trauma patient that arrives in the intensive care unit. All of the adjuncts available to the staff in the trauma bay should also be available in the ICU, from point of care testing to ultrasound. Once life-threatening issues have been addressed, an organ system approach to the patient can be implemented. Radiologic studies and reports as well as laboratory values obtained in the trauma bay must be reviewed.

Critically injured patients typically progress through four phases: the resuscitative phase, the early life-support phase, the prolonged life-support phase, and the recovery phase [1]. These can be grouped into early and late stages of ICU care. The early stage includes the resuscitative phase and early life support. The resuscitative phase is a continuation of trauma bay or operating room resuscitations and encompasses the first 24 h. Management during this phase, which often involves several concurrent treatment and diagnostic maneuvers, is focused on control of active hemorrhage, aggressive resuscitation, and restoration of tissue oxygenation. By 24–72 h, diagnosis of occult injuries is complete, and treatment aims are focused on specific organ failures during the early life-support phase. Early multiple organ dysfunction syndrome, commonly involving pulmonary, cardiovascular, and renal failure, may become apparent at this time.

After 72 h, clinical priorities shift. This later stage of ICU care includes the prolonged life-support and recovery phases. The prolonged life-support phase focuses on support of the patient with nutrition, ventilator liberation, continuation of prophylaxis regimens, and attempts to prevent secondary complications that could impair the recovery of the patient. Meticulous and vigilant ICU care is necessary during this time for prevention and early detection of complications. The duration of this prolonged life-support phase is highly variable and depends largely on injury severity and associated complications. The recovery phase is marked by the transition from ventilatory support to spontaneous breathing and removal of invasive monitoring devices. Rehabilitation with physical and occupational therapy, begun during the life-support phase, is continued and intensified. Both the patient and the family are prepared for the transition from the ICU to general patient or intermediate care unit, and plans for further convalescence and rehabilitation are developed.

Initial Assessment

Life-threatening issues may have been addressed in the trauma bay or the operating room, but a systematic and comprehensive approach aids in the assessment of the trauma patient upon admission to the ICU and avoids missed or delayed diagnoses.

Airway

A rapid assessment of the airway is necessary on arrival in the ICU. In the non-intubated patient, focus should be on a secure airway. The indications for an advanced airway are the same as in the trauma bay. Glasgow Coma Scale (GCS)

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of less than 8 from head injury or medications, significant facial fractures, bilateral mandible fractures with loss of posterior tongue support, neck swelling from injury, or evidence of inhalational airway injury should all prompt consideration for immediate intubation upon arrival to the ICU.

In the intubated patient, confirmation of a secure airway is essential. Endotracheal tubes are at risk for dislodgement or malposition (right main stem intubation or supraglottic positioning) during transfer to ICU. All intubated patients should have a chest x-ray performed upon arrival in the ICU. Rapid assessment of type and size of endotracheal tube, listening for bilateral breath sounds, and confirmation of end tidal CO_2 should also be completed. Endotracheal tubes need to be secured with either a well-positioned tube holder or tape, while a bite block can aid in the prevention of tube obstruction. Early and frequent deep endotracheal and oral nasopharyngeal suctioning can prevent atelectasis caused by heavy secretions of blood or mucous. Restraints should also be employed to avoid self-extubation.

Breathing

Auscultation of breath sounds, if not completed during the airway assessment, is an essential part of the breathing assessment. Unequal breath sounds prompt an immediate response in a search for the cause. Endotracheal tube malposition or pneumothorax is the most common cause. If hemodynamic instability is present, needle thoracostomy is performed with a 14 g needle either in the second intercostal space along the midclavicular line or in the anterior axillary line at the fourth intercostal space in order to relieve the tension pneumothorax [2]. In the hemodynamically stable patient, pneumothorax may be diagnosed with chest x-ray or ultrasound evaluation of the pleural space [3]. An occult pneumothorax not identified in the trauma bay may become apparent after the patient has been intubated and placed on positive pressure ventilation. Pneumothorax should be suspected in intubated patients with hypoxia and a sudden decrease in tidal volumes or increase in peak airway pressures.

Upon arrival to the ICU, all intubated patients should have continuous pulse oximetry monitoring implemented and an arterial blood gas drawn with consideration for placement of an arterial line if one has not already been placed. Initial ventilator settings should have a tidal volume set at 8 ml/kg or less, a respiratory rate set to the minute ventilation at 10 L/min, and positive end-expiratory pressure (PEEP) of 5 mmHg [4, 5]. If the patient presents with significant hypoxia or hypercapnia, an immediate cause should be identified.

Early hypoxia in the trauma patient could be caused by endotracheal tube malposition, pneumothorax, pulmonary contusions, pulmonary embolism, or transfusion-related lung injury (TRALI) [6]. The underlying cause should be addressed, but adjuncts including increasing the inspired oxygen concentration or increasing the PEEP on the ventilator can be used.

Hypoventilation and hypercapnia can result from oversedation and depressed respiratory rate, inadequate pain control causing splinting and decline in tidal volumes, or a central cord injury with denervation of the muscles of respiration. In both the non-intubated and intubated patients, the initial response should be directed at correcting the underlying cause. If the severity of the injury leading to the hypoventilation cannot be overcome in the non-intubated patient, then ventilatory support in the form of BiPAP or intubation must be considered.

Circulation

Initial assessment of circulation involves assessment of circulating blood volume, cardiac function, and vascular tone. Continuous ECG monitoring and an initial blood pressure should be obtained on admission to the intensive care unit. All trauma patients do not require invasive blood pressure monitoring, but an arterial line can be useful as monitoring adjunct in the patient with abnormal hemodynamics or the patient who will have frequent blood draws.

Adequate vascular access should be ensured. Two 18 g or larger intravenous lines should be used. If this is not possible, then central vascular access should be obtained. In patients requiring ongoing blood product resuscitation, this should be a high-volume cordis line and not a long triple-lumen catheter. Any central line access placed emergently in the trauma bay should be considered for removal and new placement within 24 h [7]. These trauma lines should not be changed over a wire. If intraosseous lines were used for emergency access in the patient, they should be removed and more stable access obtained within the first 24 h [7].

Any derangement in heart rate or blood pressure should be thought to be secondary to hypovolemic shock and ongoing hemorrhage until proven otherwise. Even in patients with normal vital signs but presenting to the ICU with new agitation or mental status changes, a high suspicion for bleeding must be maintained.

Ongoing bleeding when present should be corrected surgically, either by returning to the OR or by bedside procedures if possible. On occasion the trauma patient is brought from the OR after a damage control procedure and remains cold and coagulopathic. Although the transfusion trigger for most chronic ICU patients is hemoglobin level of <7.0 g/dL, this does not apply to the trauma patient in the active resuscitation phase. In the immediate aftermath of hemorrhage, hemoglobin levels may be normal as equilibration has not occurred and the hemoglobin and hematocrit levels have not declined yet. In

the acute setting, it is imperative to continue with a hemostatic resuscitation of blood products in a 1:1:1 ratio [8, 9]. Early administration of FFP and platelets, within the first 3 h after injury, has been shown to improve survival [10–12]. Patients may also have been given TXA (tranexamic acid) as part of a massive transfusion protocol. This is typically given as a one-time dose of 1 g followed by another 1 g given over 8 h [13, 14]. Massive transfusion is defined as transfusion of greater than ten units of pRBC [15, 16]. Many centers now have a massive transfusion protocol (MTP) in place that streamlines the delivery of blood products by providing them from the blood bank in a fixed ratio in continual fashion until the MTP is turned off. Much of this comes from the concept of damage control resuscitation that arose out of the military experience and involves permissive hypotension prior to surgical control of bleeding, 1:1:1 resuscitation with packed red blood cells (pRBC)/fresh frozen plasma (FFP)/platelets along with limiting total crystalloid infusion [17, 18]. Implementation of this technique hopefully allows for avoidance of acute trauma coagulopathy. Clearly a marker of injury severity, once a patient has received over 20 units of pRBC during the resuscitation, their risk of mortality increases to 50 % [19]. There is no cutoff point for the number of blood transfusions during the first 24 h above which 100 % fatality is seen and further transfusion would be futile [20, 21].

If hypovolemia and hemorrhage are not the cause of the patient's hemodynamic derangements, then the presence of other shock states including cardiogenic, obstructive, and distributive is assessed. Cardiogenic shock may result from myocardial ischemia or blunt cardiac injury. Blunt cardiac injury (BCI) will rarely cause hemodynamic instability and arrhythmias are more common. Any patient with blunt force mechanism to the sternum should be suspected to have sustained a BCI. These patients should have an electrocardiogram (ECG) performed and be monitored with continuous ECG. If the ECG and troponin are negative, then BCI can be effectively ruled out [22]. Right ventricular dysfunction may result from BCI and is responsive to volume infusion and ionotropic support if needed. Myocardial ischemia or new valvular dysfunction requires immediate attention. The continuous ECG monitor is insensitive to ST segment changes, and a 12-lead ECG better delineates changes suggestive of ischemia. Troponins and cardiac enzymes further aid in the diagnosis. A bedside cardiac ultrasound performed by the ICU provider rapidly assesses for ventricular function, valvular competence, filling, and volume status [23]. Abnormalities discovered, especially from ventricular function and valvular disease, are rapidly addressed, and a confirmatory formal cardiac transthoracic echocardiogram is obtained.

Obstructive shock can be secondary to cardiac tamponade or tension pneumothorax. Chest x-ray, focused transthoracic cardiac ultrasound, and clinical exam can point to these as causes for the shock state. Distributive shock in the trauma patient is frequently secondary to neurogenic shock from a high spinal cord injury. Septic shock on presentation is rare in the trauma patient but should be considered as mortality is directly related to timing of broad spectrum antibiotics and source control [24]. The severely injured multisystem trauma patient may present with systemic inflammatory response syndrome (SIRS) not secondary to infection but to the pro-inflammatory state induced by the multisystem trauma [25].

There are several endpoints of resuscitation that may be used to guide treatment in the trauma patient. Standard hemodynamic parameters such as heart rate and blood pressure do not adequately quantify the physiologic deficit in trauma patients. Base deficit and serum lactate concentrations from an arterial blood gas analysis can identify patients in need of ongoing resuscitation. Persistent elevations in lactate or base deficit could indicate ongoing hemorrhage or other complication [1].

Disability

The initial assessment of the patient in the ICU involves obtaining a GCS (Table 33.1) and a quick neurologic assessment including pupillary reflex and motor and sensory exam. Pupils are assessed for size, symmetry, and reactivity. Motor examination involves assessment of strength and movement in both the upper and lower extremities. Evaluation of sensory deficits and levels becomes especially important in patients with suspected spine injuries. The motor and sensory exam should be obtained if possible prior to the administration of medications that could impede the ability to obtain a reliable exam. Any new depression or change in mental status in a patient with a known intracranial hemorrhage should prompt rapid evaluation, contact with neurosurgical team, and consideration for repeat head CT [26]. Short-acting sed-

Table 33.1 Glasgow Coma Scale

Eye opening (4)	Spontaneous	4
	To command	3
	To pain	2
	None	1
Verbal response (5)	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible	2
	None	1
Motor response (6)	Follows commands	6
	Localizes to pain	5
	Withdrawals to pain	4
	Flexion (decorticate posturing)	3
	Extension (decerebrate posturing)	2
	None	1
Total		3–15

ative and pain medications are utilized to preserve the ability for a clinical neurologic exam with pause in the medication administration. Throughout the patient ICU course, close communication with the neurosurgical team is essential.

Environment/Exposure

Temperature of the patient is a critical element in the initial assessment. Central temperature monitoring with Foley temperature probe or esophageal temperature probe provides the most accurate assessment. Prevention of hypothermia (<35 °C) is the initial goal for the trauma patient presenting to the ICU. Open abdomens, large burn surface area, and prior exposure all contribute to heat loss. Patients will at times present severely hypothermic (<32 °C). This level of hypothermia results in decreased platelet adhesion, impaired cardiac function from increased systemic vasoconstriction, frequent dysrhythmias from myocardial irritability, and impaired clotting factor function. In patients who have suffered a cardiac arrest that led to their trauma, consider implementing the postarrest hypothermic protocol using 36 °C instead of 34 °C as the goal temperature [27].

A search for unidentified wounds should be undertaken as part of the initial assessment of the trauma patient in the ICU. If wounds are found, they are thoroughly examined and decisions on further workup and closure of the wounds are made. If the wound is in proximity to a joint or fracture site, the possibility of an open fracture or violation of the joint space should be entertained.

Early and Later Stages of ICU Care

Once the initial assessment of the trauma patient is complete, an organ system approach to ICU care for the patient is useful. This is utilized in both the early stage (first 72 h, resuscitation and early support phase) and the later stage (after 72 h, late support and recovery phase) of ICU care. It allows for a complete assessment of the trauma patient and minimizes missing issues that could affect outcome. During this stage of ICU care, the patient will either progress toward recovery and discharge from the ICU, worsen significantly due to complications and multisystem organ dysfunction, or plateau and remain chronically critically ill. Which path the patient takes is dictated by their burden of injury but also by the quality of ICU care they receive.

Neurologic

In the early stage of ICU care of a patient with a neurologic injury from traumatic brain injury (TBI) or spinal cord injury, focus is on prevention of secondary neuronal injury by avoidance of hypotension and hypoxia. Hyperglycemia, hypercarbia, and hyperthermia can also worsen neurologic injury. Minimizing sedative use and narcotics in this early stage allows for a reliably neurologic exam. In patients without a reliable neurologic exam, placement of intracranial pressure monitors or ventriculostomies is often necessary. Close and frequent communication with a consulting neurosurgeon is mandatory.

The guiding principle for care of the patient with TBI is maintenance of cerebral perfusion pressure (CPP). The CPP equals the mean arterial pressure (MAP) minus the intracranial pressure (ICP), CPP = MAP − ICP. To keep the injured brain well perfused, a goal CPP >60 mmHg is maintained through manipulation of ICP or MAP. The goal ICP is <20 mmHg. Maneuvers to decrease ICP include elevation of the head of the bed to greater than 30° to promote drainage of cerebrospinal fluid (CSF) and loosening cervical collar to relieve pressure on the jugular venous system. In the acute setting, hyperventilation can be utilized to decrease ICP through cerebral vasoconstriction. TBI patients should be kept within a normal range for CO_2, 35–40 mmHg, as both persistent hypo- and hypercarbia are detrimental. Mannitol (1 g/kg) or hypertonic saline can both be used for acute ICP elevations. Normothermia can be maintained with acetaminophen and cooling blankets and adequate sedation provided in order to decrease metabolic demand. Phenobarbital-induced coma and paralysis are utilized for refractory ICP elevations until definitive treatment with decompressive craniotomy can be performed. Adequate MAP is essential in patients with TBI. The first step is to ensure euvolemia. Mannitol acts as an osmotic diuretic and can lead to hypovolemia without fluid resuscitation. Once euvolemia is achieved, further fluid resuscitation can be harmful, and vasopressor therapy with an agent such as phenylephrine may be necessary. Phenylephrine has minimal effects on cerebral blood vessels and is the agent of choice to raise MAP in patients with TBI.

Injury to the spinal cord and protection of the cervical spine can significantly complicate the care of injured patient in the ICU. Frequently associated with high thoracic or cervical spinal cord injuries, neurogenic shock is related to loss of sympathetic tone. As in TBI once euvolemia is assured, further fluid resuscitation becomes detrimental. The vasodilation secondary to neurogenic shock can be treated with vasopressors such as phenylephrine or norepinephrine. Cervical spine injury can also lead to decreased cardiac inotropy and chronotropy. Atropine and possibly emergent cardiac pacing in patients with refractory bradycardia may be necessary. In patients with traumatic brain injury or spinal cord injury, hypotension must be avoided.

Cervical spine clearance in the ICU is made more difficult in cases of patient obtundation, agitation, or sedation. Options to clear the cervical spine in persistently obtunded

or comatose patients without the possibility of reliable clinical exam include CT alone, MRI, or simply leaving the collar in place [28]. There is no role for flexion-extension films in clearance of the cervical spine in the obtunded ICU patient. Each institution should develop an agreed upon and adhered to policy for cervical spine clearance in the obtunded patient.

Pain control is important throughout a patient's hospital course from the initial presentation through to discharge and rehabilitation. Pain assessment can best be accomplished with a visual or numerical pain scale. Analgesic medications are chosen based on their onset and duration of action. In the intubated patient, a continuous infusion may be needed.

Most, but not all, intubated patients will require sedative medications. In the early stages of ICU care, propofol can be an excellent medication for this purpose because of its fast onset and clearance. Continuous infusion of propofol is limited by hypertriglyceridemia and the concern for propofol infusion syndrome [29]. Alternative sedative medications may be given such as benzodiazepines. Benzodiazepines are ideally given as intermittent medications but at times a continuous infusion is required. These medications can have a significant volume of distribution and thus take an extended amount of time to wash out of the system after discontinuation. Benzodiazepines may also contribute to ICU delirium, especially in the elderly. Delirium in the trauma patient can be difficult to manage as care is required that patients do not harm themselves and the diagnosis can be clouded by TBI or withdrawal. Delirium management is the same as in other patient populations with discontinuation of possible inciting medications, reorientation, maintaining normal sleep-wake cycles, and judicious use of typical or atypical antipsychotic medications [30].

Withdrawal from alcohol or drugs is a common problem in the trauma population. Over 70 % of trauma patients will present intoxicated [31–33]. Patients who report a significant alcohol or drug use history are also at risk for withdrawal. Withdrawal often does not present until 48–72 h after admission and can be initially masked by administration of propofol and benzodiazepines in the early stage of ICU care.

In the later stage of ICU care, TBI rehabilitation and disposition plans coalesce. Work with physical and occupational therapy begins as early as feasible, and disposition planning is a multispecialty endeavor incorporating input from all of the consulting services, nursing, physical and occupational therapy, and social work.

Pulmonary

The early stage of ICU care for patients with respiratory failure revolves around prevention of secondary complications and diagnosis and treatment of the underlying cause of the respiratory failure. Once immediate issues pertaining to breathing and the pulmonary system are addressed on the initial assessment, attention is directed at mechanical ventilation management with the goal to resolve the underlying cause of the patient's respiratory failure and ventilator liberation. All mechanically ventilated are placed on a ventilator-associated pneumonia prevention bundle (Table 33.2) [34].

Table 33.2 Ventilator-associated pneumonia prevention bundle

Elevation of the head of bed to at least 30°
Daily mouth care with 0.12 % chlorhexidine mouthwash
Stress-related gastrointestinal ulcer disease prophylaxis
Deep venous thrombosis prophylaxis
Daily sedation pause for assessment of readiness to extubate

Hypoxia and possible respiratory failure result from conditions such as pulmonary edema secondary to pulmonary contusions or cardiac failure, aspiration pneumonitis, pneumonia, acute respiratory distress syndrome (ARDS), TRALI, and pulmonary embolism. Pulmonary contusions after blunt torso trauma cause parenchymal cellular destruction and alveolar space flooding with blood and debris. Large contusions may lead to a significant shunt and severe hypoxia. Treatment ranges from noninvasive to aggressive and invasive. Options include elevating PEEP to keep viable alveoli open and frequent pulmonary toilet maneuvers and suctioning to clear large airways. Advanced techniques include independent lung ventilation for unilateral injuries to limit barotrauma to unaffected lung and extracorporeal membrane oxygenation (ECMO). Similar to the flooding of alveolar spaces with blood and debris is pulmonary edema caused by acute fluid overload from aggressive resuscitation or cardiac failure after blunt cardiac injury or myocardial infarction. Transfusion acute cardiac overload (TACO) after large-volume blood transfusion also presents with pulmonary edema. TACO has been shown to occur in around 2 % of ICU patients who have received blood products [35]. Treatment of the pulmonary edema includes optimization of cardiac output with inotropes and possible diuresis to decrease afterload. Consider noninvasive monitoring with devices that measure stroke volume or pulse pressure variation or invasive cardiac output monitoring with a pulmonary artery catheter or bedside continuous transesophageal echocardiography to better optimize fluid status.

ARDS is defined by fluffy infiltrates on chest radiograph, the presence of an inciting event such, and hypoxia. The degree of hypoxia is measured by the PO_2/FIO_2 ratio. Mild ARDS is defined as $PO_2/FIO_2 < 300$, moderate ARDS $PO_2/FIO_2 < 200$, and severe ARDS $PO_2/FIO_2 < 100$ [36]. Trauma patients who have received a massive transfusion or have evidence of aspiration are at particular risk for developing ARDS [37]. Most patients who suffer aspiration have a

chemical pneumonitis and do not require empiric antibiotic therapy [38]. Antibiotics should be reserved for patients who demonstrate a bacterial source for their pneumonia.

Pulmonary embolism (PE) is unlikely during early ICU care, but should be considered in the hypoxic, tachycardic, and tachypneic patient. Patients with intracranial, spinal cord, multiple long bone, or pelvic injuries have been found to have deep venous thrombosis (DVT) rates up to 80 % without chemoprophylaxis and should be started on chemical DVT prophylaxis when injuries permit [Barrera]. While chest radiographs are often normal in appearance, an arterial blood gas may show a respiratory alkalosis with a significant A-a gradient. A 12-lead ECG most commonly is significant for sinus tachycardia and rarely shows the S1 Q3 T3 pattern indicative of right heart strain. A focused transthoracic cardiac ultrasound can be effective at identifying septal bowing, apical right ventricle, and right ventricular dilation, all signs of right heart strain and possibly a large PE [39]. D-dimer determination is unhelpful in the diagnosis of PE in the acutely injured patient. Definitive diagnosis can be made by contrast computed tomography of the chest utilizing a specific pulmonary embolism protocol. Ventilation perfusion scans may be considered in cases where the patient cannot receive IV iodinated contrast material. Initial treatment for PE is anticoagulation with heparin or low-molecular-weight heparin. Although patients reach therapeutic anticoagulation faster on low-molecular-weight heparin, an IV drip of heparin is preferred in the trauma patient at high risk of bleeding as the drip is easily stopped. Inferior vena cava (IVC) filters may be utilized in patients with pulmonary embolus and contraindication to anticoagulation or who develop a PE while therapeutically anticoagulated [40].

Other less frequent causes of hypoxia include fat embolism syndrome and transfusion-related lung injury (TRALI). Fat embolism syndrome most often occurs during manipulation of long bone fractures and femur fixation by intramedullary rodding. Signs include hypoxemia, mental status changes, and upper extremity cutaneous petechiae [41]. The diagnosis is one of exclusion and treatment is largely supportive. TRALI is an uncommon, idiosyncratic reaction to blood transfusion that can cause acute hypoxemia and respiratory failure. The incidence of TRALI in ICU patients receiving blood is 0.5 % [35]. Treatment is directed at stopping the transfusion and respiratory support.

Hypoventilatory respiratory failure results from altered mental status secondary to TBI or over sedation, chest wall injury, spinal cord injury, and intra-abdominal hypertension. For the obtunded or sedated, treatment is aimed at correcting the underlying cause of obtundation, decreasing sedation, or reversing narcotics. Obtundation from narcotics must be balanced with adequate pain control in patients with chest wall injuries. Rib fractures and chest wall contusions often cause significant pain, inhibit respiratory mechanics, and ultimately decrease minute ventilation.

Several methods of pain control are effective at treating chest wall pain. A thoracic epidural containing a local anesthetic, with or without a narcotic additive, has been shown to be effective in improving pain control in patients with chest wall pain from rib fractures [42]. In patients with thoracic narcotic-containing epidurals, it is important to note that epidural narcotics may cause systemic effects including depressed mental status and decreased minute ventilation. Systemic narcotics via a patient-controlled anesthesia (PCA) can also be effective at treating chest wall injury pain but have an even greater risk of mental status and respiratory depression. Local nerve blocks of the intercostal nerves associated with fractured ribs may also provide temporary pain relief [43].

Spinal cord injury above C3–5 obliterates diaphragm function, often necessitating early intubation in the patient with a cord injury at this level. Cord injury in the lower cervical and high thoracic region can also compromise ventilation through loss of accessory muscles such as the intercostals and sternocleidomastoids. This typically presents later in the ICU course that may lead to delayed respiratory failure from a tired, overburdened diaphragm or from increased work of breathing from the now denervated stiff muscles of the chest wall [44]. Exaggerated abdominal breathing is one indication of impending respiratory failure and early controlled intubation is recommended.

Another important consideration in the critically injured patient with hypoventilation is abdominal compartment syndrome (ACS). This constellation of symptoms includes hypotension, oliguria, and increased peak airway pressures. Plateau pressures on the ventilator are often unchanged in ACS. Increased abdominal volume from bleeding, ascites, or bowel edema after an aggressive resuscitation may lead to an increased pressure on the diaphragm and a decreased tidal volume. ACS is relieved by laparotomy and abdominal decompression.

Once the processes driving respiratory failure have been addressed, attention turns to ventilator liberation. Several factors can limit the ability to liberate from the ventilator in the trauma patient. Mental status, either depressed or agitated, can make decreasing ventilator support difficult. Care should be taken in the TBI patient that ventilator liberation will not result in hypercarbia or hypoxia. Increased pain with emergence from sedation and continuous pain medications can impair the ability to take adequate tidal volumes due to splinting.

Cardiovascular

A patient's injuries may result from a motor vehicle collision, fall, or other trauma but the reason for the car crash or the fall is often unknown. A high index of suspicion,

especially in the elderly patient population, of a cardiac cause for the fall should be maintained. A syncope workup includes a careful history and physical exam, ECG, cardiac enzymes, echocardiogram, as well as a review of the patient's medications to discover any potential causes [45]. Close review of a patient's outpatient medications and contact with their primary care provider early in their ICU course aids in the discovery of underlying medical problems and accurate medication dosing. Particular attention is required in the elderly patient population. Pre-existing arrhythmias, hypertension, and myocardial ischemia can complicate the patient ICU course. Patients should be returned to their home medication regimen as soon as possible. The patient's condition and ongoing resuscitation efforts can make this difficult. Remain aware that patients on beta blockade may not mount a tachycardic response to hypovolemia and can cloud the clinical picture.

Certain traumatic injuries require more aggressive blood pressure management. Traumatic aortic disruption in the thoracic aorta is often repaired with a stent graft. In the stable patient, this can be done within the first 48 h after injury [46]. During that time tight heart rate and blood pressure control is mandatory. The target heart rate of <80 bpm can be achieved with beta blockade or an infusion of esmolol or labetalol. The target systolic blood pressure of <120 mmHg is obtained with nicardipine or labetalol in a continuous infusion if needed. Hydralazine, a potent vasodilator, does not allow for the finer control the other agents offer and is not recommended.

Renal/Electrolytes

Acute kidney injury (AKI) is a common occurrence in trauma patients and is best treated with prevention. Estimates of the incidence of AKI in trauma patients range from 6.3 to 27 % and risk factors are listed in Table 33.3 [47]. The traditional division of AKI into pre-, post-, and intrarenal is not a classification system but is useful for thinking about causes. If left uncorrected both prerenal and postrenal AKI will result in intrarenal AKI.

Table 33.3 Risk factors for acute kidney injury

Shock
Sepsis
Age >65 years
Burns
Rhabdomyolysis
Pre-existing chronic kidney injury
Pre-existing cardiovascular disease
Exposure to nephrotoxins: radiocontrast material, aminoglycosides
Abdominal injuries
Need for mechanical ventilation

Prerenal AKI is a consequence of renal hypoperfusion. Maintenance of euvolemia is essential for the prevention of AKI. The early stage of resuscitation of the trauma patient in hemorrhagic colloids in the form of blood products with the minimization of crystalloids has been shown to be beneficial. Once resuscitated maintenance fluids in the form of Ringer's lactate or Plasma-Lyte can be used. Later in the ICU course, care is required to keep up with a patient's losses from the gastrointestinal tract, in the form of stool and naso- or orogastric tube output, wound evaporative losses, as well as losses via a V.A.C. dressing on the abdomen. Once euvolemia is assured, norepinephrine may be used for maintenance of vascular tone and arterial blood pressure as it has been shown to augment renal blood flow [47].

Postrenal AKI results from an obstruction downstream from the renal collecting system. In trauma patients this obstruction usually stems from a blockage of urinary catheter drainage by clot or malposition. External compression, iatrogenic surgical ligature, edema, urethral injury, and intrinsic stricture are other possible causes of postrenal AKI in the trauma patient.

Intrarenal or intrinsic AKI stems from impairment of the renal tubular collecting system. Prolonged renal hypoperfusion due to shock remains the most common cause of intrinsic AKI. Sepsis, rhabdomyolysis, nephrotoxic agents, as well as hyperchloremia from overuse of 0.9 % NaCl also precipitate intrinsic AKI. AKI that occurs in the early stage of ICU care is most likely attributable to the patient's trauma and subsequent hypoperfusion; later onset AKI is more likely secondary to sepsis. Patients who have received intravenous contrast for CT scan as part of the initial trauma workup have a theoretical risk of increased AKI. Some studies have suggested that intravenous contrast from the initial CT scan does not increase the likelihood of developing AKI [48, 49].

Management of new-onset AKI involves maintenance of euvolemia, avoidance of hypervolemia, and cessation of renal toxic agents. Urinalysis, urine electrolyte studies, and examination for urine casts along renal consultation should occur early in the course of AKI. Initiate renal support in the form of hemodialysis or hemofiltration early. Indications for dialysis include acidosis, severe electrolyte abnormalities, volume overload, and uremia. Subclavian access for hemodialysis lines should be avoided to prevent stenosis and preserve future access options.

Electrolyte disorders are common in the ICU trauma patient. Alkalosis, high circulating catecholamine concentrations, hypothermia, use of osmotic or loop diuretics, antifungal medications, and exogenous steroids all cause hypokalemia. Potassium levels are monitored and replaced with intravenous potassium. Hyperkalemia is often secondary to acidosis, rhabdomyolysis or crush injuries, large-volume blood transfusions, or AKI. Hypocalcemia in the

trauma patient is usually caused by dilution or administration of large volumes of citrated pRBC. Calcium chloride, 1 g IV for every four units of pRBC, or close monitoring of ionized calcium levels aids in avoiding hypocalcemia and subsequent cardiac impairment. Refractory hypokalemia or hypocalcemia is often caused by hypomagnesemia. Magnesium levels are monitored regularly and kept within a normal range. Beware of repletion with oral magnesium formulations as these often lead to diarrhea. Adequate phosphate levels are essential for providing a substrate for ATP production. Heightened awareness of phosphate levels around the time of initiation of feeds and the need for replacement helps prevent refeeding syndrome and hypophosphatemia [50].

Gastrointestinal/Nutrition

Begin enteral nutrition as soon as possible in the ICU trauma patient, ideally, within the first 24–36 h [51]. Enteral nutrition is the preferred method of delivery of nutritional support. TPN should be considered only in patients with a long-term contraindication to the use of the gastrointestinal tract for feeding. Critically ill trauma patients should receive 20–25 kcal/kg/day of nutrition. These patients are in a persistent elevated catabolic state with increased protein needs, in the range of 1.5–2.0 g/kg/day of protein. Overfeeding patients does not hasten their recovery but instead increases their risk of complications. Weekly prealbumin, albumin, and c-reactive protein (CRP) are helpful in following nutritional status. In pro-inflammatory states, prealbumin needs to be interpreted with caution. Prealbumin is an anti-acute phase reactant and will be lowered in critically ill patients. Measurement of the CRP allows for better interpretation of prealbumin levels. If the CRP is normal, prealbumin is a more accurate assessment of the patient's nutritional state.

Gastrointestinal prophylaxis against mucosal stress ulceration in the form of H2 blocker is started in all intubated patients. There is no benefit to proton pump inhibitor therapy over H2 blockers. Patients on either a proton pump inhibitor or H2 blocker at home or on steroids in the hospital should continue GI prophylaxis following extubation; all other patients should have it discontinued [52].

Hematology

Deep venous thrombosis (DVT) and venous thromboembolism (VTE) is a major cause of morbidity and mortality for the trauma patient. Several risk factors increase the risk of DVT including spinal cord injury, long bone fractures in severely injured patients, pelvic fractures, and GCS <8 and age >50 years [40]. Weekly surveillance ultrasound for DVT diagnosis increases the ability to detect asymptomatic DVT but does not affect the ability to prevent pulmonary embolism [40]. VTE prophylaxis is essential for every trauma patient. LMWH is the preferred agent for chemoprophylaxis in trauma patients [53]. Patients unable to take LMWH, because of weight, renal function, or injury, may be started on subcutaneous heparin [SQH]. SQH is the agent of choice in patients with intracranial bleeds. SQH as DVT prophylaxis can safely be started in patients with intracranial bleed that have demonstrated stability after 48 h [54].

In patients with documented DVT or PE, therapeutic anticoagulation is indicated. Anticoagulation with subcutaneous LMWH gets patients to therapeutic levels of anticoagulation faster than UFH. Tighter control of anticoagulation in the patient at risk of bleeding or needing to have anticoagulation held is possible with intravenous SQH. If a patient is not a candidate for therapeutic anticoagulation, an inferior vena cava (IVC) filter may be placed. Studies show no benefit of the combination of IVC filter and therapeutic anticoagulation for treatment of DVT or PE [55].

Infectious Disease

Nearly a quarter of all in trauma patients will have some form of infection following their injury [56]. Infections can occur at the site of injury, secondary to surgery or as a healthcare acquired infection (HAI), with pneumonia being the most common HAI in the trauma patient population. Prevention, as in so many other areas, is essential. Debridement of devitalized tissue and cleansing of traumatic wounds and prompt removal of tubes, lines, and drains are important aspects of infection prevention.

Antibiotic prophylaxis can be tailored to fit an array of injury patterns. In penetrating abdominal trauma, antibiotic prophylaxis should begin perioperatively and be completed by 24 h postoperatively. Patients with open abdomens do not require additional antibiotics aside from a single dose of an antibiotic with gram-positive coverage at the time of reoperation. Splenectomy requires vaccination against pneumococcus, *Haemophilus influenza*, and *Neisseria meningitidis* at 2 weeks postoperatively or prior to discharge from the hospital. No good evidence exists, either for or against, antibiotic prophylaxis for chest tube insertion. Prophylaxis is generally not indicated for traumatic wounds unless associated with an open fracture.

Treatment of suspected or documented infections in trauma patients follows the same principles as for other ICU patients. Broad therapy is indicted for early severe infection but should be narrowed as soon as possible based on culture data. Duration of therapy must be tailored to location, organism, and response. Prevention of infection with handwashing, meticulous aseptic technique for procedures, and prompt removal of indwelling devices remain paramount throughout the patient's hospital course.

Endocrine

Glucose control in the trauma patient aids in the prevention of secondary infection. Target glucose concentration is ≤150 mg/dL [56]. At this level of control, the risk of hypoglycemia is lessened and the same benefit as tighter glucose control is achieved. Avoidance of variability in serum glucose levels may be an important factor [57]. Insulin drips offer the tightest control modality and can be used to calculate a daily total insulin requirement in patients on stable nutritional regimen.

Adrenal insufficiency in critically ill trauma patients remains in the differential diagnosis for refractory hypotension, fever, and hyponatremia. If adrenal insufficiency is suspected, a random cortisol may be sent and steroid replacement, 50 mg hydrocortisone IV every 6 h, started. Alternatively hydrocortisone may be started empirically on any patient with escalating vasoactive support of blood pressure [24]. In these circumstances the hydrocortisone should be continued until the vasoactive medications have been weaned to off.

Musculoskeletal

In the trauma patient with multiple injuries, delayed diagnosis of fractures is possible. A thorough and complete tertiary exam with judicious use of imaging can avoid missed fractures. Fracture management involves early restoration of anatomy and function and alleviating pain. In the unstable patient, this can be accomplished with traction or external fixation. Open fractures require operative washout and debridement within 6 h, antibiotic coverage for 48 h after definitive management and stabilization. Open fractures are classified based on the Gustilo and Anderson classification (Table 33.4) [28]. Type IIIb and IIIc fractures may require external fixation for stabilization, while type II and IIIa fractures can be treated with intramedullary nailing.

Pelvic fractures are frequently encountered in the ICU trauma patient. Pelvic disruption can result in 3–4 L of blood loss into the pelvis. Pelvic binding can reduce pelvic volume and decrease bleeding. Binders do not provide mechanical stability and should be taken down every 24 h to assess for pressure necrosis. A blush, or active extravasation, seen on CT scan is an indication for urgent angioembolization of the bleeding vessel in the pelvis [58].

Long bone fractures to the femur and tibia are also frequently seen. Early operative reduction and internal fixation (ORIF) speeds the recovery of patients [59]. If ORIF is delayed because of the patient condition, traction should be applied at the bedside. Knee dislocations have a high incidence of vascular injury to the popliteal artery. Knee dislocations and tibial plateau fractures need to be closely monitored for the possibility of compartment syndrome with a low threshold for four-compartment fasciotomy [59].

Fractures of the long bones or pelvis are associated with fat emboli syndrome. Fat emboli syndrome manifests as respiratory distress, altered mental status, and petechial rash [41]. Fat emboli may occur at the time of injury or during surgical repair of the fractures. The diagnosis is one of exclusion, care is generally supportive, and prognosis for recovery is excellent.

Table 33.4 Gustilo and Anderson classification of open fractures

Type I: low energy, <1 cm wound caused by protrusion of bone or lowed velocity gunshot wound
Type II: moderate energy, >1 cm with flap or avulsion wound in the skin with minimal devitalized soft tissue and minimal contamination
Type III: high energy, extensive soft tissue injury
Type IIIa: adequate soft tissue coverage, no vascular injury
Type IIIb: significant soft tissue loss with exposed bone that requires tissue transfer for coverage
Type IIIc: vascular injury requiring repair for limb preservation

Tubes/Lines and Drains

During the trauma patient's stay in the ICU, particular attention should be paid to tubes, lines, and drains. The guiding principle is to remove any invasive line, central venous catheter, or arterial line, as soon as no longer needed. Intravenous lines placed emergently in the trauma bay should be removed promptly and new access obtained under sterile conditions. Close coordination with the surgical team on management of chest tubes and suction drains is helpful. Chest tubes can often rapidly be progressed to water seal and removed once the output is less than 200 mL a day. The original indication for placement and amount and quality of drainage from intra-abdominal drains needs to be considered prior to their removal. Subcutaneous drains are usually able to be removed once the output is less than 25 mL a day for two consecutive 24 h periods. Urinary catheters are usually removed within 48 h, unless there is an indication for continuous bladder drainage. In patients with genitourinary injuries, the catheter is maintained for longer, and discussion of timing of removal should occur between the ICU, trauma, and consultant teams.

Special Considerations

Damage Control Abdomen

Open abdomen with VAC dressing or other form of abdominal coverage is often encountered as part of damage control procedures. The physiologic state of the patient or overall burden of injury precludes closure at the first operation.

Patients are brought to the ICU for further resuscitation and correction of hypothermia and prevention of coagulopathy. After the first operation, patients may be left in discontinuity or have laparotomy pads remaining in the abdomen. In these cases the patient should return to the OR for a second operation within 24 h [60]. In all cases patients should return to the OR every 48 h until the abdomen is closed [61]. Ideally the fascia is closed by the third operation to avoid complications of the open abdomen [61]. Dynamic fascial closure techniques and optimization of fluid balance with diuresis as tolerated has been shown to improve the likelihood of fascial closure [62].

Transport

Transportation of the ICU trauma patient off of the unit for procedures or studies is a frequent occurrence and one that can be dangerous. Sufficient staff to travel with the patient and robust monitoring during transport can minimize mishaps. Every transport out of the ICU should be assessed from a risk benefit standpoint.

ICU as an OR

Clinical circumstances may dictate that movement of a patient out of the ICU is not feasible. In these cases the ICU can function as an operating room. Laparotomy or removal of a VAC dressing, although more optimally performed in the operating room, may be undertaken in the ICU. An already prepared set of separate supplies facilitates the performance of these urgent procedures. More routine procedures such as percutaneous tracheostomy or endoscopic gastrostomy tube placement may also be performed in the ICU. Again adequate preplanning and equipment are essential for successful completion of any procedure in the ICU.

Family Support/Interaction

It is essential to establish early contact with family members, to fully explain injuries, clinical condition, and prognosis. Open communication provides family members with essential information and establishes a relationship between the ICU care team and the family. Administrative facts, such as ICU procedures, visiting hours, and available services, should also be explained. Locating a living or identifying a healthcare proxy will help guide management decisions, especially in the elderly trauma patient. In the later stages of ICU care, the patient and family are prepared for the transition to a non-ICU environment.

End of Life/Gift of Life

The constellation of a trauma patient's injuries and complications may be nonsurvivable. A prior well-established relationship with the patient and the family facilitates effective communication at the end of life. This period of the patient's care can be highly emotional for family and staff and may be fraught with conflict. Involvement of a palliative care team can be beneficial. Palliative care should be engaged early with patients with severe injuries as the focus on alleviation of suffering for the patient, and support for the family can be utilized throughout the different phases of ICU care.

Discussion of end of life care in the ICU is intertwined with discussions about organ donation. Every patient who dies in the ICU should be afforded the opportunity to be an organ donor. The ICU team should never initiate discussion of donation with a patient's family and friends. When a patient has been identified as a potential donor, contact with the regional organ donation network allows for better coordination of care as well as discussion with family and loved ones about the donation.

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Immunocompromised Patients

34

Judith Anesi and Valerianna Amorosa

Introduction

In this chapter, we will discuss the care of the immunocompromised patient in the surgical ICU. We will specifically review the care of patients who have undergone solid organ transplantation (SOT), stem cell transplantation (SCT), chemotherapy, radiation, chronic corticosteroid therapy, and TNF-α (alpha) inhibitor therapy, as well as the care of patients with HIV/AIDS, chronic hepatitis B virus (HBV), or chronic hepatitis C virus (HCV) infection. These patient populations are among the most profoundly immunocompromised, but it is important to understand that immunosuppression is a spectrum and that patients who do not fall into one of these specific populations may still be significantly immunocompromised, such as patients with diabetes mellitus, chronic kidney disease, or cirrhosis. Unfortunately, there is no measure of degree of immunosuppression or risk of infection, so it is impossible to determine exactly where on the spectrum each patient resides. Studies of the special patient populations that we will address, however, give some insight into the infectious risks of those who are immunosuppressed and can be used to guide the approach to all patients with immunosuppressing conditions.

There are several general principles that apply to the management of all immunocompromised patients:

- Patients who are immunosuppressed may not present with classic symptoms of an infection and may in fact have more vague or mild symptoms than usual due to an inability to mount an inflammatory response [1]. For example, immunocompromised patients with a bowel perforation may not have significant abdominal pain or peritonitis on exam.
- Due to the subtlety of their clinical presentations when an infection is present, any abnormality in an immunocompromised host should be closely scrutinized. In particular, close attention should be paid to examining the skin, mucosa, lymph nodes, catheter entry sites, surgical incisions/wounds, subtle neurologic findings, and any bony/joint abnormalities in these patients.
- Our approach to the initial diagnostic evaluation for infection in immunocompromised hosts is summarized in Table 34.1. As infection can progress more rapidly in these patients, early and aggressive pursuit of a microbiologic diagnosis is critical, and invasive diagnostic procedures are often necessary. Refer to the specific sections on SOT, SCT/chemotherapy, chronic corticosteroid therapy, TNF-α (alpha) inhibitor therapy, HIV/AIDS, and chronic HBV/HCV for further details on our approach to diagnostic evaluation in these populations.
- Infection is not the only cause of fever in immunocompromised patients in the surgical ICU. Other common causes of fever that should also be considered include thrombosis, bleeding, and drug fever, and, in the case of SOT or SCT recipients, allograft rejection and graft-versus-host disease (GVHD).
- Early antibiotic administration in critically ill patients has been shown to confer a survival benefit, so early initiation of broad-spectrum antibiotics in these patients is critical [2, 3]. After 48 h of diagnostic and supportive care, however, antibiotics should be revisited and narrowed as appropriate.
- When an infection is diagnosed, immunosuppression should be reduced to the lowest acceptable level (except in the rare circumstance of a central nervous system infection, where reduction in immunosuppression can result in immune reconstitution inflammatory syndrome that may be dangerous due to a resultant increase in the intracranial pressure).
- Due to the complexity of these patient populations, when an infection is suspected, infectious disease specialists should be involved to help comanage these patients.

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Table 34.1 Initial diagnostic evaluation for immunocompromised hosts in the ICU

Symptoms	Initial evaluation steps
Fever	Two sets of blood cx, urinalysis and urine cx, CXR PA and lateral; further investigation based on localizing signs and symptoms
Respiratory symptoms	CXR PA and lateral
	Sputum sample for gram stain, cx (including *Legionella* cx), ± PCP stain
	Legionella urinary Ag, *S. pneumoniae* Ag
	Respiratory virus PCR panel including human *metapneumovirus*
	Cavitating/nodular lesions: sputum for AFB stain, mycobacterial cx, fungal stain and cx; serum galactomannan, β-D-glucan, cryptococcal antigen, urinary *Histoplasma* antigen → early bronchoscopy
Urinary symptoms	Urinalysis and urine cx
	Renal graft ultrasound if renal transplant recipient
	Hematuria: BK virus PCR on blood, adenovirus PCR on urine
Diarrhea	Stool cx, *C diff* toxin, O+P, adenovirus stool cx, rotavirus Ag, norovirus PCR
Skin rash	Vesicular: HSV/VZV PCR
	Target lesion: Lyme antibody
	Pustular: gram stain and cx
	Necrotic, petechial, any other description: skin biopsy and culture
Headache, altered mental status	CT head
	LP with opening pressure; CSF cell count, glucose, total protein, cytology, gram stain, cx, cryptococcal Ag (blood and CSF), HSV PCR, VZV PCR (hold extra CSF)
	May–Nov: CSF for enterovirus PCR
Leukopenia	CMV PCR, EBV PCR, parvovirus PCR
	Consider urine adenovirus PCR
	In spring/summer: peripheral smear for *Babesia*, *Ehrlichia*, *Anaplasma* if in endemic region
New anemia	Parvovirus PCR
	In spring/summer: peripheral smear for *Babesia*, *Ehrlichia*, *Anaplasma* if in endemic region

Abbreviations: *AFB* acid fast bacilli, *Ag* antigen, *C diff Clostridium difficile*, *CSF* cerebrospinal fluid, *CT* computerized tomography, *CXR* chest x-ray, *cx* culture, *EBV* Epstein-Barr virus, *HSV/VZV* herpes simplex virus/varicella zoster virus, *LP* lumbar puncture, *O+P* ova and parasite, *PA* posterior-anterior, *PCP Pneumocystis jiroveci*, *PCR* polymerase chain reaction

Solid Organ Transplant Recipients

Overview of Infectious Risks and Initial Diagnostic Evaluation

The infectious risks for SOT recipients vary over time posttransplant. In the first month after transplantation, most infections are due to (1) nosocomial infections, such as aspiration pneumonia, ventilator-associated pneumonia, catheter-related bloodstream infection, catheter-related urinary tract infection, and *Clostridium difficile*, or (2) surgical complications, including wound infections, anastomotic leaks, or ischemia of the allograft [1]. SOT recipients are at increased risk for developing these infectious syndromes with multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* species (VRE), multidrug-resistant (MDR) gram-negative rods (GNRs), or azole-resistant *Candida* species, in part due to their hospital exposure [1]. Two other important sources of infection in the first month post-SOT are (1) infection or colonization of the recipient that was untreated prior to transplantation and (2) donor-derived infections. The recipient may be the source if there was unnoticed viremia (with HIV, hepatitis B, or hepatitis C), bacteremia, or fungemia at the time of transplant; latent infection with *Mycobacterium tuberculosis* (TB), *Strongyloides*, and *Trypanosoma cruzi* that reactivates post-SOT; or colonization with *Aspergillus* or *Pseudomonas* (particularly of the lungs) that caused infection posttransplantation [4–10]. Donor-derived infections are typically due to unnoticed active infection of the allograft with bacteria or fungus at the time of transplantation [11–13]. More rarely, recipients can contract viral or parasitic infections via the donor, including herpes simplex virus (HSV), lymphocytic choriomeningitis virus (LCMV), rabies, West Nile virus, HIV, hepatitis B, hepatitis C, *T. cruzi*, or *Strongyloides* [14–19]. Patients rarely develop opportunistic infections (such as *Pneumocystis jiroveci* (PCP) or *cytomegalovirus* (CMV)) during this first month post-SOT.

The initial diagnostic evaluation and management of SOT recipients who are <1 month posttransplantation and have a suspected infection should include removing all vascular and urinary catheters, closely examining all wounds and drain outputs for signs of infection, culturing the blood and urine, obtaining a two-view chest x-ray, checking for *C. difficile*, and imaging of the allograft. The pretransplantation cultures from both the donor and recipient should be reviewed to ensure that the recipient was adequately treated for any organisms that grew on those cultures perioperatively. If the patient does not improve after this standard approach, rare donor-derived infections (such as HSV, LCMV, West Nile, rabies, HIV, hepatitis B, hepatitis C, and *T. cruzi*) should be considered as well.

When SOT recipients are between 1 and 6 months posttransplantation, opportunistic infections and reactivation of latent infections become more common due to the accumulated immunosuppression over the prior months. Prior to the widespread use of PCP and CMV prophylaxis, these organisms typically caused infection during this time period. If a SOT recipient is receiving prophylaxis, however, infection with these organisms is rare [20]. If prophylaxis has been stopped for any reason, then PCP and CMV diseases should be considered [1, 21]. PCP typically presents with fever and

respiratory symptoms including cough, shortness of breath, and hypoxia [22]. A chest x-ray may be unremarkable with PCP infection, but chest CT typically shows ground-glass opacities (though there is no specific radiographic pattern that is pathognomonic) [23]. CMV syndrome typically presents with fatigue and malaise along with leukopenia and/or thrombocytopenia, but it can also cause tissue-invasive disease of nearly any organ including pneumonitis, colitis, hepatitis, nephritis, myocarditis, pancreatitis, and retinitis [24, 25]. CMV disease can also be associated with allograft dysfunction and rejection [26]. Those at highest risk of developing CMV disease are donor/recipient pairs in which the donor was CMV seropositive and the recipient was CMV seronegative prior to transplantation [27]. Of note, CMV prophylaxis also prevents reactivation of other herpesviruses, so if CMV prophylaxis is held, HSV, VZV, and Epstein-Barr virus (EBV) can also reactivate and cause disease. Fungal opportunistic infections can also present during this time frame, including aspergillosis (most commonly with pneumonia) and cryptococcosis (most commonly with meningitis or pneumonia), though most fungal infections occur after 6 months post-SOT [28]. Latent infections can also reactivate and/or disseminate during this time period, including endemic fungi (*Histoplasma*, *Coccidioides*, *Paracoccidioides*, and less frequently *Blastomyces*), TB, *Strongyloides*, *T. cruzi*, BK virus, adenovirus, and hepatitis B (if no antiviral prophylaxis is employed).

The diagnostic evaluation for patients who are between 1 and 6 months post-SOT depends on the clinical presentation, though all such patients should have two sets of blood cultures, a urinalysis, a urine culture, and a two-view chest x-ray performed. Of note, if a patient remains hospitalized for a prolonged period after transplantation or has repeated surgical procedures posttransplant, the early nosocomial or surgical sources of infection may remain relevant as well.

- Respiratory symptoms: A chest x-ray, sputum culture, and respiratory virus polymerase chain reaction (PCR) panel should be obtained immediately, followed by chest computerized tomography (CT) and bronchoscopy if any abnormalities are found on the initial workup. Bronchoscopy specimens should be evaluated by direct microscopy (for PCP primarily), gram stain, and culture including fungal and mycobacterial culture. If there is suspicion for a fungal infection (e.g., nodular opacities on chest CT), then serum galactomannan, β-D-glucan, cryptococcal antigen, and urinary *Histoplasma* antigen can be considered as well. Of note, there are significant limitations to the utility of the galactomannan and β-D-glucan assays in the SOT population, both in terms of sensitivity and specificity, and should not be solely relied upon for making the diagnosis of a fungal infection [29, 30].
- Abdominal pain, vomiting, and diarrhea: A stool sample should be evaluated for ova and parasites (including *Microsporidia* and *Cyclospora*), culture, and *C. difficile*. Abdominal imaging, typically with a CT scan, should also be considered to evaluate for abdominal abscess. If the patient has had relevant exposures, such as travel to a tropical region, then *Strongyloides* should be evaluated for with a stool sample examination for ova and parasites and a *Strongyloides* serum antibody (though serologies can be less reliable post-SOT).
- Headache, neck stiffness, and altered mental status: An urgent lumbar puncture should be performed, and the CSF should be sent for cell counts, glucose, total protein, gram stain, culture, as well as cryptococcal antigen, fungal culture, mycobacterial culture, and HSV PCR. Extra CSF should be held in case further testing is needed, e.g., for VZV PCR, enterovirus PCR, or West Nile Ab testing. Head imaging, typically magnetic resonance imaging (MRI), should also be considered to exclude any mass lesions, and depending on the clinical scenario, CT scan prior to lumbar puncture may be appropriate to assess for cerebral edema or a mass lesion.
- Hematuria: In addition to a urinalysis and urine culture, a BK virus PCR from blood and adenovirus PCR from urine should be considered.
- Skin lesions: In general, any SOT recipient with a new rash should be evaluated by dermatology for a skin biopsy with culture, since bacterial, fungal, and viral pathogens can occasionally present first with skin manifestations when there is an underlying disseminated infection. If the lesions are vesicular, a lesion should be unroofed and sent for HSV/VZV PCR.
- Leukopenia and/or thrombocytopenia: Consider checking a CMV PCR, EBV PCR, and parvovirus PCR from blood, as well as evaluating for tick-borne diseases (with Lyme antibody and a blood smear for *Babesia*, *Ehrlichia*, and *Anaplasma*) if the patient resides in an endemic region.

When an SOT recipient is more than 6 months posttransplantation, the overall risk of infection decreases since immunosuppression is typically tapered over this time [1]. Patients do remain at increased risk for community-acquired infections, however, including community-acquired pneumonia, respiratory viral infections, and urinary tract infections. Although fungal infections can present earlier, they are more common during this time period (including *Aspergillus* and other mold infections), as are opportunistic bacterial infections such as *Nocardia* and *Rhodococcus* (which all predominantly present with respiratory symptoms and cause pulmonary infections) [28]. If CMV or PCP prophylaxis is stopped during this period, then CMV, other herpesviruses, and PCP can present at this time. The initial diagnostic evaluation of patients who are >6 months post-SOT should be largely similar to that for patients who are 1–6 months post-SOT, and we would recommend using the same approach (that is described above) based on the patient's presenting symptoms.

Empiric Therapy

Empiric therapy will depend on the patient's presenting symptoms, but in general, when a SOT recipient presents with an infectious syndrome, broad-spectrum antibiotics (and in some cases antifungals) are used initially and then narrowed based on the results of the diagnostic evaluation. It is of the utmost importance to collect cultures before beginning antibiotics as even one dose of antibiotics can make it difficult to establish a diagnosis. In general, it is recommended to start with an agent that covers gram-positive organisms including MRSA (such as vancomycin, linezolid, or daptomycin) and an agent that covers gram-negative organisms including *Pseudomonas* (such as cefepime or piperacillin-tazobactam). If the patient has a history of infection with drug-resistant organisms, those organisms should be covered as well (e.g., if the patient has a history of VRE, linezolid is preferable to vancomycin, or if a patient has a history of an MDR GNR, a carbapenem is preferable to cefepime or piperacillin-tazobactam). Examples of appropriate empiric regimens are given in Table 34.2; of note, these regimens are appropriate for patients admitted to a surgical ICU and may not be appropriate for patients who are less ill and not in the ICU.

Table 34.2 Empiric antimicrobial therapy for SOT recipients admitted to the ICU

Time post-SOT	Empiric antimicrobial therapy
<1 month	Vancomycin plus [cefepime or piperacillin-tazobactam]
	Ensure donor and recipient prior culture growth is covered
	If diarrhea present, consider PO vancomycin
	If influenza season, add oseltamivir
	If PNA symptoms, add azithromycin
	If recent abdominal surgery or on chronic TPN, consider antifungal (echinocandin or fluconazole)
	Would not empirically treat CMV or mold
>1 month	Vancomycin plus [cefepime or piperacillin-tazobactam]
	Ensure donor and recipient prior culture growth is covered
	If diarrhea present, consider PO vancomycin
	If influenza season, add oseltamivir
	If PNA symptoms, add azithromycin
	If PNA symptoms and not on PCP ppx, consider adding trimethoprim/sulfamethoxazole and prednisone
	If recent abdominal surgery or on chronic TPN, consider antifungal (echinocandin or fluconazole)
	Would not empirically treat CMV, *Aspergillus*, other molds

Abbreviations: *CMV* cytomegalovirus, *ICU* intensive care unit, *PCP P. jiroveci*, *PNA* pneumonia, *PO* oral, *SOT* solid organ transplantation, *TPN* total parenteral nutrition

Chemotherapy, Radiation, and Stem Cell Transplant Recipients

Among patients who have received treatment for malignancy, there is a wide spectrum of immunosuppression and risk for infection. The presence of cancer itself is likely immunosuppressing, and the treatment of the malignancy contributes further to a patient's immunosuppression [31]. Patients with solid tumors (e.g., breast cancer, colon cancer) who have been treated with surgery, radiation, and/or chemotherapy are considered less immunocompromised than those who have a hematologic malignancy (lymphoma, leukemia), since the degree and duration of neutropenia are typically much greater in those with a hematologic malignancy. Patients with a solid tumor who are not neutropenic should be approached similarly to the normal host, except that specific attention should be paid to the location of the tumor when looking for a source of infection, as his/her anatomy is often disrupted in that area, due to the tumor itself, surgery to remove the tumor, or radiation that may have occurred there. In patients who have undergone radiation, tissue destruction causes chronic dysfunction of the venous and lymphatic drainage in the region, which puts them at risk for infection at the site of the prior radiation [32, 33]. Part of the initial evaluation for infection should include examination and imaging of the radiation field.

Patients with a solid malignancy who are neutropenic due to chemotherapy and those with a hematologic malignancy should be approached somewhat differently than the normal host when infection is suspected, due to their increased degree of immunosuppression. The patients considered most immunosuppressed with the highest risk for infection are those with a hematologic malignancy who have undergone chemotherapy as well as SCT. We will review in detail now the approach to patients who are neutropenic and those who have undergone stem cell transplantation.

Neutropenic Patients

Overview of Infectious Risks

Patients who are neutropenic due to either a hematologic malignancy or chemotherapy are at increased risk for infection. Neutropenia in this setting is defined as an absolute neutrophil count (ANC) less than 500 cells/microliter (mL) (where the ANC is equal to the total WBC count multiplied by the percentage of neutrophils). Though all patients with an ANC <500 cells/mL are at risk for infection, those who are expected to have neutropenia for <7 days are generally considered lower risk; most patients with solid tumors fall into this group [34]. Patients who are expected to have neutropenia for >7 days or who have evidence of hepatic or renal dysfunction in addition to neutropenia are considered at

higher risk [34]. When evaluating neutropenic fever, a fever is defined as a single temperature ≥38.3 °C (101 °F) or a temperature ≥38.0 °C (100.4 °F) sustained for over an hour.

Though 10–50 % of patients with solid tumors and over 80 % of patients with hematologic malignancies will develop fever during an episode of neutropenia, most (70–80 %) never have a specific source of fever identified during the diagnostic evaluation [35]. When a specific source is identified, the majority of infections are due to endogenous flora. Coagulase-negative *staphylococci* are the most commonly isolated organisms from bloodstream isolates, which is thought to be due to the high prevalence of indwelling venous catheters in this population [36]. There has, however, been an increase in the number of drug-resistant gram-negative bacteria observed as the source of infection in these patients over the last several years [37, 38].

During the first week of neutropenia, most infections are caused by bacterial pathogens. After 7 days of neutropenia, fungal etiologies are possible, predominantly with *Candida* species. Candidiasis in these patients is typically due to mucosal infection (e.g., thrush) followed by mucosal breakdown that results in candidemia [39]. After about 10–15 days of neutropenia, molds such as *Aspergillus* become more common; they are rarely involved prior to 10–14 days of neutropenia [40, 41]. Aspergillosis predominantly causes sinus or pulmonary disease in these patients.

Initial Diagnostic Evaluation

When a patient with neutropenia develops a fever, at least two sets of blood cultures should be drawn, along with a urinalysis, a urine culture, and a two-view chest x-ray. If the patient has abdominal symptoms, a CT of the abdomen/pelvis is recommended to evaluate for neutropenic enterocolitis (or typhlitis) or intra-abdominal abscess, as well as a stool *C. difficile* assay. If there are pulmonary symptoms, then a respiratory virus PCR panel should be sent along with sputum culture. It is also reasonable to consider a CT scan of the chest to evaluate for possible pulmonary fungal infection, as this typically presents with small nodular lesions that may be difficult to appreciate on chest x-ray. A CT of the chest to evaluate for fungal infection is also reasonable in neutropenic patients who have been febrile with no clear etiology for more than 4–7 days despite antibiotic therapy, again to look for a fungal process. In those cases where fungal infection is suspected, it is also appropriate to check serum galactomannan and β-D-glucan assays, which are antigen tests for fungal infections. The galactomannan assay is specific for *Aspergillus*, while the β-D-glucan assay can be positive in the setting of *Candida*, *Aspergillus*, *Pneumocystis*, and *Fusarium* infection [42–44]. If a patient has been neutropenic for over 2 weeks and reports any sinus symptoms, then a CT of the face and endoscopic evaluation of the sinuses should be pursued to evaluate for a fungal sinus infection, including mucormycosis.

Empiric Therapy

Neutropenic fever is a medical emergency due to the rapid progression of infection seen in these patients. Initial antibiotic therapy should include at least an antipseudomonal β-lactam, such as cefepime or piperacillin-tazobactam, which should be initiated within 2 h of symptoms [45–47]. Pseudomonal coverage is recommended due to the high mortality associated with pseudomonal infections among neutropenic patients. In the setting of a penicillin allergy, aztreonam can be substituted often alongside an antipseudomonal aminoglycoside such as tobramycin. Gram-positive coverage is not a routine piece of empiric therapy, unless there is specific concern for catheter-related bloodstream infection, skin/soft tissue infection, or pneumonia. In cases where gram-positive coverage is needed, vancomycin, linezolid, or daptomycin can be added (to include MRSA coverage). The patient's prior cultures should also be reviewed to ensure there is not a history of drug-resistant organisms, for example, VRE or MDR GNRs; if a history of resistant organisms is found, the initial antibiotic therapy should cover those MDR organisms as well. If a patient has been neutropenic and febrile for more than 4–7 days despite antibiotic therapy, then consideration should be given to adding an antifungal agent with Aspergillus coverage (an echinocandin or voriconazole) [48].

Stem Cell Transplantation Recipients

Overview of Infectious Risks and Initial Diagnostic Evaluation

The infectious complications after SCT vary over time posttransplantation. At all time points, however, SCT recipients are more likely to develop infection if they are older, underwent allogeneic SCT, underwent myeloablative conditioning (as opposed to reduced intensity chemotherapy), had an unrelated or mismatched donor at transplantation, underwent T-cell depletion, have graft failure, or have developed GVHD [49].

During the first 30 days post-SCT, before the donor stem cells have engrafted and repopulated the immune system (the "pre-engraftment" period), patients are neutropenic and suffer from similar complications as described above for other neutropenic patients. Many will develop fevers during neutropenia, with similar etiologies as above. The diagnostic evaluation should follow the recommendations given for all neutropenic patients.

Following engraftment, from about day 30 through day 100 post-SCT (the "early post-engraftment" period), patients become at risk for opportunistic infections. The major risk factors for infection during this period include GVHD (and its treatment), residual mucositis, and any ongoing neutropenia. The infections to consider during this time period depend on the presenting symptoms:

- Respiratory symptoms: In addition to routine bacterial and viral causes, pulmonary fungal infections should be considered. Aspergillosis becomes more common during this time period. In addition, if a patient is not on prophylaxis, then PCP and CMV disease can present during this time period [50, 51]. In general, if there are nodular opacities on chest imaging then *Aspergillus* and other molds should be considered; if there are ground-glass opacities on chest imaging, then PCP and CMV should be considered. Initial workup should include a respiratory viral PCR panel, sputum culture, and CT scan of the chest. If there is concern for fungal pneumonia based on the chest imaging, then galactomannan and β-D-glucan from blood should be checked. In many cases, bronchoscopy will be necessary to make a microbiologic diagnosis; gram stain, aerobic/anaerobic culture, fungal culture, mycobacterial culture, and direct microscopy should be performed on the bronchoscopy specimens.
- Abdominal pain and diarrhea: In addition to routine infections (such as *C. difficile* colitis), patients should also be evaluated for CMV and adenovirus infection. If there is significant abdominal pain, a CT of the abdomen/pelvis should be considered along with a *C. difficile* assay, CMV serum PCR, adenovirus culture of stool, and colonoscopy for biopsy to evaluate for viral etiologies via histopathology.
- Hepatitis: Though an elevation in serum AST and ALT can have many causes in SCT recipients (including drug toxicities), hepatitis viruses, other viruses (including CMV, EBV, HHV6, and adenovirus), and disseminated candidiasis (hepatosplenic candidiasis) should be considered. CMV, EBV, and HHV6 can be investigated through serum PCR levels, and candidiasis can be evaluated with CT imaging of the abdomen/pelvis and blood cultures.
- Hematuria: In addition to checking a urinalysis and urine culture, patients with hematuria should also be evaluated for BK virus and adenovirus infection, which can both cause hemorrhagic cystitis [52, 53]. BK virus can be evaluated with a serum PCR level, and adenovirus can be evaluated with a urine PCR.
- Altered mental status and headache: Viral etiologies should be considered, including HSV, VZV, CMV, HHV6, EBV, and JC virus. In order to evaluate for these etiologies, lumbar puncture will be necessary. The CSF should be sent for cell counts, total protein, glucose, aerobic/anaerobic culture, fungal culture, mycobacterial culture, HSV PCR, VZV PCR, CMV PCR, EBV PCR, and HHV6 PCR. Head imaging (typically an MRI) should also be pursued.

After day 100 post-SCT (the "late post-engraftment" period), immunosuppression is typically weaned and risk for infection decreases. Of note, however, the risk for infection in SCT recipients is not limited to the period of neutropenia; it takes 6–12 months in autologous SCT recipients and 12–24 months in allogeneic SCT recipients to recover B- and T-cell immune functions, during which period they remain at increased risk for infection [49]. Infectious complications during this time period are most commonly seen in patients with GVHD requiring treatment, high-risk CMV donor/recipient pairs (CMV donor seronegative, recipient seropositive), and those who underwent myeloablative or radiation-based conditioning regimens. Among patients who are over 100 days post-SCT, the infectious considerations vary based on presenting symptoms:

- Respiratory symptoms: The etiologies and initial workup are similar to those in the early post-engraftment period. Bacterial and viral causes remain most common, but fungal etiologies (including *Aspergillus*, agents of mucormycosis, and PCP) continue to be possible. In addition, pneumonia due to *Streptococcus pneumoniae*, *Nocardia*, and mycobacteria are increased in this population especially in those receiving treatment for GVHD [54–58]. Initial evaluation is similar to those in the early post-engraftment period.
- Skin lesions: Depending on the presentation, a variety of infectious etiologies can present with skin lesions. If there are nodular skin lesions, fungal and mycobacterial causes should be considered. Vesicles and ulcers are most likely due to herpesvirus (HSV, VZV). In both of these cases, the skin lesions may represent a disseminated infection, so any new skin lesion should be evaluated by dermatology, and a skin biopsy and culture should be performed.
- Encephalitis and meningitis: The viral pathogens mentioned above for the early post-engraftment period remain relevant during this time period. In addition, infection with *Listeria monocytogenes* and *Cryptococcus* can occur during this later period and present with symptoms of meningitis [59]. The diagnostic evaluation is similar to that in the early post-engraftment period.
- Abdominal pain/diarrhea, hepatitis, and hematuria: Infectious etiologies and evaluation are similar to those recommended in the section on the early post-engraftment period.

Empiric Therapy

Initial antimicrobial therapy in SCT recipients will depend on the time post-SCT and the patient's presenting symptoms. In general, given how quickly infection can progress in these patients, it is recommended to begin with broad-spectrum antimicrobials while the diagnostic evaluation is being completed. The empiric regimens listed in Table 34.3 are appropriate for patients who have been admitted to a surgical ICU and are critically ill and may not be appropriate for patients who are less ill.

Table 34.3 Empiric antimicrobial therapy for SCT recipients admitted to the ICU

Time post-SCT	Empiric therapy if admitted to surgical ICU
<30 days	Antipseudomonal β-lactam (e.g., cefepime or piperacillin-tazobactam)
Pre-engraftment	Ensure patient's prior culture growth is covered
	If concern for pneumonia, CLABSI, skin/soft tissue infection, add MRSA coverage (vancomycin, linezolid, or daptomycin)
	If diarrhea present, consider PO vancomycin
	If influenza season, add oseltamivir
	If febrile >7 days, consider empiric antifungal (echinocandin or voriconazole)
30–100 days	Vancomycin plus [cefepime or piperacillin-tazobactam]
Early post-engraftment period	Ensure patient's prior culture growth is covered
	If diarrhea present, consider PO vancomycin
	If influenza season, add oseltamivir
	If respiratory symptoms, add azithromycin and consider empiric voriconazole for *Aspergillus* and/or trimethoprim-sulfamethoxazole for PCP depending on chest imaging
	If encephalitis symptoms, consider acyclovir IV
>100 days	See early post-engraftment period
Late post-engraftment period	

Abbreviations: *CLABSI* central line-associated bloodstream infection, *IV* intravenous, *MRSA* methicillin-resistant *Staphylococcus aureus*, *PO* oral

Patients Receiving Chronic Corticosteroids

Overview of Infectious Risks

The infectious risks associated with chronic corticosteroid use are dose dependent. The most important factor is the current or recent dose of corticosteroid (with a higher dose being associated with increased infectious risk), but it may be that the cumulative lifetime dose of corticosteroid is also associated with a proportional increase in infectious risk [60, 61].

Chronic systemic corticosteroids can increase the risk of common bacterial, viral, and fungal infections. In particular, among viruses, chronic corticosteroids have been associated with increased rates of reactivation of herpesviruses. Most notably, even low-dose corticosteroids have been associated with increased rates of VZV reactivation causing shingles [62]. Among bacteria, in addition to common pathogens (e.g., *S. aureus*), chronic corticosteroid use has been associated with increased rates of TB infection [63]. Patients taking prednisone 15 mg daily or more for 1 month or longer are at increased risk for TB [64]. There has also been an association found between inhaled glucocorticoids and increased rates of TB [65]. Among fungal pathogens, chronic corticosteroids have been associated with increased rates of candidal infections as well as PCP [66, 67]. Although not clearly delineated, it is thought that the risk of PCP is highest in those on a dose of prednisone 20 mg daily or greater for 2 weeks or longer [66]. Finally, corticosteroid use has also been associated with reactivation of the parasite *Strongyloides* [68, 69]; there is specifically an increased risk of *Strongyloides* hyperinfection syndrome where the parasite disseminates from the gastrointestinal (GI) tract to the lungs, liver, heart, and CNS and can cause pneumonia, meningitis, and gram-negative rod bacteremia due to compromise of the GI tract. Even short courses of corticosteroids of 6–17 days have led to hyperinfection and death [70].

Initial Diagnostic Evaluation

In patients on chronic corticosteroids who present with an infectious syndrome, standard evaluation should include two sets of blood cultures, a urinalysis, a urine culture, and a two-view chest x-ray. If the patient presents with respiratory symptoms and has not been on PCP prophylaxis, then PCP should be considered. This diagnosis can be pursued through bronchoscopy with direct microscopy of the clinical specimens. If the chest imaging shows upper lobe disease, TB reactivation should be considered. In this case, the patient should have sputa sent for AFB smear and mycobacterial culture. If the patient is from an endemic area, *Strongyloides* should be considered as well and should be evaluated with a *Strongyloides* antibody test and stool ova and parasites. *Strongyloides* should also be considered when a patient on chronic corticosteroids from an endemic area presents with unprecipitated gram-negative rod bacteremia or meningitis. If a patient on chronic corticosteroids presents with a new rash that is vesicular, consideration should be given to the diagnosis of VZV or other herpesviruses; this can be confirmed through unroofing a vesicle and sending a viral PCR on the vesicle fluid, though empiric treatment can be initiated without confirmation of the diagnosis via PCR if the presentation is consistent with HSV/VZV infection.

Empiric Therapy

In a patient on chronic corticosteroids who is admitted to the surgical ICU, standard broad-spectrum antibiotics that cover gram-positive organisms including MRSA and gram-negative organisms including *Pseudomonas* should be used empirically (such as vancomycin and cefepime). These

antibiotics should then be scaled back and narrowed based on the results of the diagnostic evaluation. If the patient presents with severe respiratory disease, it is reasonable to start empiric PCP therapy with trimethoprim/sulfamethoxazole and prednisone. If the patient has upper lobe disease concerning for TB and has risk factors for TB, empiric TB therapy (with isoniazid, rifampin, ethambutol, and pyrazinamide) can be considered. If there is concern for disseminated strongyloidiasis, then the patient should be given ivermectin. No empiric therapy is required for viral reactivation and should only be used when there is evidence of a herpetic rash; in that case, acyclovir can be employed.

Patients Receiving TNF-α (Alpha) Inhibitor Therapy

Overview of Infectious Risks

Immunomodulators are being increasingly used across a wide variety of diseases and have been found to increase the risk of infection [71, 72]. Different agents have been associated with different specific infections but there are several infectious concerns that apply to all patients who are on TNF-α (alpha) inhibitors. The risk of infection appears to be highest shortly after initiation of therapy and diminishes over time [73].

In terms of bacterial infections, TNF-α (alpha) inhibitors have been shown to increase the rate of perioperative bacterial infection among patients undergoing an orthopedic procedure [74]. There have also been reports of increased rates of septic arthritis (predominantly due to *S. aureus*), *Listeria* meningitis and bloodstream infections, *Legionella* pneumonia, and mycobacterial infections (including both TB and non-TB mycobacteria) among patients on TNF-α (alpha) inhibitors [75–79]. Of note, TB is more likely to present in a disseminated fashion with extrapulmonary sites involved (rather than just pulmonary infection) in patients on TNF-α (alpha) inhibitor therapy [80, 81]. Due to the increased risk of TB reactivation seen with TNF-α (alpha) inhibitors, patients who are starting this class of therapy should be screened and treated for latent TB infection prior to initiating the TNF-α (alpha) inhibitor [81].

There is less data available about the impact of TNF-α (alpha) inhibitors on viral infections, though they may have deleterious effects on patients with chronic hepatitis B infection; in particular, TNF-α (alpha) inhibitors have been associated with reactivation of hepatitis B [82–85]. Because of this, it is recommended that TNF-α (alpha) inhibitors be avoided in patients with untreated chronic hepatitis B infection and in those with significant liver disease due to hepatitis B or C [86]. There is conflicting data on whether TNF-α (alpha) inhibitors are associated with increased rates of herpes zoster infection, and it is not yet clear if the rate of zoster infection exceeds that of the general population of patients with autoimmune disease [87, 88].

With regard to fungal infections, there has been a link found between TNF-α (alpha) inhibitor use and increased rates of infection. In particular, increased rates of pneumonia due to PCP, *Aspergillus*, and the endemic fungi *Histoplasma* and *Coccidioides* have been reported, as well as increased rates of cryptococcal meningitis [76, 89–91].

Initial Diagnostic Evaluation

When a patient who is receiving TNF-α (alpha) inhibitor therapy is admitted to the surgical ICU with suspected infection, two sets of blood cultures, a urinalysis, a urine culture, and a two-view chest x-ray should be checked. Additional workup will depend on the presenting symptoms:

- Joint pain and new effusion: Arthrocentesis should be performed to evaluate for septic arthritis. The synovial fluid should be sent for cell counts, gram stain, crystal evaluation, and culture.
- Respiratory symptoms: A sputum culture, respiratory virus PCR panel, and chest x-ray should be checked in all such patients. Due to the increased risk for *Legionella*, a urinary *Legionella* antigen should also be sent. If the chest imaging is concerning for TB with granulomatous changes or upper-lobe infiltrates, then sputa should also be sent for AFB smear and mycobacterial culture. If the chest x-ray is relatively normal, then a chest CT should be performed to evaluate for fungal pneumonia (looking for nodular opacities suggestive of *Aspergillus* or ground-glass opacities suggestive of PCP). If the chest CT is concerning for PCP (with ground-glass opacities) or fungal pulmonary infection (with nodules), then bronchoscopy should be performed, and the bronchoscopy specimens should be sent for direct microscopy, gram stain, aerobic/anaerobic culture, mycobacterial culture, and fungal culture.
- Headache, neck stiffness, and altered mental status: An LP should be performed, and the CSF should be sent for cell counts, glucose, total protein, gram stain, aerobic/anaerobic culture, mycobacterial culture, fungal culture, and a cryptococcal antigen assay.
- Hepatitis: With a new elevation in the patient's AST and/or ALT, HBV and HCV serologies as well as viral loads should be sent.

Empiric Therapy

Empiric therapy for patients on TNF-α (alpha) inhibitors admitted to the surgical ICU should be similar to those for normal hosts including an agent that covers gram-positive

organisms including MRSA and one that covers gram-negative organisms including *Pseudomonas* (such as vancomycin and cefepime). If the patient presents with respiratory symptoms, it would be reasonable to also include *Legionella* coverage, with azithromycin or a respiratory fluoroquinolone (such as levofloxacin or moxifloxacin). If the chest imaging reveals nodular opacities concerning for fungal pneumonia, then empiric coverage for aspergillosis can be added with voriconazole. If the patient presents with meningitis symptoms, the patient should be given empiric bacterial meningitis coverage with vancomycin and ceftriaxone, as well as *Listeria* coverage with ampicillin, and *Cryptococcus* coverage with amphotericin until the CSF studies are completed.

Patients with HIV/AIDS

Overview of Infectious Risks and Initial Diagnostic Evaluation

The degree of immunosuppression experienced by an HIV-infected patient depends on the degree to which his/her virus is controlled: among those with chronically well-controlled viral replication, the immune system is relatively normal, and they should not be approached any differently than a normal host; among those with uncontrolled viral replication, the immune system may be abnormal, and they may be at risk for opportunistic infections, particularly if the CD4 absolute count is <200 cells/mL or the CD4 percentage is <14 %. In patients with HIV, it is important to know both the CD4 absolute count and the CD4 percentage of lymphocytes, as critical illness can suppress the absolute count, but the percentage will remain stable, and thus the percentage will give a more accurate picture of the patient's degree of immunosuppression. If the CD4 percentage is <14 %, the patient is at risk for opportunistic infections as well as at increased risk for standard bacterial and viral infections. Of note, patients with a CD4 percentage >14 % but uncontrolled viral replication are still at increased risk for several infections, including candidal infections (e.g., thrush), bacterial folliculitis including MRSA infection, and *Streptococcus pneumoniae* infections [92–94].

HIV-infected patients who have a CD4 percentage <14 % are at risk for opportunistic infections that are not commonly seen outside of immunosuppressed hosts. All HIV-infected patients who are admitted to the ICU with suspected infection should have two sets of blood cultures drawn, a urinalysis, a urine culture, and a two-view chest x-ray performed. The additional workup will depend on the presenting symptoms:

- Respiratory symptoms: The patient should be evaluated for PCP in addition to standard causes of pneumonia if his/her CD4 count is <200 cells/mL. Of note, PCP can be present despite a clear chest x-ray. PCP is diagnosed via bronchoscopy and direct microscopy of BAL samples [95, 96].
- Headache and neck pain: Patients with a CD4 count <100 cells/mL who present with neurologic symptoms should be evaluated for toxoplasmosis and cryptococcal meningitis in addition to standard causes of meningitis and encephalitis. Since *Toxoplasma* typically causes a mass lesion, head imaging should be checked first, ideally with a brain MRI. If a lesion is seen, then neurosurgery should be consulted to discuss brain biopsy (to distinguish *Toxoplasma* from CNS lymphoma in some cases). If head imaging is negative, an LP should be performed. In addition to standard studies of the CSF, a cryptococcal antigen assay should be sent from the serum and CSF [97]. Of note, patients with HIV and cryptococcal meningitis may have relatively unremarkable CSF studies (with just an elevated protein or opening pressure). It is critical that the opening pressure be measured and, if elevated, lowered into the normal range via CSF drainage.
- Diarrhea: There are several gastrointestinal protozoans that can cause diarrhea in patients with AIDS. In particular, patients with uncontrolled HIV and diarrhea should be evaluated for *Isospora* (also known as *Cystoisospora*), *Giardia*, and *Cryptosporidium* through stool examination for ova and parasites. Patients with a CD4 <50 cells/mL are also at risk of CMV disease, which can affect almost any organ but particularly the GI tract and CNS (causing colitis and retinitis most commonly). A CMV PCR can be sent from the serum, but in order to establish a diagnosis of CMV colitis, a colonoscopy will be necessary in order to get tissue biopsies for histopathological review. Patients with severe CMV involvement of the GI tract can present rarely with perforation.
- Nonspecific sepsis syndrome: Patients with a severely low CD4 (<50 cells/mL) are at risk for disseminated *Mycobacterium avium complex/intracellulare* (MAC/MAI) infection (in addition to standard causes of sepsis). This is diagnosed by sending a MAC/MAI isolator from the blood [98]. A potential noninfectious etiology for a sepsis syndrome in a patient on antiretroviral therapy with an elevated serum lactate is a lactic acidosis caused by HIV medications (some nucleoside reverse transcriptase inhibitors in particular). If this is suspected, the patient's antiretrovirals should be held. Odd manifestations of syphilis can also occur in HIV-infected persons, and it is reasonable to check a serum RPR in an ill patient with HIV.

For HIV-infected patients in the ICU, it is also important to recognize that HIV-positive patients are at slightly higher risk of hypoadrenalism, so in cases of critical illness, it may be reasonable to use stress-dose corticosteroids while evaluating for hypoadrenalism [99].

Empiric Therapy

HIV-positive patients with controlled viral replication should receive the standard empiric antibiotics for their presenting symptoms. No additional antimicrobials are necessary. In patients with a low CD4 count (e.g., CD4 <200 cells/mL), however, additional empiric antibiotics may be warranted, depending on the presenting symptoms:

- Respiratory symptoms: If there is no clear alternative explanation for the respiratory symptoms, it is reasonable to empirically treat for PCP while awaiting bronchoscopy with trimethoprim/sulfamethoxazole and prednisone.
- Meningitis symptoms: If a patient with AIDS presents with headache, neck pain, and/or altered mental status, he/she should be empirically treated for cryptococcal meningitis (in addition to standard bacterial meningitis) while awaiting CSF results. Empiric therapy should include amphotericin ± flucytosine.
- Nonspecific sepsis syndrome: In addition to standard empiric therapy, it is reasonable to add coverage for disseminated MAC/MAI if the patient has a CD4 count <50 cells/mL with a combination regimen that includes a macrolide.

Outside of these specific scenarios, standard empiric antibiotics can be used while awaiting diagnostic evaluation.

Antiretroviral (ARV) Use in the ICU

When an HIV-positive patient is admitted to the ICU, his/her ARVs ideally should be continued without any missed doses. Of note, ARVs are generally only available in oral formulations, so enteral access is needed in order for them to be continued. If there is no enteral access available, then all of the ARVs should be stopped together. The patient should not be given pieces of the regimen without the entire regimen as this can cause HIV resistance. If all of the ARVs are stopped at the same time, there is minimal risk of developing resistance [100].

When HIV-positive patients are being started on new medications in the ICU, it is also important to check for drug-drug interactions with their ARV regimen. In particular, patients who are on a protease inhibitor regimen that includes ritonavir or cobicistat may have significant drug interactions [101, 102].

Patients with Chronic Hepatitis B or C Infection

Overview of Infectious Risks

Patients with chronic hepatitis B or C infection may be marginally immunosuppressed, but should generally be approached in a similar fashion to normal hosts. The one caveat to this approach is if the chronic hepatitis infection has resulted in liver cirrhosis, as cirrhosis can cause a moderate degree of immunosuppression and increased risk for infection [103]. A cirrhotic patient's susceptibility to infection appears to be highest when the cirrhosis is decompensated [104]. The most common source of infection in patients with cirrhosis is spontaneous bacterial peritonitis (SBP), which is typically due to gram-negative organisms [105]. Of note, patients with cirrhosis are also more likely to have urinary tract infections, pneumonias, and bacteremias; they also appear to have a disproportionate number of fungal infections (predominantly due to *Candida* species, though they are also at risk for cryptococcal infection) [105, 106].

Initial Diagnostic Evaluation

When patients with cirrhosis are admitted to the surgical ICU with suspected infection, they should have two sets of blood cultures, a urinalysis, a urine culture, and a two-view chest x-ray performed. In addition, these patients should always have a paracentesis performed to evaluate for SBP regardless of whether the patient reports significant abdominal pain.

Empiric Therapy

When a patient with cirrhosis is admitted to the ICU with suspected infection, broad-spectrum antibiotics should be used initially including an agent that covers gram-positive organisms including MRSA and one that covers gram-negative organisms including *Pseudomonas* (such as vancomycin plus cefepime). If there are no signs of sepsis but the patient presents with GI bleeding, then he/she should be empirically treated with ceftriaxone for 7 days for presumed SBP due to the increased risk for SBP during GI hemorrhage [107]. Given the increased risk for candidal infections, it is also reasonable to empirically cover disseminated candidiasis with an echinocandin or fluconazole in a cirrhotic patient who is critically ill while awaiting diagnostic results.

If a patient is admitted to the ICU while undergoing treatment for hepatitis B or C, those treatments should be continued if at all possible (unless there is a concern that drug toxicity contributed to the patient's illness). The medications are only available in oral formulations, so enteral access will be needed.

Conclusion

In this chapter, we reviewed the care of immunocompromised patients in the surgical ICU, focusing on those in which infection is suspected. We reviewed the management of patients who have undergone solid organ transplantation, stem cell transplantation, chemotherapy, radiation, chronic corticosteroid therapy, and TNF-α

(alpha) inhibitor therapy and those with HIV/AIDS or chronic HBV/HCV. With these patient populations, clinicians need to maintain a high degree of suspicion for infection as they will often not present with classic symptoms, and infection can progress rapidly. In general, there is a broader differential of organisms that can cause illness in these hosts, so careful attention must be paid to their degree of immunosuppression, epidemiologic exposures, and prior infectious history. Comanagement with an infectious disease specialist is recommended.

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Transplantation

35

Adam S. Bodzin and Ronald W. Busuttil

Introduction

The necessity for high-quality intensive care units (ICUs) in abdominal organ transplantation is essential to the outcomes of these patients. In most scenarios, patients undergoing liver transplantation require a stay in the ICU, whereas kidney and pancreas transplant patients' need for ICU care may vary from institution to institution. It must be pointed out that in this era of organ shortage and higher model for end-stage liver disease (MELD) patients undergoing liver transplantation, the ICU is becoming even more critical in the pathway of successful transplants. ICU organization may vary widely, from being run by anesthesiology, surgery, or medical intensivists, but the take-home message does not change. Patients are sicker now more than ever at time of transplant, and exhaustive, detail-oriented critical care is necessary for success.

A brief word should be mentioned that in some centers, fast-tracking patients is feasible in regard to certain patients undergoing liver transplantation. Taner et al. demonstrated that only 1.9 % of patients required admission to the ICU after being fast-tracked to the ward, which is remarkable. The factors affecting ICU admission were MELD at time of transplant, BMI, operative time, transfusion requirements, and age [1, 2]. This is an exciting prospect that may be beneficial to patients and a cost-saving measure, but unfortunately this does not apply to many regions across the country who are often transplanting patients that are in the ICU on life support.

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Cardiovascular

Given that liver transplantation is such a physiological stress on the human body, close attention to blood pressure, volume status, and cardiac performance is crucial in the early postoperative period. An initial electrocardiogram is standard immediately postoperatively to help in determining any arrhythmias and assessing early electrolyte disturbances, which maybe be present when admitted from the operating room.

Furthermore, close attention to perfusion initially is important as the vascular anastomoses are at more risk to have complications when the blood pressure remains low. It should be noted that most patients with cirrhosis have lower systemic vascular resistance (SVR), and their cardiac function is often hyperdynamic at baseline. There is no set pressure at which is needed to perfuse the liver; however, abrupt changes in blood pressure can be detrimental to vascular anastomoses and to the transplanted organ itself. It should be noted that abrupt changes in blood pressure or continued hypotension should be avoided, and prompt repeat lab values must be checked with a high index of suspicion for ongoing hemorrhage. If the patient is not bleeding, the use of vasopressors or inotropes based on SVR and cardiac function should be used. In most cases, for liver transplant patients, norepinephrine and/or vasopressin is first line [3, 4].

As far as cardiac performance, many of these patients undergo placement of a Swan-Ganz catheter prior to the start of liver transplantation, and this can be used in the ICU for monitoring of cardiac function, although their use remains variable between centers. Echocardiography may be used in adjunct or to replace the use of Swan-Ganz catheters when needed. More recently during liver transplantation, uncalibrated arterial pressure waveform analysis was compared with pulmonary artery catheters; however, they did not correlate and thus is not an acceptable alternative of measuring cardiac output during liver transplantation [5].

Volume management of the post-transplant liver recipient is a complex concern, as much of the literature in ICU

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management of volume administration does not support the use of albumin and blood transfusion; however, we must realize that transplant patients are different and must be treated as such. Blood transfusion in the immediate postoperative period can be used slightly more liberally in transplant patients, especially when unclear whether there is ongoing bleeding. The use of albumin postoperatively for volume expansion is used fairly frequently in liver recipients as well, although its benefits remain suspect even in the transplant population [6, 7]. Additionally, it is often acceptable to use crystalloid running maintenance fluids such as 5 % dextrose with either 0.45 % or 0.9 % normal saline. One must take into account the electrolytes including sodium and potassium which may be abnormal in cirrhotic transplant recipients when choosing fluids [8].

Pulmonary

After transplantation, patients should be weaned toward extubation as soon as possible, and this may be done in the operating room. Extubation immediately after liver transplantation has been shown to be safe with no increased risk in reintubation [9–11]. Early extubation in these patients can decrease ventilator-associated pneumonia but also may decrease venous congestion through the liver. The use of positive pressure ventilation may increase the intrathoracic pressure thus decreasing flow from the intrahepatic vena cava. It should be noted, however, that not all patients are amenable to early extubation as many have been admitted in the ICU pretransplant with prolonged and debilitating encephalopathy; thus, each patient should be treated individually. It is not uncommon to have post-transplant oxygenation difficulty that may or may not have been present prior to transplant. This must be worked up using a standard algorithm that one might use for any ICU patient. Oftentimes this may be related to pretransplant volume overload, pleural effusions, iatrogenic pneumothoraxes, ascites, or change in abdominal domain [9].

Acute respiratory distress syndrome (ARDS) and transfusion-related lung injury (TRALI) are other complications that may affect the pulmonary status of transplant recipients. Factors which may influence the development of ARDS are severe reperfusion syndromes, increased blood loss, longer operative time, as well as infectious processes [12]. In severe ARDS, patients should be treated as per standard protocol with high-frequency, low-volume ventilation. The use of increased positive end expiratory pressure (PEEP) should be used with caution as it has been shown to decrease hepatic outflow, increase stasis in the portacaval system, and decrease cardiac output in these patients, but data remains controversial. It has also been shown in one study that flow was not diminished in the hepatic artery, hepatic vein, and portal vein with increased PEEP [13].

Furthermore, it is important to discuss hepatopulmonary syndrome (HPS) as many of these patients suffer from this physiologic burden and even gain exception points for transplant because of it. HPS involves an increased A-a gradient, liver disease, and lastly intrapulmonary vascular dilations. It is usually diagnosed by means of contrast echocardiography with physiology involving functional shunting as well as increased nitric oxide. The treatment begins preoperatively and includes garlic, pentoxifylline, and methylene blue, which may be restarted post-transplant, but the gold standard in therapy is liver transplantation. These patients with the improvement of ICU care have outcomes similar to patients without HPS. In one small series, there has been a reported 64 % 10-year survival after liver transplant for HPS. The quality outcomes following transplant with HPS are accompanied by long intensive care stays and aggressive pulmonary optimization. These patients should be kept volume negative if hemodynamics allow using diuresis and even initiating continuous hemodialysis as necessary along with the addition of supplemental oxygen over long periods of time [14–16].

Assessment of Graft

Post-transplant evaluation of the liver allograft function varies widely among centers with no accepted protocol. Some centers obtain routine ultrasound in the first 24 hours while others only image if clinically applicable. It is important for the surgical team to communicate in detail with the ICU team regarding any concerns they may have, as some grafts may have more tenuous vascular connections than others, which might prompt quicker evaluation and action. Intraoperative variables that increase the rate of primary nonfunction (PNF) and delayed graft function should also be relayed to the ICU and include massive transfusion, reperfusion syndrome, and prolonged warm ischemia time. In addition to communicating regarding technical aspects of the operation, the team should impart information regarding the donor quality and hemodynamic changes in the operating room especially in regard to reperfusion syndrome as these may affect liver enzymes and function in the first few days. When it comes to donor quality, one must recognize that age greater than 60, >30 % macrosteatosis, cold ischemia time >12 h, and donation after cardiac death (DCD) donors are all independent variables that are more associated with PNF [17, 18, 19]. It is important to be cognizant of the current definition of early allograft dysfunction which includes bilirubin >10 mg/dL, INR ≥1.6, and alanine or aspartate aminotransferases >2,000 IU/L all on day 7 [20]. The workup for graft dysfunction and lab abnormalities is complex, and a diagnostic and treatment algorithm is helpful in the management in these critically ill patients (Fig. 35.1).

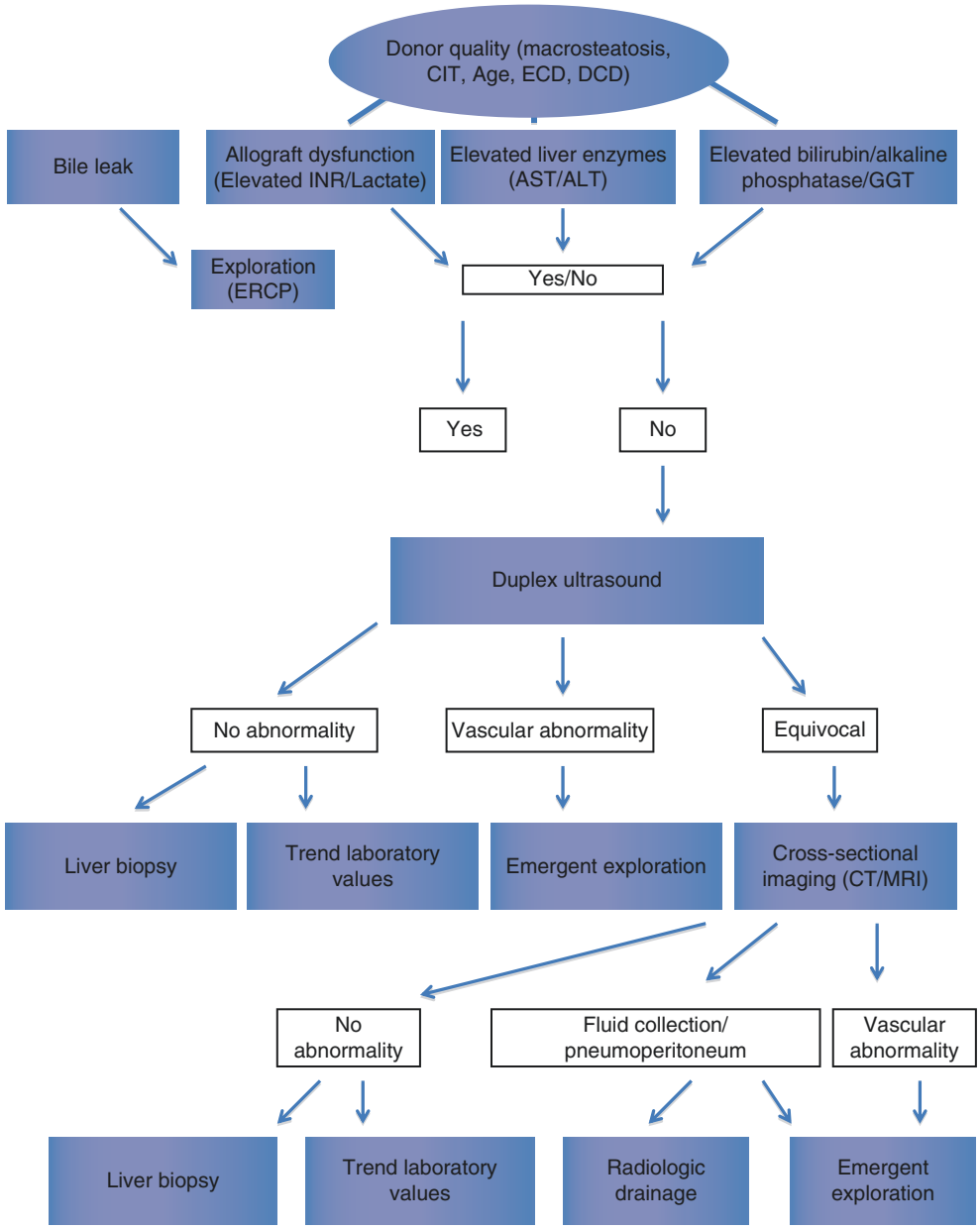

Fig. 35.1 Evaluation and management of allograft dysfunction after liver transplantation. Abbreviations: *CIT* cold ischemia time, *ECD* expanded criteria donor, *DCD* donation after cardiac death, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* gamma glutamyl transferase, *CT* computed tomography, *MRI* magnetic resonance imaging, *ERCP* endoscopic retrograde cholangiopancreatography

Laboratory values are essential in the initial evaluation of the liver allograft; however, timing for drawing these labs may vary. It should be noted that these values will be elevated with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in the thousands at times. These levels are markers of hepatic necrosis, which may rise over the first 24–48 h but should begin to decline as the graft recovers. A graft with a greater ischemia-reperfusion injury, steatosis, or prolonged warm and cold ischemia times may play a role in the trajectory of lab trends which is why communication regarding the donor quality and intraoperative events is crucial in the understanding of lab trends [21].

Synthetic liver function in the early postoperative setting should be evaluated looking at the prothrombin time or international normalized ratio (INR). The INR, which is often elevated preoperatively, should gradually trend down as the liver begins to function and make coagulation factors. Correction of INR with fresh frozen plasma is clinician dependent but most times should be reserved for actively hemorrhaging patients or those with concerns for intracranial hemorrhage. In addition to INR, blood glucose is an important marker as glycogenolysis and gluconeogenesis rely on the new implanted allograft. Furthermore, lactate is an important marker for liver function; however, it can be elevated for a variety of reasons; thus, the entire clinical scenario must be scrutinized to rule out other causes as well [21].

Alkaline phosphatase and bilirubin may be used in the postoperative period to evaluate the excretory function of the

liver; however, they may also be elevated when the liver is injured and undergoing hepatic necrosis. For this reason, isolated increasing bilirubin or alkaline phosphatase should be further assessed as they can also be presenting factors for vascular complications. The half-life of bilirubin is considerably longer than AST and ALT, and its rise and decline may lag behind other lab values. In addition to alkaline phosphatase, γ-glutamyl transferase (GGT) is another canalicular enzyme that can be used to assess biliary obstruction. These two enzymes usually begin their rise postoperative day 4 and can rise well over three times normal, eventually declining [21].

In addition to the labs mentioned above, platelets, PTT, and fibrinogen should be checked serially to correct any ongoing coagulopathy especially in the setting of ongoing bleeding. All transplant physicians have different thresholds regarding correcting continued hemorrhage and coagulopathy; thus, adequate communication between teams continues to be ongoing theme to high-quality comprehensive care.

Imaging

Lab values that do not trend in the direction one might expect in the perioperative period deserve interrogation. The first evaluation in both liver and kidney transplantation is usually a duplex ultrasound of the transplanted graft looking for an array of possible postoperative complications. One might even perform a quick bedside evaluation in the ICU to rule out peri-graft hematoma if suspicious which could cause compression necrosis or even decrease vascular flow to and from the graft placing it at risk for failure. The use of duplex ultrasound should be the standard of care in the ICU for any concerning lab values or graft dysfunction after transplantation. Formal duplex ultrasound can evaluate the inflow of the hepatic artery and portal vein, and outflow via the hepatic veins and inferior vena cava. Ultrasound may also show biliary ductal dilatation or fluid collection, which may prompt further evaluation of the biliary system to rule out obstruction or ongoing bile leak. Ultrasound is a very versatile, quick, noninvasive, and cost-effective means of imaging in the early period and should be used as a screening tool. The use of duplex ultrasound initially after liver transplantation is most often used to rule out hepatic artery thrombosis, which occurs in up to 9 % of the recipients [22]. Normal resistive indices (RIs) are usually between 0.6 and 0.9, but one should always review the ultrasound wave forms as they can be revealing, showing some compromise with normal RIs seen in the report. The intrahepatic arteries must be evaluated in order to be a complete study and if absent should warrant further imaging or exploration if concerned. RIs greater than 0.9 may be due to resistance within the liver, which may be from injury to the liver parenchyma post-reperfusion or edema. The portal flow should be evaluated to rule out portal vein thrombosis looking at velocity, which should be greater than 25 cm/s [21].

If there are troublesome findings on ultrasound, this may prompt further studies and/or interventions. Concerning arterial findings should prompt exploration, arteriography with interventional radiology, or computed tomography (CT) depending on the clinical scenario and timing. CT should be done with contrast, but it is common for these patients to suffer acute kidney injury (AKI) post-transplant, which makes CT or arteriogram less appealing in this setting. MR angiography and venography can also be limited in the setting of AKI due to the risk of nephrogenic systemic fibrosis [23]. Due to the limitations of imaging in the setting of AKI, one might opt to explore the patient, as this is a more definitive means of assessing the vasculature. As for biliary complications, concerning findings might prompt either magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiography. Venography should also be performed when clinically indicated for possible Budd-Chiari syndrome post-transplant. It should be noted that in the early postoperative setting, operative intervention is often the key to success and should not be delayed.

Lastly, if all technical concerns have been ruled out usually over the first 24–48 h of graft dysfunction, one must consider liver biopsy to rule out acute rejection or other sources of graft dysfunction. This may be approached via the transjugular or the percutaneous approach, and the choice may be determined by the patient's clinical status. If the patient has ascites and coagulopathy, transjugular liver biopsy may be more appropriate; however, they remain more costly, require interventional radiology, and yield slightly less tissue as compared to percutaneous biopsies [24].

Renal

Unfortunately current trends are showing that more patients are being transplanted at higher MELD scores oftentimes related to rising creatinine associated with acute or chronic renal failure. More and more patients are being transplanted approaching a need for dialysis or having already begun. Hepatorenal syndrome (HRS) is a common etiology for preoperative renal failure. Diagnostic criteria include the presence of the following: ascites, creatinine >1.5 mg/dL, no improvement of creatinine after 2 days of fluid or albumin challenge with withdrawal diuretics, absence of shock, withdrawal of nephrotoxic medications, and lack of intrinsic renal disease and a normal ultrasound [25]. Roughly 40 % of patients with cirrhosis and ascites will develop HRS. It is caused by a physiologic state that includes, hyper-dynamic cardiac function, decreased SVR, low arterial blood pressure, and renal vasoconstriction [26]. The gold standard treatment for this complication of liver disease is liver trans-

plant as patients with HRS have only slightly worse long-term outcomes after LT than those without it. They do however have a higher incidence of postoperative morbidity, early mortality, and longer length of stay [27].

Renal dysfunction post-transplant may reach 17–95 % in some studies, and some patients will require renal replacement therapy for the first time after transplant, which not surprisingly increases mortality in these patients. Risk factors that have been associated with early ARF are preoperative ARF, MELD, hypoalbuminemia, duration of vasopressor support, and worsened graft function. In addition, other factors that affect the later onset of renal failure include infections, reexploration, and contrast-induced nephropathy, as imaging is common in the postoperative setting. Furthermore, drug-induced tubular injury is also a significant contributor to renal failure in these patients as calcinuerin inhibitors (CNIs) as well as aminoglycosides are commonly used for both immunosuppression and antibiosis, respectively [28]. Treatment of immediate renal failure in the post-transplant setting is multifaceted. Depending on the recipient, lowering or delayed use of CNIs may be the first step, along with management of blood glucose and blood pressure according to standard intensive care protocols. One must also rule out thrombotic microangiopathy, which can be difficult to diagnose etiology for ARF in post-transplant patients. One must recognize a hemolytic anemia and thrombocytopenia to make this diagnosis and initiate plasmapheresis if necessary. BK virus should also be ruled out as a cause of renal dysfunction in patients that undergo kidney transplant as well as simultaneous liver and kidney transplant [29].

Management of renal failure in the post-transplant setting is complicated and requires thoughtful management of nephrotoxic medications and close monitoring of fluid balance. Treatment may include fluids, diuretics, as well as continuous renal replacement and intermittent hemodialysis. Hepatic encephalopathy, MELD score, intraoperative blood loss, and deceased donor graft have all been found to be predictors for need for continuous renal replacement therapy (CRRT) post-transplant. Creatinine has been a marker that has been variable in its reliability since many of these patients have reduced muscle mass, poor protein intake, hyperbilirubinemia, and reduced hepatic synthesis of creatinine. With patients being transplanted at higher MELD scores and more marginal deceased donor grafts being used, the use of CRRT will become more commonplace in ICUs. Unfortunately the use of CRRT post-transplant has been associated with higher mortality [30].

Central Nervous System

Commonly patients undergoing liver transplantation have preoperative hepatic encephalopathy of varying degrees. Those with severe encephalopathy are often unresponsive and ventilated prior to transplant; thus, after transplant, it may take a while for their mental status to return to baseline. It is important to recognize that roughly 8–47 % liver transplant recipients have varying degrees of neurologic complications ranging from continued encephalopathy to seizures and intracranial hemorrhage [8, 31]. Patients with preoperative hepatic encephalopathy have been shown to have less brain volume and decreased cognition post-transplant [32]. In the evaluation of these patients, the clinician must have a host of information starting with preoperative grade of encephalopathy, intraoperative hemodynamics and coagulopathy, and then postoperative neurologic status as well as immunosuppressive levels in order to accurately diagnose and manage these issues. Additionally, patients with acute liver failure must be assessed frequently both before and after transplant given the high risk for cerebral edema and herniation. All treatment of neurological conditions should be done in a team setting with intensivists, neurologists, and neurosurgeons in select cases.

Unfortunately transplant patients are also at higher risk for seizures given the use of calcinuerin inhibitors such as tacrolimus and cyclosporine. Careful attention to seizure history and medications is necessary to avoid such events. Reports have documented up to 5–12 % of patients suffering seizures after undergoing LT. Administration of immunosuppressive agents must be managed with caution in patients suffering postoperative seizures, generally trying to run a lower level of calcinuerin inhibitors [33, 34].

Furthermore, intracranial hemorrhage is a known complication following liver transplant, as these patients are inherently coagulopathic often times with platelets <10 K, INR > 3, and fibrinogen <150. It can often go unnoticed and must be in the differential whenever patients do not wake up after transplantation, suffer focal deficits, or demonstrate changes in mental status. Intraoperative hypotension, massive transfusion, and coagulopathy have been shown to be potential risk factors for intracranial hemorrhage, which is why communication from the operating room to the ICU is imperative. For this reason, often centers will have some preventative transfusion parameters, but they vary from center to center [35, 36].

Sedation is another ICU problem post-transplant, as many of these patients remain encephalopathic; thus, a balance must be determined with pain control being a priority. Midazolam, propofol, fentanyl, morphine, dilaudid, and dexmedetomidine are used most commonly, but careful attention must be paid to renal and hepatic clearance of these drugs as many of these patients suffer from decreased renal function as well as delayed liver allograft function. Much like non-transplant patients, combined ventilator and sedation weaning protocols with daily sedation interruptions should be performed as this has been shown to decrease time on the ventilator, ICU stay, and mortality [37].

Infectious Disease

Diagnoses of post-transplant infections may be difficult and ultimately remain one of the most common causes of post-transplant mortality. It is important to look at temporal relationships when diagnosing infections after any solid organ transplantation, which may include donor-derived infection; thus, knowing donor serologies and cultures is necessary (Table 35.1). With regard to both kidney and liver transplant patients, those undergoing re-transplantation, on the ventilator pre-transplant, and undergoing hemodialysis and the type of biliary anastomosis are all risk factors for increased infectious processes [37–39]. Certain induction agents such as thymoglobulin, often used in kidney transplantation, may increase risk of infection; hence, communication regarding medications given in the operating room is essential.

Immediately after transplantation, the most common infections include superficial site infections (SSIs), urinary tract infections (UTIs), blood-borne infections including those associated with indwelling catheters, as well as pneumonia which are often associated with prolonged intubation both pre- and post-transplantation. Moreover, studies have shown that increased blood loss is associated with increased postoperative infection [40]. Patients in general are given standard perioperative antibiotics through the first 24 hours after surgery unless they have suspected infection at time of transplant or immediately after.

It is essential to recognize that fungal infection in the immediate postoperative period remains more common than in the standard surgical ICU patient as a result of immunosuppression. *Candida albicans* is the most frequently seen postoperative infectious fungal source; however, *Aspergillus fumigatus* must not be overlooked as a source of severe infection for patients in the post-transplant period. Patients with presumed sepsis must be immediately treated empirically, which may include third- or fourth-generation cephalosporins, piperacillin-tazobactam, quinolones, vancomycin, metronidazole, or carbapenems. In addition antifungals should be initiated with azoles such as fluconazole, itraconazole, or voriconazole or caspofungin depending on the degree of instability and suspected source [37].

As these patients remain very immunocompromised, one must be weary of activation of the herpes simplex virus (HSV) as well as cytomegalovirus (CMV) once on immunosuppression. Both these viruses can have a host of presentations and can be quite severe. Whereas HSV might normally cause oral lesions, this might manifest systemically with encephalitis, meningitis, or even hepatitis. CMV can also be a source of colitis, CNS infection, or relatively early liver dysfunction causing hepatitis and should be ruled out in the setting of elevated liver enzymes as well as signs of unsourced infection. Prophylaxis against viral infectious processes again is variable but may include acyclovir, valaciclovir, valganciclovir, and ganciclovir [41]. Clinicians must be mindful of these drugs in the ICU as they may cause neutropenia and may need to be adjusted for this as well as renal impairment.

Other opportunistic infections need to be placed into the differential as immunosuppression may trigger inactive infections including cryptococcous, toxoplasmosis, tuberculosis, histoplasmosis, pneumocystis infections, and coccidiomycosis, which can all be life-threatening. In some cases, these rare infections may present within the first month post-transplant and should be considered if etiology remains unsourced. The clinician must be mindful that many of these infections are endemic to a specific geographic region, which is helpful in the diagnosis. Risk of these infections can be lowered by the use of prophylactic agents fluconazole and trimethoprim-sulfamethoxazole being some of the more common agents used [21, 37].

Immunosuppression

Immunosuppression in transplant patients varies widely as expected with a host of agents used that have evolved dramatically over the years, and the most common classes of medications are described in Table 35.2. CNIs are almost universally used immediately after transplant, and their mechanism of action and pharmacology must be understood

Table 35.1 Infections in the early post-transplant setting

Category	Site/source	Common infections	Time period post-transplant	Common therapy
Bacterial	SSI, UTI, PNA, intra-abdominal abscess, catheter	*S. aureus*, *E. coli*, *Klebsiella*, *Proteus*, *Enterococcus faecalis*	Immediately	Vancomycin, third- and fourth-generation cephalosporins, aminoglycosides, piperacillin-tazobactam, carbapenems
Fungal	Catheter, PNA, UTI	*Candida*, *Aspergillus*,	0–2 months	Fluconazole, caspofungin, amphotericin B,
Viral	Hepatitis, CNS, PNA	HSV, CMV	HSV – immediately CMV – 1 month	aciclovir, valaciclovir
				Ganciclovir, valganciclovir, foscarnet, cidofovir, Cytogam

SSI surgical site infection, *UTI* urinary tract infection, *PNA* pneumonia, *CNS* central nervous system, *HSV* herpes simplex virus, *CMV* cytomegalovirus

in order to safely manage post-transplant patients. This class of medications is usually administered twice daily and includes cyclosporine and tacrolimus both which work similarly yet have slightly different side effect profiles.

Their mechanism of action involves the formation of complexes with cytoplasmic receptor proteins, cyclophilin with cyclosporine, and FK-binding protein 12 with tacrolimus, which then binds with calcineurin ultimately inhibiting the expression of cytokines that usually promote T-cell activation. Subsequently there is a decrease in T-cell proliferation thus diminishing the immune response to the allograft. Based on improved outcomes with regard to rejection, most people are placed on tacrolimus presently. These drugs must be monitored very closely in the early ICU setting post-transplantation as absorption may vary between patients [42, 43].

While managing transplant recipients, it is imperative that one has an understanding of the toxicities of these drugs as they can be life-threatening as they have a narrow therapeutic window [43]. First, nephrotoxicity is one of the most common toxic effects of these drugs. This is a major concern as CNIs are commonly used in the regimen for kidney transplantation. These drugs cause renal vasoconstriction damaging the renal arteriole. This is a reversible effect that is often dose related. In the ICU setting, one might evaluate this effect in terms of a similar picture as to a prerenal scenario. Overtime damage to renal parenchyma can result in end-stage renal disease and ultimately dialysis with the pathologic features of chronic interstitial fibrosis. CNIs may also cause a syndrome similar to thrombotic thrombocytopenic purpura (TTP) called thrombotic microangiopathy, and this may be primarily renal or may be systemic similar to TTP.

Next, these drugs may cause relatively severe hyperkalemia, which may require treatment. Oftentimes these patients may have baseline potassium above 5 mEq/L. The clinical picture is similar to a type IV renal tubular acidosis with a hyperchloremic acidosis. They also cause hypertension which may be present in the early postoperative period. The mechanism for new onset hypertension in these patients is multifactorial including renal vasoconstriction causing sodium retention, decrease in nitric oxide production, and activation of the renin-angiotensin-aldosterone system [44].

Some other side effects include hypertrichosis, alopecia, gingival hyperplasia, and hyperlipidemia. In addition these drugs can damage pancreatic islets, ultimately contributing to new onset or worsening diabetes mellitus. Both drugs may also cause neurotoxicity although it is more commonly seen with tacrolimus use and in some cases require a switch to cyclosporine. Findings may include tremors, headache, insomnia, and seizures and are often dose related, and levels may be adjusted both in the inpatient and outpatient setting with symptoms usually resolving [44, 45].

Lastly when discussing CNIs, it is important to discuss drug interactions as many ICU post-transplant patients are on a host of medications that may alter circulating levels of the drugs. The most common drugs that induce P-450 and may increase CNI levels include a number of calcium channel blockers, the azole family of antifungals that are often used in prophylaxis after transplant, and erythromycin.

Next mycophenolate mofetil (MMF) and mycophenolic acid (MPA) are the second agents used in most solid organ transplants. They only differ in the fact that MMF is the pro-drug of MPA and has a slightly different side effect pro-

Table 35.2 Common immunosuppressive medications: mechanisms, side effect profiles, and major interactions

Class	Drug examples	Mechanism of action	Major side effects	Major interactions
Calcineurin inhibitors	Tacrolimus, cyclosporine	Protein complex binds to calcinuerin inhibiting T-cell proliferation	Nephrotoxicity, neurotoxicity, thrombotic microangiopathy, hyperkalemia, hypertension, hypertrichosis, glucose intolerance, gingival hyperplasia	Azoles (antifungals), calcium channel blockers, erythromycin
Inhibitor of purine synthesis	Mycophenolate mofetil, mycophenolic Acid	Reversible inhibition of IMP dehydrogenase blocking de novo purine synthesis decreasing lymphocyte proliferation	Nausea, diarrhea, leukopenia, anemia, thrombocytopenia	
Corticosteroids	Methylprednisolone, prednisone	Inhibits cytokine production decreasing T-cell activation	Hypokalemia, myopathy, glucose intolerance, hypertension, lymphopenia, cataracts, weight gain, wound healing, cosmetic changes, psychological disturbances	
mTOR inhibitors	Sirolimus, everolimus	Blocks *target of rapamycin* protein inhibiting G1 to S phase of cell cycle and ultimately T-cell proliferation	Wound healing(sirolimus), hepatic artery thrombosis (sirolimus), glucose intolerance, proteinuria,	

IMP inosine-5′-monophosphate

file. MPA is a reversible inhibitor of inosine monophosphate dehydrogenase, which is the rate-limiting enzyme that is involved with production of guanosine nucleotides needed for de novo purine synthesis. This ultimately leads to decreasing proliferation of lymphocytes, as do the CNIs, but by a different mechanism. MPA is enteric coated and differs in GI profile of side effects which are often dose dependent. Diarrhea is the most common effect of these drugs, but patients may also experience nausea, bloating, and colitis. In addition to GI side effects, patients may suffer from leukopenia, anemia, as well as thrombocytopenia. In this setting, dosing must be lowered or the drug may even need to be stopped for a short period to allow recovery of blood counts.

The third class of drugs in the triple-drug regimens is corticosteroids, which have been key to immunosuppression for over 50 years. These drugs block cytokines IL-1, IL-2, IL-3, IL-6, and TNF-α and chemokines, among others. This results in lessened T-cell activation providing its immunosuppressive effect. The side effect profile for corticosteroids includes hypokalemia, myopathy, glucose intolerance, hypertension, lymphopenia, cataracts, hyperlipidemia, wound healing, cosmetic changes, and psychological effects. In the post-transplant setting, psychological effects may be sometimes confused with CNI neurotoxicity and should be carefully evaluated as changes to medications can lead to rejection and graft dysfunction [46].

Another group of drugs called mTOR inhibitors are becoming more commonly used in the current immunosuppressive regimens for renal sparing and neurotoxicity seen with higher dose CNI use. The two most commonly used drugs today are sirolimus and everolimus. The mechanism of action for these drugs are similar to CNIs, in that they bind cytoplasmic-binding proteins, which then interacts with the *target of rapamycin* protein ultimately inhibiting lymphocyte proliferation at G1 to S phase of the cell cycle [44]. The use of mTOR inhibition in liver transplantation for hepatocellular carcinoma remains an attractive option as these drugs have antiproliferative effect as well as dysregulating the mTOR signaling pathway of tumorigenesis [47].

Side effects of mTOR inhibitors differ from CNIs in that the nephrotoxicity is rarely seen when not in combination with CNIs. These drugs do however have an incidence of causing new onset proteinuria, which must be screened for prior to starting these drugs. Wound healing has been shown to be decreased with the use of sirolimus and most of the time should be delayed until after 4–6 weeks post-surgery as it can cause wound dehiscence as well as other wound complications. Much like the other medications mTOR inhibitors can cause glucose intolerance and hyperlipidemia. It is important to note also that hepatic artery thrombosis has been reported in a higher incidence with the use of sirolimus and should be considered when working up graft dysfunction [44].

Conclusion

One can understand the importance of ICU care in transplantation as many factors must be understood in order to safely manage these patients' postoperative course. The graft is sensitive to any insult thus understanding of all facets from hemodynamics to medications is essential in ferrying these people to a successful transplant. The continuing theme in this comprehensive care is communication between the transplant and ICU teams as specific knowledge of the patient and donor can guide treatment plans.

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Intensive Care in Obstetrics

36

Corrina Oxford and Mauricio La Rosa

Introduction

Obstetric patients requiring admission to the intensive care unit (ICU) comprise less than 2 % of the pregnant or postpartum population in the United States [1, 2]. The incidence is between 0.7 and 13.5 per 1,000 deliveries [2]. The care of gravid patients can be challenging, and clinicians must be prepared for management decisions that are in the best interest of the mother while minimizing deleterious effects to the fetus, if possible. Achieving this balance requires a multidisciplinary approach which should include maternal-fetal medicine obstetric specialists. One must have an understanding of the physiologic nuances in pregnancy that inform high-acuity management as well as safety of medications, imaging, and procedures for optimal maternal and fetal outcomes. In this chapter, we will review the scope of pregnant patients requiring high-acuity care with an emphasis on clinical caveats to consider in these patients that may be unfamiliar to non-obstetric intensivists.

Scope of the Problem

The most common reasons for ICU level care in this population are related to obstetric complications with hypertensive disorders of pregnancy (preeclampsia, eclampsia, HELLP syndrome, hypertensive crisis) and postpartum hemorrhage (abruption, previa, placenta accreta, uterine atony, retained products of conception). Trauma, cerebrovascular accidents, and drug overdose are the most frequent non-obstetric indications for ICU admission in these patients. Risks of requiring ICU admission during pregnancy include maternal age, race, hospital acuity, delivery volume, and source of admission [3].

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Overall peripartum patients admitted to the ICU have lower mortality rates than the general population and benefit from a tendency to be younger with less comorbid conditions [3]. Unfortunately, up to two-third of deaths occur in women prior to reaching the ICU. The care of these patients requires a multidisciplinary approach that may include the involvement of obstetrics/maternal-fetal medicine, intensivists, obstetric anesthesia, interventional radiologists, neonatologists, nursing, pharmacists, and organ-specific subspecialists.

Maternal Morbidity and Mortality

Mortality nomenclature surrounding pregnancy is defined by the World Health Organization (WHO) as [4]:

- Maternal death: the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.
- Late maternal death: the death of a woman from direct or indirect obstetric causes more than 42 days but less than 1 year after termination of pregnancy.
- Pregnancy-related death: the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death.
- Direct obstetric deaths: those resulting from obstetric complications of the pregnant state (pregnancy, labor, and puerperium), from interventions, omissions, incorrect treatment, or a chain of events resulting from any of the above.
- Indirect obstetric deaths: those resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy.

The maternal mortality rate in the United States (US) is currently 11–30 maternal deaths per 100,000 live births. This is markedly lower than that of developing countries in South

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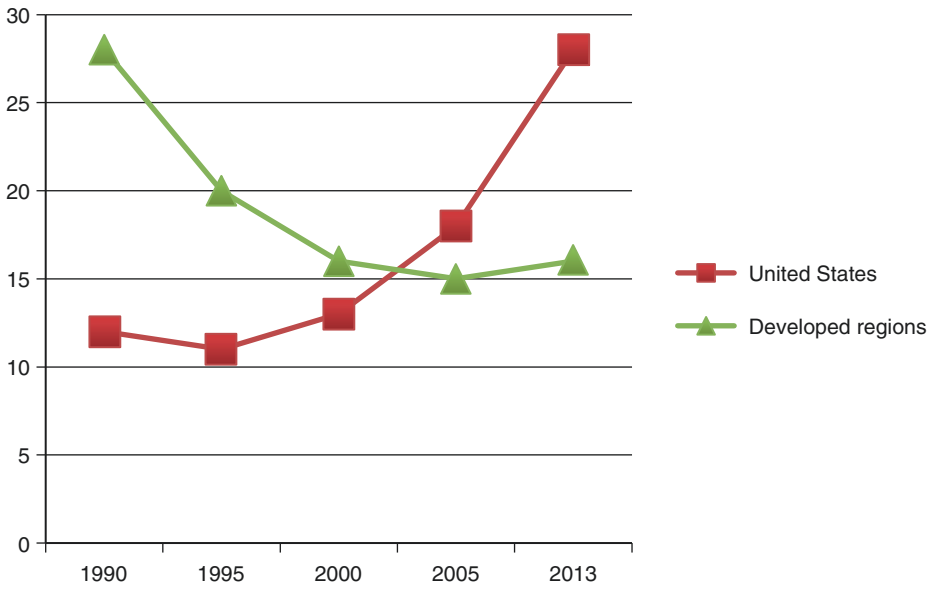

Fig. 36.1 Maternal mortality rates in developed countries. Since 2005, rates in the United States have surpassed those of other developed regions [4]

America, Africa, and India where the maternal mortality rate ranges 101–300+ maternal deaths per 100,000 live births. Common contributors to maternal mortality globally are delays in seeking care often associated with socioeconomic or cultural barriers, accessibility to healthcare services, and quality of medical care provided. Despite the overall low rate of maternal mortality in the United States relative to the developing world, our maternal mortality rate is steadily increasing and has now surpassed that of other developed countries according to the WHO (Fig. 36.1).

Mortality in mothers increases dramatically with age. Women above 40 years old have the higher risk of mortality compared with younger mothers. This relation remains the same in within different ethnicities [5]. Considerable racial disparities exist in regard to pregnancy-related mortality. According to the most recent CDC report, the ethnic divide is dramatic with maternal mortality rates of 11.7 deaths per 100,000 live births in white women, as compared to 35.6 deaths per 100,000 live births in black women, while other races are affected on the order of ~17.6 deaths per 100,000 live births collectively.

Maternal mortality is markedly increased in patients that require ICU admission. During 2006–2010, the pregnancy-related mortality ratio was 16.0 deaths per 100,000 live births in the United States [3]. On the other hand, maternal mortality in the United States for patients admitted to the ICU is close to 3.4% [6]. This number is significantly lower than the 14% incidence of maternal mortality in ICU patients among developing countries [6].

Historically, there has been less attention paid to maternal morbidity as it was difficult to capture with various definitions of what qualifies for morbidity in pregnant or postpartum women. Currently there is a growing emphasis in the United States in diminishing maternal morbidity. The

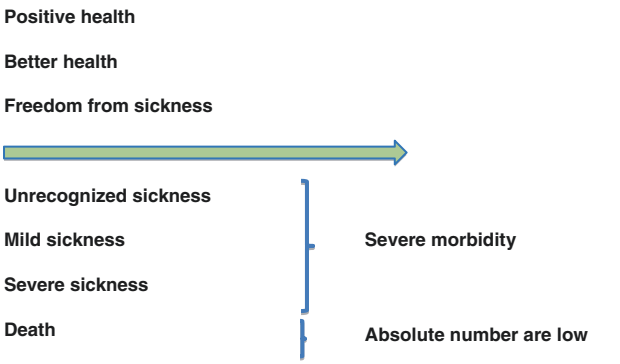

Fig. 36.2 Maternal mortality for an individual hospital occurs infrequently; however morbidity is far more common. This makes the case for safety initiatives that focus on reducing severe maternal morbidity as a way to reduce the maternal mortality rate in the United States

rationale in focusing on maternal morbidity is based on the observation that clinical status is a progression on a spectrum of positive health to death, and maternal death is often preceded by severe maternal morbidity (see Fig. 36.2).

One challenge in addressing maternal morbidity, however, has been an inconsistent approach among US hospitals in defining and auditing maternal cases. Maternal morbidity has been broadly regarded to include the need for ICU level care and presence of organ system dysfunction, but the degree of dysfunction and significance of clinical impact are variable among hospitals, thus contributing to epidemiologic inaccuracies in the past. One method to delineate severe maternal morbidity by the WHO involved application of the sequential organ failure assessment (SOFA) score to maternal cases and found an anticipated correlation between number of severity markers and risk of maternal mortality (see Table 36.1) [7].

Callaghan et al. from the CDC published epidemiologic data in 2012 on severe maternal morbidity based on cases in the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP) which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) and represents a stratified sample of ~20 % of all US community hospitals. In this review of 49,346,974 deliveries and 738,124 postpartum hospitalizations between 1998 and 2009: 597,920 (1.2 %) of women experienced severe maternal morbidity (SMM), with 493,397 (82.5 %) of events occurring during delivery and 104,523 (17.5 %) occurring in the postpartum period. They found in the latter years (2008–2009) that there was at least 1 severe maternal complication for every 10,000 obstetric hospitalizations. The trend in maternal morbidity during the study period from 1998 to 2009 showed an astonishing 75 % increase in morbid maternal events during delivery hospitalizations ($p < 0.05$) and a 114 % increase among postpartum hospitalizations (see Fig. 36.3). Across all time periods from 1998 to 2009, maternal blood transfusion requirement was the leading marker for severe maternal morbidity with the strongest association in those who received >3 units of packed red blood cells (PRBCs) [6].

Table 36.1 The WHO severity markers used to assess maternal morbidity [7]

	Group A	Group B
Cardiovascular dysfunction	Shock	pH <7.1
	Lactate >5	Use of continuous vasoactive drug
		Cardiac arrest
		Cardiopulmonary resuscitation
Respiratory dysfunction	Acute cyanosis	Gasping
	RR >40 or <6	PaO_2/FiO_2 <200
	O_2 <90 % (for one hour)	Intubation and ventilation not related to anesthesia
Renal dysfunction	Oliguria	Creatinine >3.5
		Dialysis for ARF
Coagulation/hematologic dysfunction	Clotting failure	Platelets <50,000
	Transfusion >5 PRBC	
Hepatic dysfunction	Jaundice	Bilirubin >6.0
Neurologic dysfunction	Metabolic coma	Coma/loss of consciousness for >12 h
	Stroke	
	Status epilepticus	
Uterine dysfunction	Hysterectomy	

The rate of SMM in academic hospitals is impacted by a greater number of high-risk pregnancies and referrals. Grobman et al. in 2014 [8] published a review of data from 25 academic hospitals in the Maternal-Fetal Medicine Unit (MFMU) Network and showed an SMM rate of 2.9 per 1,000 births (95 % CI 2.6–3.2). The frequency of associated SMM factors is shown in Fig. 36.4. Postpartum hemorrhage, hypertensive disorders, and acute cardiopulmonary events represent the most common causes of SMM.

In January 2015, the Joint Commission released an updated definition of SMM to allow for better tracking of cases which is essential for assessment of resource allocation, consistency in research, and development of safety protocols in obstetric care nationally. A sentinel event as defined by the Joint Commission is "a patient safety event (not primarily related to the natural course of the patient's illness or underlying condition) that reaches a patient and results in any of the following: death, permanent harm, or severe temporary harm." For obstetrics, the new definition for severe temporary harm focused on SMM defined as a pregnant or postpartum woman receiving four or more units of PRBCs and/or ICU admission.

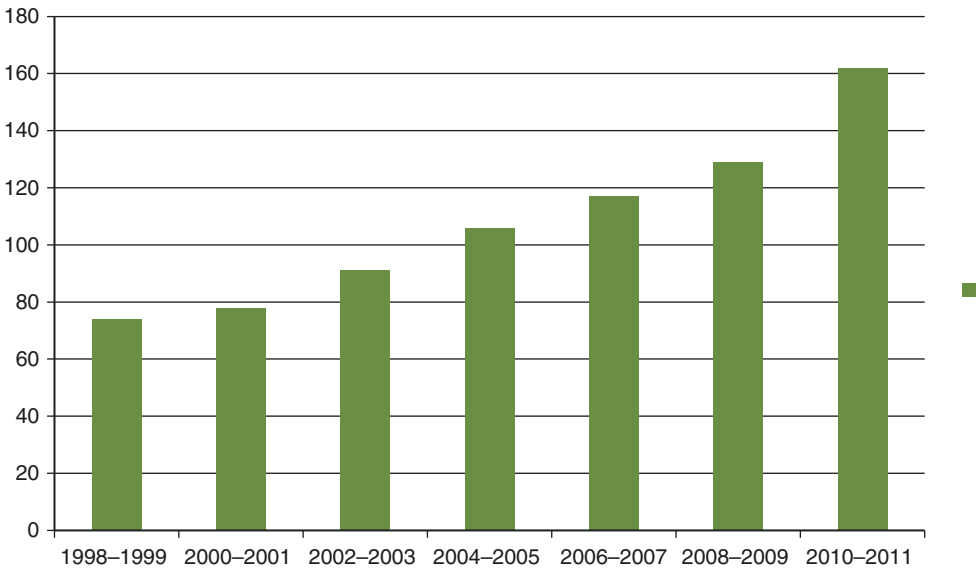

Fig. 36.3 Severe maternal morbidity during hospitalization in the United States [6]

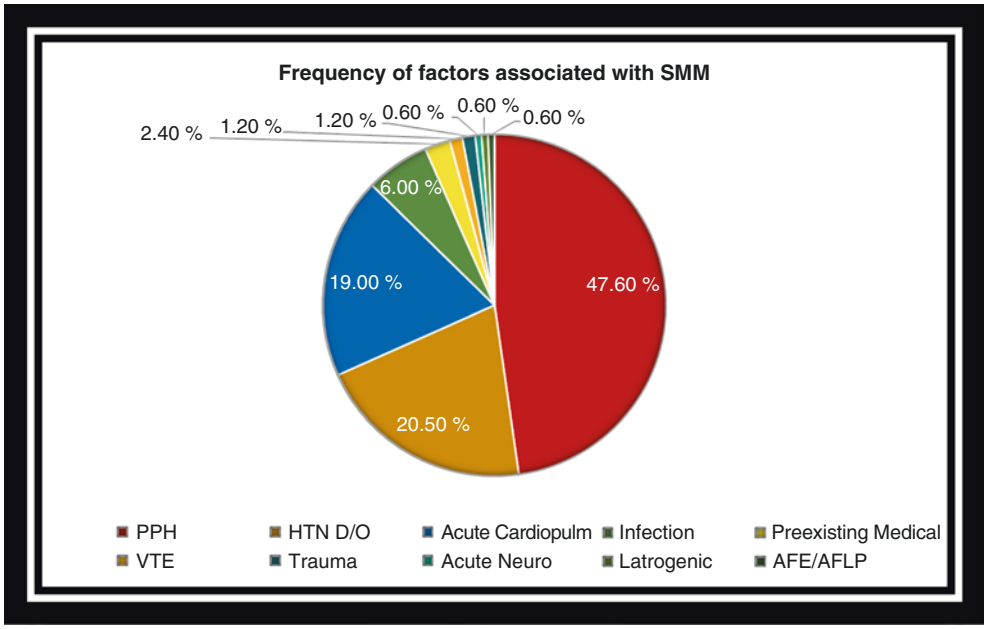

Fig. 36.4 Frequency of factors associated with severe maternal morbidity (SMM). *PPH* postpartum hemorrhage, *HTN D/O* hypertensive disorders, *VTE* venous thromboembolism [8]

Table 36.2 MEOWS score [10]

	3	2	1	0	1	2	3
Systolic BP	<80	80–89		90–139	140–149	150–159	≥160
Diastolic BP				<90	90–99	100–109	≥110
Respiratory rate	<10			10.0–17	18–24	25–29	≥30
Heart rate	<60			60–110		111–149	≥150
O_2 requirement				Room air	24–39 %		≥40 %
Temperature	<34		34–35	35.1–37.9	38–38.9		≥39
Conscious level				Alert			Not alert

Predictors of Mortality at Admission

In nonpregnant patients, prediction models have been used to determine the risk of death at admission to the ICU. Among nonpregnant women, the Acute Physiology and Chronic Health Evaluation (APACHE), the Simplified Acute Physiology Score (SAPS), and the Mortality Predictor Model (MPM) have demonstrated reliable predictive values. None of these perform well in the obstetric population. The main reason for the poor performance in gravid and recently postpartum patients is that they do not account for the normal physiologic changes of pregnancy or include markers for pregnancy-associated conditions such as HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet syndrome) and often overestimate the risk of maternal mortality [9]. The positive predictive values of the Systemic Inflammatory Response Syndrome and Modified Early Warning scores are 0.9–1.7 and 0.05, respectively, in obstetric patients and cannot be used to reliably predict ICU transfer, sepsis, or death in pregnant women.

For this reason, in the United Kingdom (UK), a Modified Early Obstetric Warning System (MEOWS) was created (Table 36.2). This tool was developed to better identify women in risk of clinical deterioration. The area under the curve was 0.96 (95 % CI 0.94–0.96) for the clinical score [10].

With a universal SMM definition by the Joint Commission and recent advancements in medical technology with machine-based learning, hospital systems can develop reliable electronic track and trigger Obstetric Early Warning Systems to respond to early signs of maternal clinical deterioration in an effort to reduce progression of maternal morbidity to mortality and can be anticipated to impact other outcomes like maternal length of stay and readmission rates.

Physiologic Changes in Obstetrics and Clinical Implications

There are well-known physiologic changes during pregnancy that can affect the management of a patient in the ICU. Understanding these alterations during pregnancy is a very important tool to improve maternal and fetal outcomes and inform management of the critically ill mother.

Cardiovascular

During a normal pregnancy, there is a significant increase of the blood volume starting at 8 weeks of gestation. During the first two trimesters, the stroke volume and cardiac output increase [11]. The cardiac output in pregnancy increases approximately 30–50 % in singletons and 50–70 % in multiple-gestation pregnancies. There is a concomitant decrease in the systemic vascular resistance (SVR, mediated by progesterone) and pulmonary vascular resistance (PVR) on the order of 20 % and 34 %, respectively. The increased volume and cardiac output do not compensate for the dramatic decrease in SVR, and, as a result, blood pressure decreases in pregnancy. The blood pressure starts to decrease as early as 8 weeks, with its nadir in the midtrimester. The diastolic blood pressure and the mean arterial pressure (MAP) are the most affected during pregnancy. As blood volume increases during the course of pregnancy, maternal blood pressure approaches that of the woman's prepregnancy levels. An important concept to keep in mind is that blood pressure during pregnancy should not be equal or higher than prepregnancy [12, 13]. When it does, hypertensive disorders of pregnancy are most often the explanation.

There is almost no change in the central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) despite the increase in volume, due to the marked progesterone-mediated decrease in PVR. On the other hand, there is a decrease in colloidal oncotic pressure, making pulmonary edema more common. Women with preeclampsia are prone to the development of non-cardiogenic pulmonary edema because of decreased colloid oncotic pressure and increased capillary permeability with increased hydrostatic pressure. Preeclamptic patients may experience very high afterload at a rate and magnitude far exceeding their baseline SVR that can lead to cardiogenic pulmonary edema as well which can be difficult to distinguish from peripartum cardiomyopathy. Any peripartum patient with pulmonary edema and preeclampsia should be evaluated with a transthoracic echocardiogram to distinguish cardiogenic from non-cardiogenic causes.

During pregnancy, cardiac remodeling and cellular hypertrophy occur, reflected in the EKG as left ventricular hypertrophy (wall mass increases up to 50 %) and slight left axis deviation. Encroachment of the gravid uterus on the diaphragm also physically shifts the heart in a more leftward direction which also contributes to the left axis deviation seen on EKG. A right axis deviation on EKG is not normal in pregnancy and should be further investigated if noted. On chest X-ray, an increased cardiac silhouette, straightening of the border of the left side of the heart, and prominence of the pulmonary conus are seen. All the chambers, in particular the left atrium, increase in size, making arrhythmias more common. Finally, there is a mild physiologic pulmonary and tricuspid regurgitation due to overall cardiac enlargement from volume engorgement that occurs with the hypervolemic state of pregnancy [14].

Starting around 20 weeks of gestational age, the uterus is large enough to cause compression of the aorta and inferior vena cava (IVC) resulting in supine hypotensive syndrome. This phenomenon can cause reduced venous return leading to a 30 % decrease in cardiac output and drop in blood pressure when a gravid patient beyond 20 weeks (or less with multiple gestations) lies directly flat on her back. A lateral tilt relieves aortocaval compression and rapidly improves cardiac output [15].

Based on these particular effects during pregnancy, the American Heart Association (AHA) recommends the following variants when performing the Advanced Critical Life Support (ACLS) on gravidas with a 20-week or more sized uterus [16–18]:

- Lateral uterine displacement
- Avoid medications through lower-extremity vascular access as they may not circulate.

The amount of blood going to the uterus increases with each trimester. In nonpregnant women, only 2 % of the cardiac output reaches the uterus. However, by the third trimester, 20 % of the cardiac output is shunted to the uteroplacental circulation. This translates to ~500–700 cc per minute and explains the massive amount of bleeding that can occur in a very short period of time in postpartum hemorrhage. During labor and immediately postpartum, ~300–500 cc of blood are added to the maternal circulation from the uteroplacental unit. This "autotransfusion" of labor and dramatic increases in cardiac output put women with cardiac conditions (particularly valvular disease and pulmonary HTN or stenosis) at risks for pump failure and arrhythmias, which warrant close monitoring intrapartum and during the immediate postpartum period. Cardiac output (CO) increases throughout labor from 17 to 34 % above the baseline nonlaboring state and is attenuated in women with regional anesthesia. Obstetricians take advantage of the hemodynamic attenuation afforded with regional anesthesia in laboring women with known cardiac conditions to allow candidacy for vaginal delivery. The cardiac output returns to normal around 12 weeks postpartum [19, 20].

Heart rate increases slightly in pregnancy as a compensation for the low SVR, to maintain cardiac output, as early as 7 weeks and increases about 10–20 % above baseline by term. Tachycardia above this level can be deleterious in women with certain conditions. For example, in mitral stenosis, when the valve area falls below 1.5 cm^2, filling of the left ventricle during diastole is compromised and results in a fixed cardiac output. These women rely on diastolic filling which is heart rate dependent. Maternal tachycardia can severely limit LV filling in these patients, compromising the ability to maintain a normal BP, and can result in cardiogenic

pulmonary edema and shock as well as poor uteroplacental blood flow leading to potentially harmful fetal effects.

During the second stage of labor, when delivery occurs, a healthy mother can lose up to 30 % of her blood volume with little or no change in hemodynamics or hematocrit. This is due to the gestational hypervolemia that occurs in pregnancy. The average blood loss during vaginal delivery is ~500 cc and 1,000 cc with cesarean section. Women with hypertensive disorders of pregnancy, particularly severe preeclampsia, do not expand their blood volume as robustly as normal gravidas and will show signs of shock earlier with less blood loss. Postpartum, there is a mobilization of extracellular fluid accumulated in pregnancy to the intravascular space and an expected diuresis that occurs on days 2–3 in vaginal deliveries and 4–5 with cesarean sections. Failure to have the normal postpartum diuresis may lead to high intravascular volume and pressure resulting in cardiogenic pulmonary edema.

Invasive Central Monitoring

Pulmonary artery (PA) catheterization is used less commonly in the ICU as compared to the past and is being replaced by less-invasive imaging methods (echocardiogram, IVC ultrasound, arterial pressure waveform monitors) to monitor hemodynamics in critically ill patients. It should be emphasized however that a randomized control trial was performed showing no survival benefit in pregnant women with PA catheter due to the poor correlation between the central venous pressure and the pulmonary capillary wedge pressure in pregnant women, in particular if patient has preeclampsia [21]. That being said, there remain indications for PA catheter placement during pregnancy [22]:

- Hypovolemic shock unresponsive to initial volume resuscitation attempts
- Septic shock with refractory hypotension or oliguria
- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective intravenous antihypertensive therapy
- Acute respiratory distress syndrome (ARDS)
- Intraoperative or intrapartum cardiac failure
- Severe mitral or aortic valve stenosis
- New York Heart Association (NYHA) class III or IV heart disease in labor
- Amniotic fluid embolism
- Adult congenital heart disease

The logistics of invasive monitoring on labor and delivery can be very challenging due to limited staff available to troubleshoot and interpret data, equipment for monitoring, and locations where monitors may be available (can be logistically impossible to labor a woman in the OR who needs central monitoring in most hospitals with obstetric services). Oftentimes as a result, women who may benefit from invasive monitoring who are in a location without this capability will end up delivering via cesarean or having a vaginal delivery without monitoring.

Pulmonary

There are structural and mechanical respiratory changes in pregnancy. Regarding the structural changes, the nasopharynx becomes edematous with increased mucous secretion resulting in reduced upper airway dimensions. These changes make endotracheal intubation more challenging, and low threshold for early intubation is highly recommended as one can anticipate a difficult airway in pregnancy. Because of anticipated oropharyngeal edema, the internal diameter of the endotracheal tube used for intubation of a pregnant patient should be 0.5–1.0 mm smaller than in nonpregnant women [23, 24].

There are also some changes in the structure of the thorax. The subcostal angle increases from 68° to 103° (an ~50 % increase), the transverse diameter of the thorax increases by 2 cm, and the circumference increases by 5 cm. There is also decreased chest wall compliance.

The mechanical respiratory changes are described in Table 36.3. The most significant changes are a decrease in functional residual capacity (FRC) by 10–25 % in the third trimester and can exceed the upper limit in obese women. That in combination with an increase in oxygen consumption results in overall decreased oxygen reserve toward the end of pregnancy. The forced expiratory volume in the first second (FEV1), ratio of FEV1 to forced vital capacity, and peak flows remain unchanged during pregnancy [23]. The Bohr curve in pregnancy is shifted to the right, lowers the affinity of hemoglobin for oxygen, and results in increased oxygen delivery to the placenta and maternal tissues.

Table 36.3 Lung volumes in pregnancy

Measurement	Respiratory rate	Vital capacity	Inspiratory capacity	Tidal volume	Inspiratory reserve volume	Functional residual capacity	Expiratory reserve volume	Residual volume	Total lung capacity
Changes during pregnancy	Unchanged	Unchanged	Increased 5–10 %	Increases 30–40 %	Unchanged	Decreased 20 %	Decreased 15–20 %	Decreased 25 %	Decreased 5 %

There is also a progesterone-mediated increase in respiratory drive at the level of the medulla and a resultant increase in tidal volume (VT) and minute ventilation. With this, pregnancy is a state of chronic respiratory alkalosis with compensatory metabolic acidosis. Hyperventilation and decreased PCO_2 are directly related to increased VT not respiratory rate (RR). The normal PCO_2 during pregnancy is between 27 and 32 mmHg. If a pregnant woman later in gestation is found to have a PCO_2 consistent with non-gravid patients, this is considered abnormal and represents CO_2 retention which should be further investigated. The bicarbonate level is normally 18–21 mEq/l to compensate for the decrease in PCO_2 and does not represent a primary metabolic acidosis. As a result of this partial compensation, the normal pH during pregnancy is 7.4–7.45. The increase in MV and lower PCO_2 are essential to maintain a maternal-fetal CO_2 gradient to allow for fetal CO_2 off-loading.

The fetal PCO_2 is approximately 10 mmHg higher than maternal when uteroplacental perfusion is normal. It is important to understand that the fetus develops in a CO_2-rich environment and needs the lower maternal CO_2 tension and the resultant transplacental gradient enabling fetal CO_2 to be readily diffused across the placenta into the maternal venous circulation for gas exchange enabling fetal CO_2 to be readily diffused across the placenta into the maternal venous circulation for gas exchange out of the maternal-fetal unit via the maternal lungs. Pathologic pulmonary conditions that increase maternal CO_2 levels will alter the transplacental gradient, allowing for fetal CO_2 retention as well. The fetal pH is normally 0.1 units lower than maternal pH which is also important when reviewing mechanical ventilation and maternal-fetal acid-base interactions.

During a normal labor, especially in the second stage (full cervical dilation and pushing), the mother tends to moderately hyperventilate in the process, and this drives her CO_2 levels down which increases the maternal-fetal CO_2 gradient in favor of fetal CO_2 off-loading. That being said, excessive ventilation can be deleterious. Forced maternal hyperventilation can contribute to fetal acidosis. This has been demonstrated in animal models by Motoyama et al. in 1965: when the maternal PCO_2 falls to 15–20 mmHg or she becomes very alkalotic with pH approaching 7.6, uteroplacental vascular spasm occurs, decreasing circulation and increasing fetal acidosis as oxygen delivery to the fetus is compromised, and fetal CO_2 is not circulated as well across the placenta [25]. When the fetus is unable to off-load its CO_2, in the setting of inadequate oxygenation, this compromises fetal aerobic (oxidative) metabolism of carbohydrate as an energy source and converts to the anaerobic pathway where higher levels of lactate are produced above the fetal baseline, and the accumulation of lactic acid leads to metabolic acidosis. In this way, which is a difference from adults is the fetus can transition seamlessly from a respiratory to metabolic acidosis.

All of the above must be kept in mind when the question of parameters for mechanical ventilation arises as permissive hypercapnia with low-tidal volume ventilation has not been well studied in obstetric patients. Mechanical ventilation is almost the same in pregnant and nonpregnant patients with some exceptions. In pregnancy, $PaCO_2$ should be adjusted between 30 and 32 mmHg, maintaining the normal respiratory alkalosis and transplacental gradient. The risk of fetal acidosis increases as the PCO_2 approaches 60 mmHg due to uteroplacental vascular spasm, much in the same way as it occurs with excessive maternal hyperventilation [26]. It is important that anyone caring for a pregnant patient who requires mechanical ventilation understands that extremes of ventilation are avoided for the benefit of the mother and fetus.

Hematologic

In pregnancy, physiologic dilutional anemia is normal. There is an important increase in the red blood cell mass (around 20 %) but a higher increase in plasma volume. Women gain an additional 40–50 % of their pre-gravid blood volume, or approximately 1,300 cc of plasma in a singleton pregnancy [27, 28]. Regarding the white blood cell (WBC) count, there is a rise during each trimester. During the first trimester, the upper limit is 9,900/mm^2, 12,200/mm^2 during the second and third trimesters, and as high as 30,000/mm^2 during labor and immediately postpartum [29]. The WBC changes make the diagnosis of SIRS or sepsis more difficult.

The Sepsis in Obstetrics Score (SOS) shows correlation with admission to ICU for sepsis, positive blood cultures, and fetal tachycardia. The cutoff used for sepsis prediction is ≥6, with a sensitivity of 88.9 % and a specificity of 99.2 % [30, 31]. See Table 36.4 for parameters and Table 36.5 for scoring.

In pregnancy and the postpartum period, there is a prothrombotic state, which increases the risk of thromboembolic events around sixfold compared to baseline. This is secondary to an increase of factors I, VII, VIII, IX, and X. There is also a decrease of protein S (more than C) starting early in pregnancy [30, 32, 33].

Renal

There are a number of important physical and functional changes of the gravid genitourinary system to keep in context when managing sick pregnant or peripartum patients. Because of increased plasma volume and flow, the kidneys increase approximately 1 cm in length. The collection system dilates (calyces, pelvis, and ureters), typically greater on the right due to a slight dextrorotation of the uterus, and, as a

Table 36.4 Sepsis in obstetrics score (SOS) parameters [30]

Variable	High abnormal range				Normal	Low abnormal range			
Score	4	3	2	1	0	1	2	3	4
Temperature	>40.9	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	<30
Systolic BP					>90		70–90		<70
Heart rate	>179	150–179	130–149	120–129	≤119				
Respiratory rate	>49	35–49		25–34	12–24.0	10–11.0	6–9.0		≤5
Sat O_2 %					≥92 %	90–91 %			<85 %
WBC	>39.9		25–39.9	17–24.9	5.7–16.9	3–5.6	1–2.9		<1
Immature neutrophils %			≥10 %		<10 %				
Lactic acid			≥4		<4				

Table 36.5 Sepsis in obstetrics score (SOS) scoring [30]

Scoring system	Sensitivity	Specificity	PPV	NPV
SOS	88.90 %	99.20 %	16.70 %	99.70 %
REMS	77.80 %	93.30 %	11.10 %	99.70 %
MEOWS	100 %	77.60 %	4.60 %	100 %

result, imaging studies in the late second and third trimesters will typically note mild-to-moderate hydronephrosis. This finding can persist up to 4 months postpartum. Severe hydronephrosis is not a physiologic finding. Increased urinary stasis from progesterone relaxation of detrusor smooth muscle and pelvic compression by the expanding uterus contribute to a higher risk of urinary tract infection (UTI) in pregnant patients. Symptomatic UTIs and asymptomatic bacteriuria should be treated in pregnancy. Development of pyelonephritis risks preterm birth, maternal sepsis, and ARDS.

Functionally, there is an increase in the renal plasma flow during pregnancy, which normalizes 12 weeks after the delivery. The creatinine clearance starts to increase as early as 6 weeks of gestation. There is a reduced upper limit of normal maternal serum creatinine at 0.8 mg/dL due to the increase in glomerular filtration rate (GFR). Blood urea nitrogen (BUN) levels also decrease in pregnant women [34–36]. Although pregnant mothers often report increased urinary frequency, the actual daily urine volume is not significantly altered from nonpregnant patients [37]. Urinary protein excretion at the 95th percentile is approximately 260 mg over 24 h and adds validity to the presence of >300 mg of urinary protein a day (which corresponds well to a urinary protein-to-creatinine ratio of >0.3), as a criteria establishing the diagnosis of preeclampsia [37]. In women with preexisting proteinuria, protein levels in urine increase even in the absence of preeclampsia. Magnesium sulfate, the drug of choice to reduce the risk of eclamptic seizure in women with preeclampsia, is almost completely renally excreted, and the dose or rate administered must be decreased in gravidas with evidence of renal insufficiency (i.e., creatinine >1.3 mg/dL in pregnancy).

The water retention that occurs in pregnancy is hormonally mediated. Increased estrogen drives renin production early in pregnancy which increases angiotensinogen conversion to angiotensins I and II leading to increased aldosterone levels. Despite the increase filtered sodium load (due to the increase in GFR), increased aldosterone and deoxycorticosterone in pregnancy create a larger increase in tubular reabsorption of the filtered sodium resulting in a net retention of ~1 g Na daily. The latter contributes to the gestational hypervolemia of pregnancy. Because greater water is retained with sodium, there is an overall decrease in serum sodium concentration in pregnancy down to an average of 136 mmol/l and slightly decreased plasma osmolality from 290 down to 280 mosmol/l.

Glycosuria is common in pregnancy, because there is a decrease in distal tubular reabsorption of glucose. Spurious increases in glycosuria are intermittent and do not correlate well with blood glucose. Hence, glucose can be present in maternal urine with a normal finger stick, and this is physiologic [37].

Gastrointestinal

There are few changes to the maternal gastrointestinal tract that significantly impact high-acuity care. The notion of prolonged gastric emptying time associated with increased aspiration rates in pregnancy has been challenged. Gallbladder stasis does occur and can result in higher rates of stone formation. Otherwise, liver function tests are not significantly different with the exception of elevated alkaline phosphatase from placental production and decreased albumin from plasma dilution (by up to 30 %). Coagulation times and aminotransferase levels are not affected by normal pregnancy; changes in these values represent pathology.

Pathology in Pregnancy

Cardiac

As previously stated, deaths from maternal cardiac disease are increasing and now account for up to 50 % of all maternal

Table 36.6 Antihypertensive medications in pregnancy

Drug	Dose	Route	Frequency	Side effect	Max dose
Hydralazine	5–10 mg	IV/IM	15 min	Nausea, emesis, hypotension, palpitation	20 mg IV/30 mg IM
Labetalol	20 mg	IV	10 min	Nausea, emesis, hypotension, bronchospasm	300 mg
Nifedipine	10–20 mg	PO	30 min	Hypotension, palpitation, avoid with magnesium sulfate	50 mg
Nicardipine	5 mg/h	PR	Titrate every 5 min	Peripheral edema, tachycardia	10 mg/h
Nitroprusside	600–1000 mcg	PR/PO	Titrate every 5 min	Hypotension, increased intracranial pressure, rebound hypertension	4 mcg/kg/min

deaths in the ICU. Currently, only approximately 4 % of pregnancies are complicated by cardiac disease, but this number is on the rise as the maternal population becomes older and affected by other comorbidities associated with cardiac risks. The strongest predictors of maternal complications as outlined by the CARPREG study, prospectively designed to evaluate pregnancy outcomes in 617 pregnancies complicated by maternal cardiac disease, are:

- A history of heart failure, transient ischemic attack, cerebrovascular accident (CVA), or arrhythmia
- Prepregnancy New York Heart Association functional status >class II
- Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, or peak left outflow gradient >30 mmHg)
- Ejection fraction <40 %

In this population, the most commonly encountered complications were pulmonary edema and arrhythmias [38]. Women with known cardiac disease are also known to be at risk for heart failure with intolerance of gestational hypervolemia. Patients with known pulmonary hypertension or a history of peripartum cardiomyopathy without systolic recovery are advised against pregnancy as maternal death is prohibitively high in these women. If necessary, supportive medications can and should be used in pregnancy. Milrinone is a safe inotrope to use in gravid patients. Sildenafil or tadalafil can also be used in women with symptomatic pulmonary hypertension. ACE inhibitors are contraindicated in pregnancy but enalapril has been regarded as safe for breastfeeding by the American Academy of Pediatrics in mothers who delivered term infants.

Preeclampsia-Eclampsia

Preeclampsia is a condition that occurs only in pregnancy. It is defined as elevated blood pressure (SBP > 140 or DBP > 90) and proteinuria after 20 weeks of gestation. When preeclamptic patients are admitted to the ICU, it is typically for severe cases with associated refractory hypertension, neurologic dysfunction (eclamptic seizure, stroke), renal failure, liver failure, pulmonary edema, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), and disseminated intravascular coagulation [39]. Women with preeclampsia have a loss of intravascular oncotic pressure. As a result, they have a total body water overload but with intravascular depletion and tend to have hyperdynamic cardiac function. These women may have altered renin and aldosterone activity in pregnancy and may not expand their total blood volume as robustly as women without preeclampsia. This altered volume state limits the ability of these women to tolerate hemorrhage. Because of low oncotic pressure, leaky capillaries, and higher hydrostatic pressure, these patients are also predisposed to non-cardiogenic pulmonary edema [40, 41].

The first goal in management of preeclampsia with severe features is to stabilize the mother. Severely elevated blood pressure in pregnancy (SBP >160 mmHg or/and DBP >110 mmHg) is associated with stroke and other obstetric complications such as placental abruption. It is recommended that severe range blood pressure is treated within 15 min of noting the elevation using intravenous antihypertensive agents (Table 36.6). Treatment goals and urgency are also informed by the patient's baseline state. If the patient had systolic BPs in the 180s mmHg range consistently prior to pregnancy, an SBP of 160s mmHg is relatively normal for her, and dropping her BP rapidly to a normotensive range can risk decreasing placental perfusion as it is directly correlated with maternal MAP.

Another key point in the management of preeclampsia with severe features is the prevention of eclamptic seizures. The Magpie trial showed a significant decrease of seizures in this population when given magnesium sulfate (therapeutic range of 4.8–8.4 mg/dL). Again, caution should be used in patients with impaired renal function, although there is little risk with commonly prescribed repletion doses for hypomagnesemia. The signs and symptoms of magnesium

Table 36.7 Pharmacologic agents used for uterine atony

Agent	Dose	Route	Frequency	Side effect	Contraindication
Oxytocin (Pitocin)	10–80 units	IV/IM	Continuous	Nausea, emesis, water intoxication	None
Methylergonovine (Methergine)	0.2 mg	IM/IU	2–4 h	Nausea, emesis, hypertension	Hypertension, preeclampsia
15-methyl prostaglandin F2 (Hemabate)	0.25 mg	IM/IU	15–90 min	Nausea, emesis, diarrhea, flushing	Asthma
Prostaglandin E2 (dinoprostone)	20 mg	PR	2 h	Nausea, emesis, diarrhea, fever	Hypotension
Misoprostol	600–1,000 mcg	PR/PO	One dose	Tachycardia, fever	None

toxicity are dose dependent with loss of deep tendon reflexes at serum levels of 8.5–12 mg/dL, respiratory paralysis at 12–16 mg/dL, abnormal cardiac conduction >18 mg/dL, and cardiac arrest when levels are >30 mg/dL. The half-life of magnesium sulfate is 4 h in women with normal renal function. Treatment for magnesium toxicity consists of discontinuing the infusion, supportive measures, and administering on one-gram intravenous of calcium gluconate every 5–10 min as necessary [42–48]. Calcium chloride is appropriate to use for patients with impaired hepatic function as calcium gluconate requires hepatic degluconation for biologic activity, whereas calcium chloride provides immediately available calcium.

Pulmonary edema occurs in 2–3 % of patients with preeclampsia and, as stated above, can be non-cardiogenic. Treatment includes supportive measures, diuresis, and afterload reduction. Pulmonary edema is considered a sign of end-organ damage and is an indication for delivery. Patients with preeclampsia can have oliguric acute kidney injury, and some reported improved outcomes with the use of a PAC to guide fluid management in preeclamptic patients who have oliguric acute kidney injury unresponsive to volume resuscitation [39].

Hemorrhage

Causes of hemorrhage in pregnancy are abruption, placenta previa or accreta, uterine rupture, uterine inversion, and postpartum hemorrhage. Postpartum hemorrhage is defined as more than 500 ml after a vaginal delivery or more than 1,000 ml after a cesarean section. Hemorrhage is still the leading cause of maternal death worldwide. In the United States, there has been a significant decrease in the rates of maternal death associated with hemorrhage [43, 44].

As described above, there is an expansion of blood volume in pregnancy. Because of this, the hypovolemia clinical signs are almost always delayed. Signs such as tachycardia and mild hypotension are seen after losing 1,200–1,500 ml of blood (20–25 % of total volume) [43–46]. Management of hemorrhage is centered around control of the bleeding source and volume support. Massive obstetric hemorrhage is managed with blood products based on requirements, and most hospitals with obstetric services now have hemorrhage protocols to address the rapid bleeding that can occur. Recall that the uterus consumes 20 % of the cardiac output at term and can translate to a 500–700 cc per minute blood loss in obstetric hemorrhage. When hemorrhage is massive and has not responded to 2 l of crystalloids, the repletion should be performed in a ratio of 1:1:1 of packed red blood cells, fresh frozen plasma (FFP), and platelets [47]. There are medical and surgical approaches to stop the bleeding. The medications used in the peripartum are oxytocin, misoprostol, 15-methyl prostaglandin, and methylergonovine [46–48]. The doses and contraindications are described in Table 36.7.

If bleeding has not improved with uterotonic medications, uterine tamponade devices such as the Bakri balloon ®, Foley balloons, or packing often stop bleeding. Intraoperatively, one can place O'Leary stitches to ligate the uterine arteries for bleeding control and/or use a B-Lynch suture to externally tamponade the uterus or perform hypogastric artery ligation with care to avoid the ureters. If the patient is bleeding consistently but slowly and is stable enough to transfer to an interventional radiology suite, then bilateral uterine artery embolization would be a recommended option. The rate of success is more than 90 %. One advantage of angioembolization is the potential to use absorbable gelatin sponge (Gelfoam). This product reabsorbs after 2 weeks, making future fertility more likely [44, 48]. When medical management and other surgical or alternative measures fail, hysterectomy may need to be performed [49, 50].

Amniotic Fluid Embolism

Amniotic fluid embolism or anaphylactoid syndrome of pregnancy is a rare but catastrophic event. The incidence is around 1 in every 40,000 deliveries, and the mortality is as high as 60 %. The pathophysiology, although not completely understood, appears to be secondary to a cascade of abnormal activation of pro-inflammatory mediator systems similar to that of the systemic inflammatory response syndrome, in

association of fetal antigens in maternal circulation during the delivery process or within 30 min after. The signs and symptoms associated with this are hypotension, dyspnea, cyanosis, disseminated intravascular coagulopathy, loss of consciousness, cardiac arrest (typically PEA arrest), and seizure-like activity. There are no specific treatments or cure for this entity, and management is supportive. There are case reports of the use of tranexamic acid in the management of AFE but more evidence is needed before standards aside from supportive measures can be endorsed. With an appropriate level of care, the mortality in the United States has decreased from 60 % to almost 20 % for the cases [51].

Trauma Management

Care of the maternal trauma case is interdisciplinary and requires high-level communication and coordination of all service lines responding to the emergency. The ideal team would have the involvement of emergency department faculty, obstetric or maternal-fetal medicine, neonatology, obstetric anesthesia, trauma surgery, and the respective nursing support. Understanding the nuances of evaluating these patients is highly important to maintaining situational awareness and a good outcome. The primary and secondary surveys should be performed keeping the following caveats in mind:

Primary Survey

- Airway: gravid patients can be expected to have oropharyngeal edema, making securing an airway potentially difficult, and consideration of early intubation in these patients with an ETT that is 1 mm smaller in internal diameter is advised. A laryngeal mask airway (LMA) can be used safely to provide a means to ventilate a patient who is unable to be intubated; however it is not considered a protected airway.
- Breathing: In the late second to early third trimester, the uterus displaces the diaphragm upward. If the patient has a suspected pneumothorax and is visibly pregnant, the chest tube should be placed higher than in nonpregnant patients in the third or fourth intercostal space.
- Circulation: leftward uterine displacement with a one- or two-handed technique is paramount to maintain or augment maternal cardiac output. Avoid lower-extremity lines in the gravida who is visibly pregnant as iliac compression could compromise circulation of resuscitative medications. Two large-bore IVs should be placed, and she should be typed and cross-matched for blood products early in preparation for any bleeding injuries; placental abruptions do not always present classically and bleeding can be concealed. Signs of hemorrhagic shock present late in pregnant patients, and one should be prepared to replace blood volume with products. Vasopressors should be used for those in shock getting volume resuscitation at the doses for nonpregnant patients. If cardioversion or defibrillation is required, the voltages used are not different in pregnancy and will not harm the fetus.
- Disability: always consider the postictal state from eclampsia as a cause for altered mental status or decreased alertness.
- Exposure: always assess for entry and exit wounds, if trauma is due to a firearm and an exit wound is not present, the bullet could be lodged in the fetus inside the uterus.

Secondary Survey

It is implicit that the mother is stabilized first before evaluation of the fetus occurs in maternal trauma. The fetus is part of the secondary survey. Once the primary survey is complete with said considerations in mind, then a second comprehensive physical exam is performed where the fetal heart tones can be checked by Doppler or ultrasound. If the mother is stable and the pregnancy is viable (23 weeks in some institutions), then fetal monitoring may be indicated and should be guided by the obstetric service. Ultrasound is also performed once the mother is stable to establish placental location, amniotic fluid volume, fetal viability, presentation, gestational age, and estimated fetal weight. A bedside-expanded maternal focused assessment with sonography for trauma (FAST) ultrasound can be reliably performed to quickly assess for evidence of hemoperitoneum, pericardial effusion, and pneumo- or hemothorax. Lab testing and other imaging (i.e., CT or X-rays for orthopedic injuries) occur in the secondary survey. In hospitals with quick turnover, a high Kleihauer-Betke result for fetal cells (with HbF) in the maternal circulation is of concern for maternal-fetal hemorrhage, and the obstetric team should be alerted as the result could inform delivery timing. Fetal monitoring in the viable pregnancy may show late decelerations (occur following a contraction) and can indicate a placental abruption has occurred or is in process. The obstetric team should be involved as early as possible in these cases to guide maternal care management and decisions on fetal expectant management versus delivery. The obstetric team will help guide counseling on possible pregnancy termination in previable cases [52].

Perimortem Cesarean Section

A perimortem cesarean section is indicated for maternal cardiac arrest and unsuccessful cardiopulmonary resuscitation. The cesarean section should be started at 4 min of cardiac

arrest with the goal to deliver the fetus delivered by 5 min after maternal arrest for optimal fetal outcomes [53]. If the pregnancy is beyond 25 weeks gestation, there is a 45 % fetal and 72 % chance of maternal outcomes historically [54–56].

The uterine evacuation can also improve the venous return. The technique to use is a Pfannenstiel incision with a low-transverse uterine incision if the lower uterine segment is well developed or a classical-vertical uterine incision for preterm or malpresentation [44, 49].

Summary

Care of the gravid or recently postpartum patient can be challenging if one does not know what to expect in this population. With a better understanding of the common high-acuity events in pregnancy and the impact of their physiologic alterations, the reader will be better equipped to manage these patients collaboratively with the obstetric service for the best outcomes.

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The Pediatric Patient Cared for in the Adult ICU

37

Zoë Maher and Michael L. Nance

Initial Resuscitation of the Pediatric Intensive Care Patient

Physiology of Shock

There are many similarities between the physiology of pediatric and adult shock, including the types of circulatory shock: hypovolemic, cardiogenic, obstructive, and distributive (Table 37.1). Pediatric patients, however, may demonstrate more subtle manifestations of the shock state, leading to potential for delayed recognition. Additionally, the response to states of altered ventricular preload, cardiac contractility, and vascular resistance is different in pediatric patients than adults. Cardiac output (CO) is more heavily dependent on heart rate (HR) than stroke volume (SV) in the young pediatric population as ventricular myocyte mass is still developing. Additionally, children are able to mount a significant and lasting increase in systemic vascular resistance (Fig. 37.1). Therefore, in contrast to adults, pediatric patients in states of shock may manifest tachycardia without hypotension [37]. It is critical to recognize shock state before the development of hypotension. Upon recognition of shock, volume resuscitation, inotropic support, and vasoactive therapy must be rapidly implemented. Early consideration of adjunctive support measures such as extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), and ventricular assist devices (VADs) may improve outcomes for pediatric patients in refractory shock.

Broselow™ System

The Broselow™ color-coded system is designed for estimation of pediatric weight and endotracheal tube size based on body length. This color-coded bag provides a number of resuscitation adjuncts, including the Broselow™ tape which assists in medication dosage estimation and the Broselow™ bag which are color-coded, size-based procedural supplies. The Broselow™ system is helpful in the early resuscitation of the critically ill pediatric patient and

Table 37.1 Physiologic changes in pediatric shock states

Type of Shock	Preload	Afterload	Contractility
Hypovolemic	↓	↑	N
Cardiogenic	↑	↑	↓
Obstructive	↓	↑	N
Distributive	↑ or ↓ or N	↓	↑

From Wheeler [64], with permission from Springer

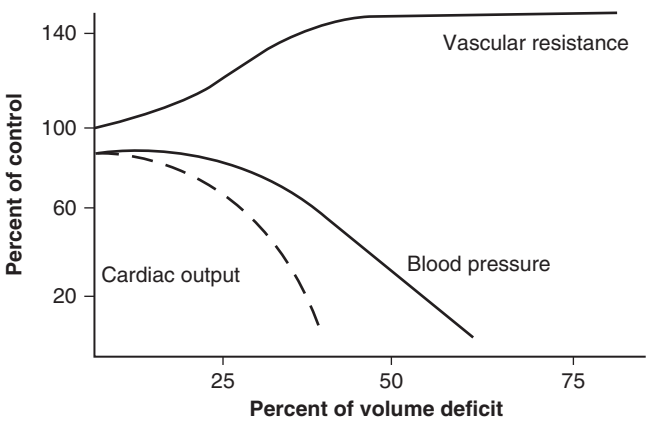

Fig. 37.1 Physiologic compensation in pediatric hypovolemic shock (From Wheeler [64], with permission from Springer)

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should be maintained at any center with the possibility of managing pediatric patients. However, Nieman et al. have recently called into question the accuracy of the tape owing in part to the challenge of weight-based dosing in the obese population [42].

Pediatric Airway Management

The majority of pediatric cardiac arrests result from ventilatory arrest and are only rarely due to a primary cardiac etiology. Therefore, successful management of the pediatric airway is of critical importance. Of note, up to 10% of all pediatric ICU intubations are considered difficult, owing in part to the anatomic challenges of the pediatric airway [23].

Anatomic Considerations

Anatomic differences between the pediatric and adult airway persist until the airway has reached anatomic maturity between the ages of 8 and 14 years. Most significantly the pediatric airway differs from the adult in terms of (1) relatively larger occipital size increasing risk of supine position airway obstruction; (2) maximal narrowing of the airway at the cricoid cartilage due to cylindrical shape of the airway; (3) relatively larger tongue size; (4) relatively narrow and short trachea; (5) more acute nasopharyngeal angle; (6) larger, floppy epiglottis; and (7) more cephalad and anterior larynx (Figs. 37.2 and 37.3). These differences must be considered when managing the pediatric airway.

Basic Airway Management

Basic airway control should begin with the three Ps: position favorably, prevent aspiration, and promote gas exchange. Favorable positioning can be accomplished with a jaw thrust in combination with the head lift-chin tilt maneuver if no cervical spine injury is suspected. The placement of a nasopharyngeal airway, or an oral airway in the obtunded patient with no gag reflex, should then be followed by bag-mask ventilation. Aspiration risk can be minimized with initial application of cricoid pressure in the unresponsive patient and application of the minimal positive pressure required to generate chest rise [5, 40]. Chest rise indicates adequate volume of ventilation.

Advanced Airway Management

The pediatric advanced airway has classically been managed with the placement of an endotracheal tube. However, laryngeal mask airway (LMA) application has been broadening among the pediatric population in recent years [57]. The tip of this supraglottic airway device is designed to oppose the epiglottis providing an airway seal upon cuff inflation. However, caution must be exercised to avoid overfilling the LMA cuff as this can lead to airway obstruction or pharyngeal nerve injury [43]. The LMA can be used as a temporizing airway or as a conduit for the placement of an endotracheal tube or other adjuncts to permit intubation. First-generation devices are not designed to prevent aspiration of gastric contents and should be used only when endotracheal intubation is not possible. Second-generation devices are capable of drainage of gastric contents, though they are not yet widely available [26]. Methods for approximating pediatric LMA size include using the combined width of the patient's second, third, and fourth digits or the following formula proposed by Ho et al.: weight (kg) of patient $= 2^{2\times LMA}$, where LMA is the size and cuff inflation volume (ml) $= 5 \times$ LMA [25].

Endotracheal Intubation Considerations

Length-based estimation and age-based formula estimation are both acceptable means of choosing endotracheal tube size, offering comparable accuracy. Additionally, approximation of endotracheal tube diameter by the fifth digital circumference has been written about by authors such as King et al. who concluded that this method is inferior to age-based formulas and should be reserved for situations in which age is unknown [31].

The most widely applied age-based estimation formulas are the Cole and Khine formulas. Cole's formula predicts uncuffed endotracheal tube size as equal to (age 4) + 4, whereas Khine's formula predicts cuffed endotracheal tube size as equal to (age/4) + 3 [30, 58]. For length-based estimation, the Broselow™ tape and color-coded system provide guidance for endotracheal tube sizing. Uncuffed endotracheal tubes are generally reserved for patients less than 8 years of age, though recent data has challenged the assertion of cuffed endotracheal tubes is unsafe for children in this age range [58]. In addition to careful consideration of endotracheal tube size, appropriate selection of type and length of laryngoscope is also critical (Table 37.2).

Fluid Resuscitation

Resuscitation strategy in the critically ill pediatric patient begins with venous access. Venous access considerations include size and length of the catheter and available sites for access. In the adult patient, rapid replacement of volume necessitates the placement of large bore access such as a 14 gauge peripheral catheter or an 8.5 French central catheter. However, the same volume replacement can be accomplished in a 20 kg 7-year-old using two 20 gauge

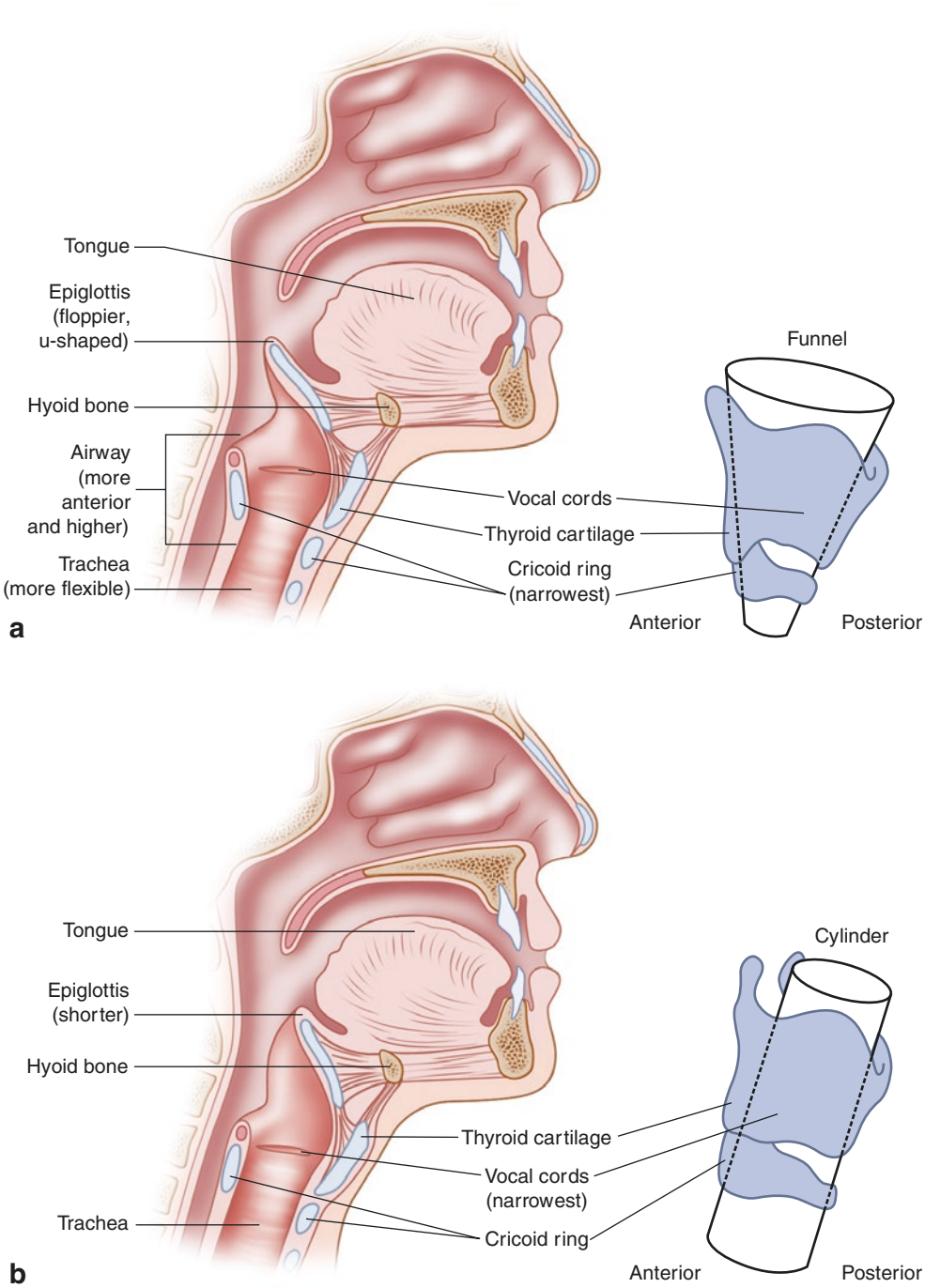

Fig. 37.2 Anatomy of the pediatric (**a**) and adult (**b**) airway (From Wheeler [64], with permission from Springer)

catheters or using one 22 gauge catheter with a 10 cc syringe for fluid boluses in a 5 kg child [24]. Resuscitation to clinical goals should be modified based on the etiology of the shock state. End points should include normal mental status, less than 2 seconds capillary refill, normal central and peripheral temperature, adequate urine output of greater than 1 cc/kg/h, and normal age-adjusted pulse and blood pressure (Table 37.3). In the case of hypovolemic shock, a 20 cc/kg bolus of crystalloid should be the initial choice for fluid management, followed by a second bolus of the same in the case of failure to respond. If hemorrhagic shock is suspected, a 10 cc/kg blood product transfusion should be considered to replace the second or third crystalloid bolus. Hypotension does not develop in hemorrhagic shock until up to 50 % of the blood volume has been lost in the pediatric population. Therefore, early recognition and intervention are critical.

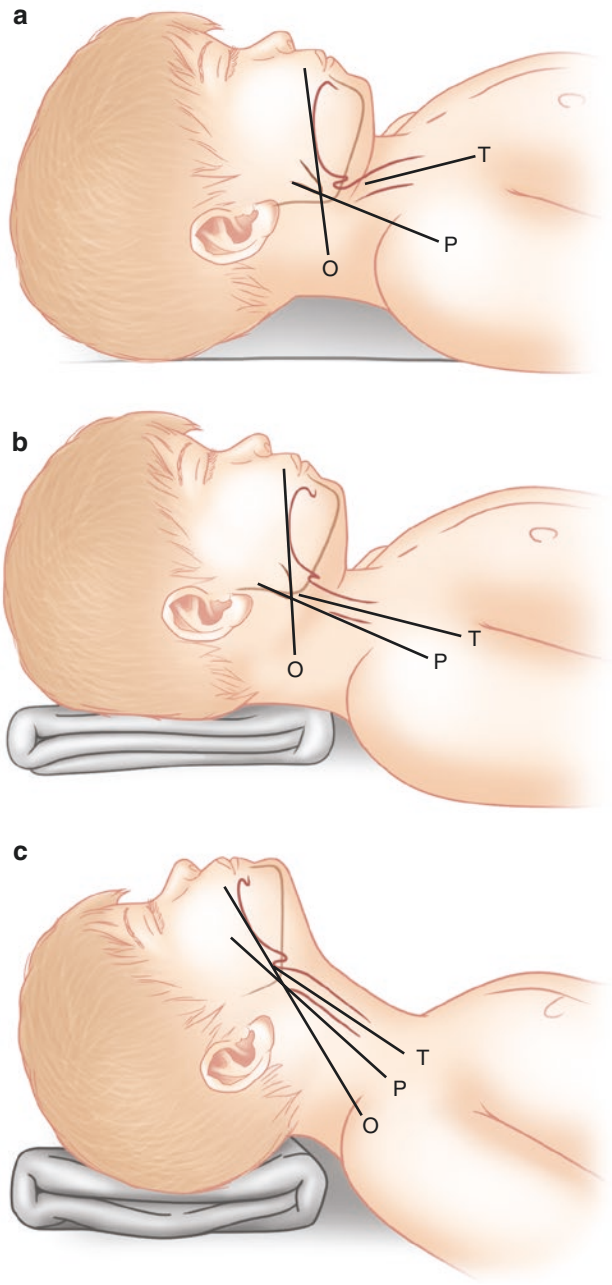

Fig. 37.3 Positioning for pediatric airway alignment (From Wheeler [64], with permission from Springer). Abbreviations: *O* oral axis, *T* tracheal axis, and *P* pharyngeal axis

Table 37.2 Pediatric laryngoscope selection

Child's weight (kg)	Laryngoscope
0–3	Miller 0
3–5	Miller 0, 1
5–15	Miller 1
12–20	Macintosh 2
20–30	Macintosh 2, Miller 2
>30	Macintosh 3, Miller 2

From Wheeler [64], with permission from Springer

Table 37.3 Normal age-adjusted vital signs

Age	Heart rate (beats per minute)	Blood pressure (mmHg)	Respiratory rate (breaths per minute)
Premature	120–170	55–75/35–45	40–70
0–3 months	100–150	65–85/45–55	35–55
3–6 months	90–120	70–90/50–65	30–45
6–12 months	80–120	80–100/55–65	25–40
1–3 years	70–110	90–105/55–70	20–30
3–6 years	65–110	95–110/60–75	20–25
6–12 years	60–95	100–120/60–75	14–22
>12 years	55–85	110–135/65–85	12–18

Pediatric Traumatic Brain Injury

For pediatric trauma patients with traumatic brain injury (TBI), as in adults, prevention of secondary brain injury resulting from hypoxia or hypotension is essential. In addition to maintenance of cerebral perfusion pressure (CPP) above 40 mmHg, the literature supports avoidance of hypoxemia, defined as PaO_2 less than 60 mmHg [32, 46, 47, 61]. Conceptually, maintaining CPP and systemic blood pressure will improve cerebral blood flow (CBF), though some data challenges the notion that these are predictable relationships [45]. According to guidelines for the acute management of pediatric TBI published by the Brain Trauma Foundation [32], consideration should be given to:

1. Hypertonic saline infusion for severe TBI with associated intracranial hypertension:
   (a) Dose 3 % normal saline at 0.1–1 cc/kg/h to maintain ICP <20 mmHg.
   (b) Monitor and maintain serum osmolarity 360 mOsm/L.
2. Moderate hypothermia (32–33 °C) for up to 48 h following severe TBI
3. Avoidance of prophylactic severe hyperventilation (PCO_2 <30 mmHg) during the first 48 h after injury

Corticosteroids are NOT recommended in the acute management of pediatric TBI, as they have been shown to provide no benefit and may increase the risk of inhospital infection [18].

Pediatric Analgesia and Sedation

General Approach

Pediatric patients in the intensive care unit may experience pain related to a medical condition, surgical procedure,

Table 37.4 Anesthetic agents for pediatric populations

Inhalational anesthetic agents
Benzodiazepines
Opioids
Phenothiazines
Butyrophenones
Antihistamines
Chloral hydrate
Etomidate
Ketamine
Barbiturates
Propofol
Alpha-adrenergic agonists

From Wheeler [65], with permission from Springer

endotracheal intubation, or other procedures. Anxiety and agitation may compound pain and be precipitated by the separation from parents and familiar environment, sleep deprivation, and loss of self-control and the ability to self-sooth [54]. Attention to analgesia and sedation for the pediatric patient is therefore essential. Tolerance, withdrawal, and physical dependency on sedative and analgesic medications have long been reported in the adult literature, and building evidence documents the occurrence in the critically ill pediatric population as well [59]. As such, children who are exposed to long-term infusions of these medications should be observed for evidence of withdrawal and consideration given to slowly tapering these medications.

Medication Dosing

Pediatric medication dosages are weight based and should be calculated and/or confirmed with the aid of a pediatric dosing chart or pharmacist. The Broselow™ tape includes a number of medications utilized in the acute resuscitation of the critically ill child, including sedatives and analgesics. Table 37.4 outlines a number of options for analgesia and sedation.

ICU Procedural Considerations

Central Venous Access

The comparatively small vein size and need for procedural sedation or analgesia make the placement of a pediatric central venous catheter (CVC) more challenging than in the adult patient. Considerations prior to the placement of a CVC should include the indication for central access, technical factors, and risk and benefit of chosen placement site. Indications for central access include inadequate peripheral venous access, the need to administer noxious medications, hemodynamic monitoring, and extracorporeal therapies.

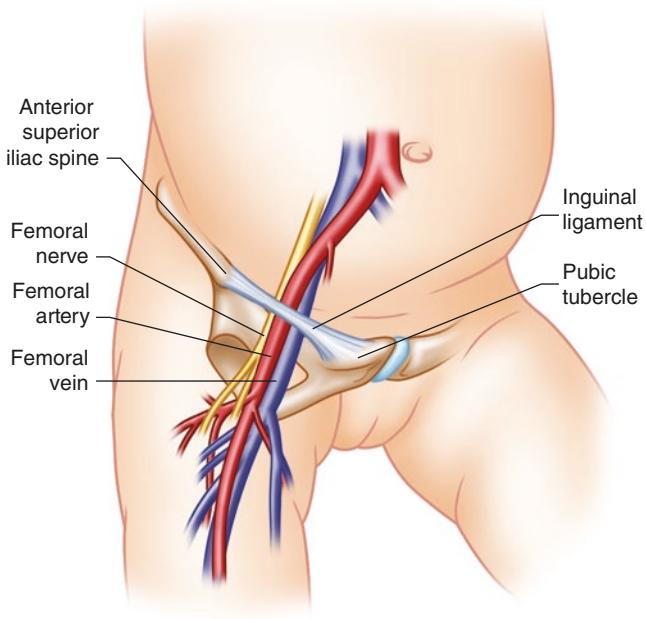

Fig. 37.4 Anatomic landmarks for pediatric femoral venipuncture (From Wheeler [64], with permission from Springer)

Indication for CVC insertion, contraindications, including coagulopathy and risk of sedation administration, and complication profile should guide site choice [12]. The presence of coagulopathy and risk of airway compromise with sedation should lead the practitioner to consider the femoral venous site. In a study of 121 critically ill pediatric emergency department patients requiring central venous access, the majority (83 %) were cannulated via the femoral vein with the remainder accessed via either the subclavian or internal jugular approach [10]. This might reflect the presence of a contraindication to other sites or the relative technical ease with which the anatomic landmarks for a femoral CVC can be identified (Fig. 37.4) [1]. However, the mechanical complication rate of femoral access may be higher than that of the internal jugular vein [62]. The internal jugular is often chosen over the subclavian approach due to the compressibility of the jugular and the improved success rate for CVC placement with the use of ultrasound as an adjunct [8, 64].

Intraosseous Access

When CVC catheter placement is not possible, intraosseous (IO) access can safely and effectively provide a route for administration of fluid resuscitation, blood products, and noxious medications [2]. This route should only be utilized temporarily, and the practitioner should be familiar with

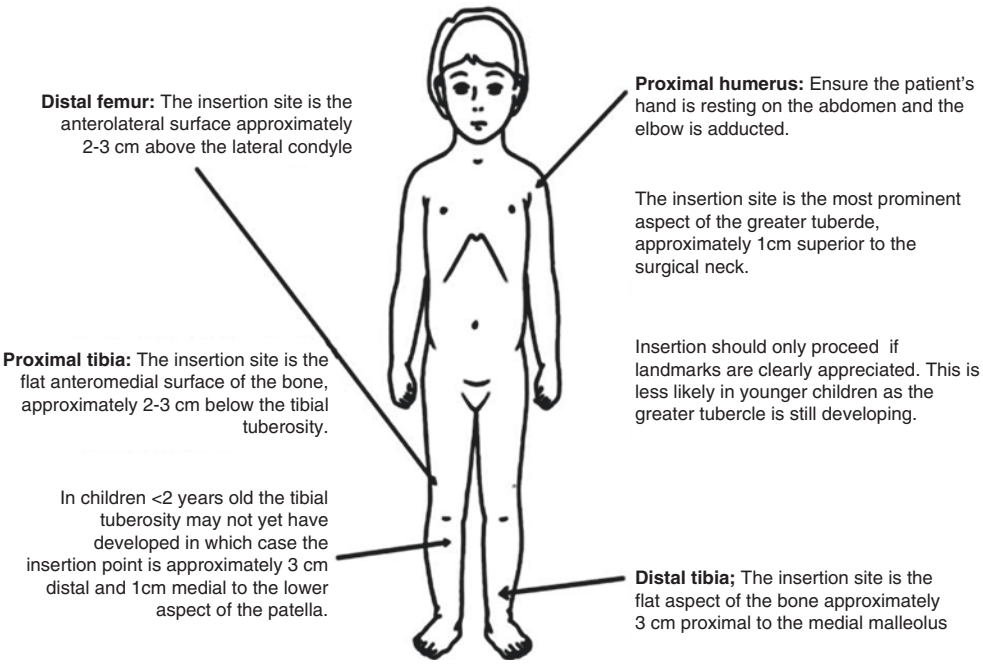

Fig. 37.5 Pediatric intraosseous line insertion sites (From Scott-Warren and Morley [52], used with permission)

insertion technique to avoid complications of IO placement, including osteomyelitis, bone fracture, and soft tissue infiltration leading to ischemia or compartment syndrome [2, 41].

Technical considerations for the placement of the Arrow EZ IO ™ are outlined below [52], (Fig. 37.5):

1. Identify anatomic site for the placement: distal femur, proximal humerus, proximal tibia, and distal tibia.
2. Needle set selection:
   A 45 mm needle (yellow hub) should be considered for proximal humerus insertion in patients 40 kg and greater and patients with excessive tissue over any insertion site.
   A 25 mm needle (blue hub) should be considered for patients 3 kg and greater.
   A 15 mm needle (pink hub) should be considered for patients approximately 3–39 kg.
3. Insertion: ensure the 5 mm mark is still visible above the skin to confirm adequate depth.
4. Insertion completion: removal of the drill apparatus, sterile dressing, and aspiration of the marrow:
   If child is responsive to pain: slow infusion of weight-based IV lidocaine via intraosseous line
   If child is unresponsive to pain: prime intraosseous line with saline
5. Connect fluid and pressurize up to 300 mmHg.

Arterial Access

Indications for arterial access include the need for frequent arterial blood gases or continuous blood pressure. The radial artery is the preferred site as it is easily compressible, intact collateral flow can be easily documented using the Allen's test, and restraint of the limb is simple to accomplish in the uncooperative patient. Additionally, in the case of pediatric patients with congenital heart disease, the right radial artery most closely approximates cerebral perfusion pressure and oxygenation. Other acceptable sites include the dorsalis pedis, femoral, axillary, and brachial arteries. The brachial and femoral sites increase the risk of malperfusion of the distal extremity, while the femoral site additionally increases the risk of unrecognized retroperitoneal hematoma and site or blood stream infection. Ultrasound is a useful adjunct for the placement of arterial catheters as it has been demonstrated to improve the first-attempt success in the pediatric population [21]. Arterial catheter size selection is critical, as appropriate size selection will reduce the risk of catheter-associated complications such as vasospasm, thrombosis, and embolism (Table 37.5).

Table 37.5 Pediatric arterial catheter sizing

Artery	<10 kg	10–40 kg	>40 kg
	Catheter gauge (French)	Catheter gauge (French)	Catheter gauge (French)
Radial, dorsalis pedis, brachial	22, 24	22	20, 22
Femoral or axillary	18, 20 (3.0–4.0)	16, 18 (4.0–5.0)	14, 16, 18 (5.0–6.0)
Umbilical	(3.5–5.0)		

Intubation

Length-based estimation and age-based formula estimation are both acceptable means of choosing endotracheal tube

size, offering comparable accuracy. Additionally, approximation of endotracheal tube diameter by the fifth digital circumference has been written about by authors such as King et al. who concluded that this method is inferior to age-based formulas and should be reserved for situations in which age is unknown [31].

The most widely applied age-based estimation formulas are the Cole and Khine formulas. Cole's formula predicts uncuffed endotracheal tube size as equal to (age 4)+4, whereas Khine's formula predicts cuffed endotracheal tube size as equal to (age/4)+3 [30, 58]. For length-based estimation, the Broselow™ tape and color-coded system provide guidance for endotracheal tube sizing. Uncuffed endotracheal tubes are generally reserved for patients less than 8 years of age, though recent data has challenged the assertion cuffed endotracheal tubes are unsafe for children in this age range [58].

Tube Thoracostomy

Drainage of intrapleural air, blood, effusion, or empyema can be accomplished with the placement of a thoracostomy. The nature of the effluent should guide choice of a tube thoracostomy or pigtail thoracostomy. For drainage of pneumothorax alone, pigtail catheters have been shown to be equally efficacious with reduced tube site discomfort when compared to tube thoracostomy [34]. However, in a study by Petel et al., drainage of empyema by tube thoracostomy was compared to drainage by pigtail catheter [44]. Failure rate was higher among patients treated with pigtail drainage (43 % vs 14 %, $P=0.045$), but duration of illness was shorter (18.3 ± 1.0 vs 25.6 ± 3.5 days, $P=0.048$) [44]. This difference may have been related to clogging of the tube and resultant incomplete drainage of the empyema. Similar concerns have led many practitioners to choose large bore tube thoracostomy over pigtail drainage of hemothoraces. The placement of a pigtail catheter is accomplished by sterile Seldinger technique in the fifth intercostal space and requires local anesthetic only. The placement of a tube thoracostomy begins with local anesthetic and analgesia and may require sedation depending on patient tolerance. A skin incision is placed one rib level below the fifth intercostal space in the anterior to mid-axillary line. The soft tissue and muscle are bluntly spread down to the level of the rib, and the pleural cavity is entered just above the rib. The tube is advanced over a clamp into the pleural space. The tube should then be connected to a closed drainage system and sutured in place.

Ultrasound

Considerable data exists on the benefits of ultrasound guidance in the placement of peripheral and central venous access in the pediatric population, including reduction in time to the placement and fewer attempts [14]. Ultrasound guidance for the placement of femoral or internal jugular central access is now considered standard of care based on data indicating improved success rates and decreased overall complication rates [38]. Ultrasound may also be useful in the pediatric patient in assessing for the presence of fluid in the pleural space and to guide successful drainage when present [35].

Indications for ECMO

Indications for consideration of extracorporeal membrane oxygenation (ECMO) differ between the neonatal and pediatric population. Cases of neonatal severe respiratory failure refractory to maximal medical management, with a potentially reversible etiology, should prompt consultation for transfer to an EMCO center. In the pediatric population (age greater than 30 days to 18 years), consideration for ECMO is best within the first 7 days of mechanical ventilation at high levels of support. Outcomes after ECMO in the neonatal and pediatric population are better than those in their adult counterparts. In 2015, survival to discharge or transfer among neonatal and pediatric patients treated with ECMO for respiratory failure was 74 % and 57 %, respectively. In the patient with adequate cardiac performance, venovenous cannulation is the preferred route. In larger children, as in adults, access sites include the jugular and femoral sites.

Psychosocial Considerations in Pediatric Intensive Care

Caring for a critically ill child also necessitates care for the family of the sick child as well. Excellent communication with the family requires special attention. An approach to this communication is outlined in Box 37.1. The presence of family members during acute resuscitation has been a debated topic, with evidence that parental presence during resuscitation efforts is perceived by parents as beneficial to both themselves and the patient [7]. Despite this, acceptance of parent presence is mixed among providers, with nursing staff and senior physicians demonstrating higher levels of acceptance [39]. Given that up to 25 % of children demonstrate negative psychological and behavioral outcomes within the first-year post-discharge from a critical care environment, the psychosocial health of the critically ill patient also warrants additional attention [50]. Care should be taken to minimize pain and anxiety for the child during the ICU admission.

Box 37.1: Suggestions for Physician Communication with Families

1. Arrange for a quiet room to sit with the family, unhurried and away from the demands of the unit.
2. Talk to them in simple terms about what is happening to their child, what you are attempting to do, and the chance for and against the child's recovery.
3. Ask them for their questions and their input, respecting cultural and religious perspectives and recognizing the need for interpreter services.
4. Empathize with the frustration, fears, temptations, and anxieties with which they struggle.
5. Do not judge them on their thoughts. Instead, acknowledge and validate feelings.
6. Try to meet with them regularly and more frequently, even for short periods, to keep them updates on their child's condition.
7. Designate a specific team member to deal with the family when the stay in the ICU is prolonged. Families have difficulty relating to multiple physicians.
8. Encourage the family's continued involvement with the other members of the family.
9. Always remember to bear with them and tolerate silence as well as their own ways of expressing their emotions.
10. When the parent has been directly responsible for what has happened to the child, take whatever action is required to provide for the immediate and future safety of the child as well as the other children in the family. Do so, however, without being judgmental of those involved.

From Wheeler et al. [66].

The Adult ICU Patient with Congenital Disease (Pediatric Disease)

Pulmonary Considerations

Cystic Fibrosis

Many patients with cystic fibrosis (CF) survive to adulthood and will require critical care at some point. The majority of the cystic fibrosis-related complications leading to ICU admission will be pulmonary or gastrointestinal.

Respiratory Complications

The most common adulthood pulmonary complications include pneumothorax, hemoptysis, and acute respiratory failure [56]. Pneumothorax is a very common complication of CF, occurring in greater than 3 % of all CF patients, and is caused by mucus plugging of the airways with alveolar air trapping [20]. Diagnosis is made with chest X-ray (CXR) or computed tomography (CT). Up to one third will recur, and failure of conservative management leads to surgical intervention in up to 70 % of cases [19]. Therefore, unlike small, asymptomatic pneumothoraces in other populations which are often observed for resolution, standard treatment is tube thoracotomy drainage irrespective of size or symptoms. Massive hemoptysis is common in the CF population owing to the frequency of pulmonary infection leading to chronic inflammation and bronchial artery angiogenesis [56], [9]. Diagnosis is made by clinical suspicion, CXR, CTA, and, in select circumstances, bronchoscopy. Management should include reversal of CF-induced, vitamin K-deficient coagulopathy and consideration for bronchial artery embolization [56]. Up to 80 % of CF patients eventually succumb to respiratory failure resulting from progression of obstructive airway disease. CF patients with acute-on-chronic respiratory failure should be managed with antibiotics, bronchodilators, and aggressive pulmonary toilet, including consideration for bronchoscopy in the case of larger airway plugging [56]. Noninvasive positive pressure ventilation (NIPPV) has been demonstrated to improve chest symptoms, exertional dyspnea, nocturnal hypoventilation, and peak exercise capacity in patients with stable CF [63]. However, in the CF patient with acute-on-chronic respiratory failure, NIPPV should be viewed as a bridge to transplant [36]. Intubation is associated with poor outcome in this population, likely related both to overall disease progression leading to hypercapnia and the inability of conventional ventilation to manage this hypercapnia, but may be necessary in the case of respiratory fatigue [53]. For patients with irreversible causes of acute-on-chronic respiratory failure due to CF, a lung transplant center should be involved in the initial management decisions.

Gastrointestinal Complications

Pancreatitis and distal intestinal obstruction syndrome (DIOS) may result in ICU admission of an adult patient with cystic fibrosis. Pancreatitis in this patient population is treated similarly to the management in the non-CF patient, with hydration and analgesia as the cornerstones [29]. DIOS occurs in up to 22 % of CF patients and is more commonly found in patients with concomitant pancreatitis, likely owing to the increased viscosity of the high-fat stool in these patients [15], [29]. Symptoms of DIOS mimic those of mechanical bowel obstruction with obstipation, nausea, vomiting, and colicky abdominal pain as primary manifestations. Treatment of DIOS should focus on conservative medical management including enemas or oral treatment with meglumine diatrizoate,

laxatives, or N-acetyl-cysteine [15]. Surgery should be reserved for those with failure of aggressive medical therapy.

Cardiac Considerations

Congenital Heart Disease

As a result of tremendous advances in the care of infants born with congenital heart disease (CHD), over 85 % of these patients now survive to adulthood [60]. Admission to the adult ICU may be unrelated to the primary congenital defect or may be for reoperation of the primary defect or correction of a defect recognized in adulthood. Understanding the pathophysiology of the primary defect should inform multisystem management decisions. Additionally, patients with adult congenital heart disease (ACHD) require special consideration in the ICU due to increased incidence of cardiac, pulmonary, renal, and hepatic dysfunction related to the primary congenital defect and the increased perioperative mortality risk in those with thyroid, renal, and hepatic dysfunction [48, 51]. These considerations will be the focus of this section.

Cardiac Arrhythmia

Cardiac arrhythmias are a leading cause of sudden cardiac death (SCD) in the ACHD population and can be incited by postoperative state or systemic illness [51]. Risk factors for SCD include documented "prior SVTs (predominantly atrial flutter or fibrillation), increased QRS duration, QT dispersion, and moderately to severely impaired systolic function of the systemic and/or subpulmonary ventricle" [33]. Despite this association, the most common arrhythmia leading to SCD is ventricular fibrillation [33]. Because of this association, critically ill patients with ACHD and high-risk features for SCD, including sustained ventricular tachycardia and cardiac arrest, should be considered for implantable cardioverter-defibrillator (ICD) placement [17, 51].

Heart Failure

Patients with ACHD frequently develop heart failure, and therefore advanced cardiac monitoring may be necessary in the ICU. Noninvasive evaluation of cardiac function with transthoracic echocardiography (TTE) should be done for all critically ill ACHD patients. Consideration for transesophageal echocardiography (TEE) includes the presence of congenital heart defects, as the imaging quality and reproducibility of this modality are superior. Ongoing need for hemodynamic assessment should prompt consideration for the placement of a miniaturized TEE, with recent data indicating that brief training in the placement of these probes is sufficient to permit accurate collection of hemodynamic data [11].

Cardiopulmonary

The incidence of right-sided heart dysfunction is higher in this population than in other groups as is the incidence of pulmonary vascular disease [6]. Given this, it is very important to minimize the cardiac effects of ventilator support. As such, PEEP should be minimized when possible, and pulmonary vasoconstriction should be avoided by optimizing $PaCo_2$ and preventing hypoxemia [51]. A recently published scientific statement from the American Heart Association on Congenital Heart Disease in the older adult is an excellent review and guide on this topic [6].

Acute Kidney Injury

Up to 50 % of adults with CHD have chronic kidney disease (CKD), and among those with moderate to severe impairment, baseline mortality is three times higher, and perioperative mortality is significantly increased [13, 48]. Those with cyanotic CHD are most likely to develop CKD, the pathogenesis of which is related to hypoxia, activation of the renin-angiotensin system as a result of marginal systemic cardiac output, and prior exposure to cardiopulmonary bypass [51]. Management of critically ill ACHD patients with CKD must include careful attention to volume status and early intervention to prevent intravascular volume overload. Consideration should include early continuous venovenous hemodialysis (CVVHD) where appropriate [16].

Hepatic Dysfunction

Cardiac cirrhosis with portal hypertension and ascites is common in the ACHD population owing to the physiologic effects of chronic venous congestion and exposure to hepatotoxic insults [51]. There are a number of potential contributors to venous congestion pathogenesis, including right-sided heart failure, single-ventricle physiology, chronic left-sided heart failure, and systemic-pulmonary shunting. Many ACHD patients are additionally exposed to the hepatotoxic effects of transfusion, cardiopulmonary bypass, and hepatotoxic medications, including anti-arrhythmics [3]. The pattern of hepatic dysfunction may guide diagnosis, with isolated transaminitis indicating hepatic ischemia and low flow, hyperbilirubinemia and elevated prothrombin time indicating passive congestion, and cholestatic jaundice indicating ischemic cholangiopathy or obstruction [3]. Additionally, ACHD patients with hepatopathy have an increased risk of hepatocellular carcinoma and therefore should be screened regularly with serum AFP levels and imaging [3].

Hematologic

Adults with cyanotic CHD are at increased risk for both thromboembolic and bleeding complications [22]. Chronic cyanosis leads to secondary erythrocytosis, and more than one third of patients with cyanotic CHD have iron-deficient

anemia [55]. These two factors contribute to a state of blood hyperviscosity, putting these patients at increased risk of thromboembolic events [28]. Despite this, the same population is hypocoagulable due to impaired fibrinogen function and therefore at risk for bleeding complications [27]. Given the competing nature of hematologic derangements in this patient population, decisions about thromboembolic prophylaxis and modulation of bleeding risk must be individualized.

Neurologic Considerations

VP Shunt Complications

Ventriculoperitoneal shunt (VPS) placement is the most common treatment modality for hydrocephalus. Adults with chronic VPS in place since childhood are at risk for the development of similar complications to those identified in any patient with a VPS, including shunt occlusion, disconnection, infection, and abdominal cavity complications, but with a higher frequency of these complications over a lifetime [49]. Shunt occlusion should be considered in any patient with a VPS presenting with headache, depressed mental status, and/or emesis. Diagnoses can often be made on CT scan of the head demonstrating hydrocephalus [4]. Management of this complication nearly always requires surgical shunt revision. Disconnection of the shunt should be suspected if focal swelling is noted along the tract of the shunt or if signs or symptoms of increased intracranial pressure are noted. The site of shunt fracture can often be identified on plain X-ray. Treatment of symptomatic shunt fracture should include revision, though some controversy surrounds the management of asymptomatic shunt fracture.

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Organ Donor Management

38

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History of Organ Donation

The processes of organ donation and transplantation have developed considerably over the past decades. As early as the beginning of the twentieth century, there were successful reports of transplantation of human skin and cornea [1, 2]. However, it was not until 1954 that the first successful solid organ transplant between identical twins was reported at the Peter Bent Brigham Hospital, Boston [3]. The advancement of immunosuppressive therapy over the years and the improvement in life-sustaining therapy have increased the potentials for cadaveric organ donation.

In 1968, the Harvard Commission outlined the first standard set of criteria for brain death [4]. The Uniform Anatomic Gift Act was also passed into law during this time, legalizing cadaveric organ donation for transplantation. Because of the widening gap between organ demand and supply in the 1990s, the concept of donation after cardiac death (DCD) was introduced for patients with irreversible conditions whose hearts ceased to beat after withdrawal of life-sustaining therapy [3]. By 2000, the US Department of Health and Human Services introduced the "Final Rule" for organ procurement and transplantation to ensure broader and fair allocation of available organs to the patients with the most urgent medical conditions [5].

Other advances have been made in recent years to improve the quality and quantity of organs available for the transplantation to meet the demands of the ever-growing population of recipients. Organ donation is rapidly becoming a common and culturally accepted practice, while transplantation has become the preferred treatment for end-stage solid organ failure. The rest of this chapter will highlight the important parts of the organ donation process and recommendations for improved donation outcomes.

Identifying Potential Donors

There are three major sources of organs used for transplants. These are from cadaveric "brain-dead" donors (donors after neurologic determination of death, DNDD), cadaveric "cardiac death" donors (donors after circulatory determination of death, DCDD), and living (related and unrelated) donors. Currently, the majority of transplanted organs come from donors after neurologic determination of death. In 2014, there were 23,715 (80 %) deceased donor transplants, while there were only 5,817 (20 %) living donor transplants [6].

The vast majority of cadaveric "brain-dead" donors die from cerebrovascular accidents (CVA), head trauma, and anoxia [7]. Since nearly 50,000 US residents die from TBI and nearly 142,000 citizens die from CVA per year, these two causes of death are likely going to make large contributions to the organ pool in the coming years [8].

In the course of patient care, it is important to be expectant and proactive in identifying individuals that may potentially donate organs and taking the next necessary steps toward organ recovery.

Referral of Potential Donors

Once the potential donors have been identified, organ procurement organizations (OPOs) must be involved in the management of the donation process. This referral step should be taken as early as possible because early referral is associated with better outcomes including higher consent rates and conversion rates [9]. Early referral gives the OPOs the opportunity to form relationships with the caregivers, educate them on the details of the process, and attend to the

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unique ethical and social needs of each situation. In a study of families that denied donation, it was found that 53 % of them did not receive adequate education, and the next of kins that decided against donation usually had less understanding of brain death than those that agreed to donation [10].

Of note, the task of obtaining consent to donate should not be carried out by the physician but should be left to the staff of the OPOs since they have the necessary training and experience.

Team Management Approaches to Donation

Like any successful process, the organ donation process requires teamwork. Aside from the primary physician, other members of the healthcare team play critical roles in guiding the families and supporting them in their grief. A senior physician should interact with the families early in the process and be identified as a ready source of support.

The presence of OPO staff housed within the hospital is also crucial for optimal donation outcomes. These in-house coordinators are usually nurses trained in organ procurement, and they form strong bonds with donor families, providing support, ensuring the timings of discussions are appropriate, and adapting the approaches to the cultural backgrounds of the families. They also ensure timely donor referral via donor surveillance, organize regular staff education sessions, and daily monitor the donation activities of the hospital. Implementation of in-house coordinators has been shown to increase consent and conversion rates significantly [11]. Hospitals that operate this system have been shown to have up to 28 % greater consent rates and 48 % greater conversion rates when compared to other hospitals with similar resources but without in-house coordinators. Other improvements in outcomes shown after the implementation of in-house coordinators include higher referral rates, lower family decline rates, and increased organs transplanted per donor [12]. This effect is more marked in centers with minority populations [11–13]. Increases in consent rates of up to 88 % have been shown in blacks after the implementation of in-house coordinators in Level I trauma centers. The reasons for the better outcomes in hospitals with in-house coordinators can be linked to the better access they have to the patients and the ease of relationship building with the clinical and management staff of the hospital [13].

Neurological Criteria for Determination of Death

Since the criteria for brain death were first outlined by the Harvard Commission in 1968, there have been several modifications to adapt to the evolving clinical and ethical climates. The recent 2010 evidence-based recommendations for the determination of brain death among adult patients published by the Quality Standards Subcommittee of the American Academy of Neurology state that the apnea test is a safe method for determining neurological death [14]. Other important aspects of the evaluation for neurological death include response to pain, pupillary response, oculocephalic reflex, corneal reflex, and the cold caloric reflex test.

Although there are several variations of the apnea test, the commonly accepted method is recommended by the American Academy of Neurology. This involves preoxygenating the patient with 100 % oxygen for 10 min and ensuring arterial pCO_2 of 35–45 mmHg, core temperature of 36.5 °C (97 °F), and systolic blood pressure above 90 mmHg. Arterial blood gas (ABG) should be drawn at the beginning of the test. A cut nasal cannula is slid to approximately the level of the carina to deliver 100 % oxygen at 8 L/min. Once the pulse oximeter is confirmed to be working, the ventilator is disconnected. The presence of spontaneous respiratory movements is then assessed. A fall of the pulse oximeter readings below 90 % or systolic blood pressure below 90 mmHg indicates completion of the test. Ventilatory support should be resumed and ABG drawn. If the patient tolerates the test for 10 min, then the test is also ended and the patient is placed back on the ventilator and an ABG is drawn. For both scenarios, if the ABG measures a pCO_2 above 60 mmHg or 20 mmHg above the pCO_2 measured on the initial ABG, the apnea test result is considered positive, and the diagnosis of brain death is made.

Once the assessment of neurological death is made, family members should ideally be informed. On religious grounds, however, some families would prefer not to be informed about brain death. In several states such as New York and New Jersey, it is illegal to make the declaration of death by neurologic criteria if the family or individual previously objected to the concept of brain death based on religious beliefs [15]. Under these circumstances, the physician is required to continue medical support. In addition, the number of physicians required to diagnose brain death, as well as the type and need for confirmatory tests, varies among and within countries.

Donation After Circulatory Determination of Death

Historically, because the "Dead Donor Rule" stipulates that patients be declared dead before the removal of life-sustaining organs, operations for donation were performed with organs from donors who had recently died of cardiopulmonary arrest. As the idea of death evolved to include the concept of a neurologic determination of death, patients with catastrophic brain injuries became a substantial source of organs for transplantation once declared dead by neurologic criteria. Because their hearts were still beating, their organs

were better preserved than the previous donors who had been declared by cardiopulmonary criteria. In the last two decades, however, the scarcity of organs available for transplantation has renewed the interest in "non-heart-beating donors" or donation after cardiac death (DCD).

Based on recommendations of the Institute of Medicine, there are increasing numbers of organs being obtained from patients that were declared dead following the cessation of circulatory function, rather than neurological death [16]. Donation after circulatory determination of death (DCDD) has increased the supply of organs available for transplantation and now accounts for about 12 % of deceased organ donors in the USA [17, 18]. This option has been used when a patient or the patient's surrogate desires to withdraw life support but would like to donate organs. Following the withdrawal of life support and resuscitative interventions, the patient is declared dead after permanent circulatory arrest has occurred [16, 19]. Importantly, long-term graft survival of DCDD organs, particularly kidneys, appears to be similar to that of donation after neurological determination of death (DNDD) organs [20–24].

Pathophysiology of Brain Death

Neurologic death is caused by the herniation of cerebral contents due to supranormal intracranial pressures. Early pontine ischemia results in a catecholamine surge with hypertension, known commonly as the first stage of the Cushing's reflex. As ischemia progresses caudally to the vagal nucleus in the medulla oblongata, the loss of baroreflector reflexes and unopposed sympathetic activity results in a profound hyperdynamic state [25]. This sympathetic vasoconstriction causes compromise of end-organ perfusion.

As the brain continues to herniate, a sudden cardiovascular collapse can develop, in part due to direct catecholamine-induced myocardial injury and subsequent cardiac dysfunction, as well as destruction of pontine and medullary vasomotor centers [26, 27]. The effects of this hemodynamic instability can cause marked damage to potentially donatable end organs. Profound hypotension develops due to loss of sympathetic tone, amplified by the development of diabetes insipidus (DI) due to an infarcted posterior pituitary.

The physiologic changes that manifest as different portions of the brain become injured during the herniation process present a multifaceted challenge to the treating intensivist. These physiologic alterations result in diffuse vascular regulatory disturbances and widespread cellular injury [28]. Major swings in hormone levels are seen. Severe alterations also occur in metabolism, immunology, and coagulopathy [29–31]. Understanding these physiological responses is important for the optimal care of the injured patient and maximal utility of donated organs.

Systemic Sequelae of Brain Death

Cardiovascular System

Two distinct, and in many ways, opposite, profiles of hemodynamic activity are seen during the process of neurologic death. Brain stem ischemia causes a catecholamine surge as the medulla endeavors to maintain cerebral perfusion pressure and improve local tissue oxygenation. This response manifests as increases in heart rate, blood pressure, cardiac output, and systemic vascular resistance. This surge of catecholamines can challenge the balance between myocardial supply and demand. Several autopsy studies have demonstrated left ventricular subendocardial necrosis [32, 33]. ECG changes and cardiac arrhythmias are common and are thought to be due to both metabolic and electrolyte abnormalities, as well as infarction of the conduction system. The use of standard antiarrhythmic therapy is appropriate. An important caveat to remember is that vagus nerve disruption in the brain stem may result in a bradyarrhythmia which is resistant to the effects of atropine, and a beta-adrenergic agonist such as isoproterenol or epinephrine may be required [34]. Untreated arrhythmias may become completely refractory to management if not treated early and aggressively.

The second phase of cardiovascular activity, characterized by hemodynamic collapse, coincides with brain stem herniation and results in the loss of sympathetic activity causing profound vasodilatation, myocardial depression, and low levels of serum catecholamines. The hemodynamic effects can be amplified by hypovolemia due to diabetes insipidus which is often present concurrently. Additional myocardial depression may be due to a concurrent reduction in triiodothyronine (T3) production as well as direct mitochondrial inhibition.

Cardiac catheterization may be more selectively employed for donors >55 years of age and younger patients with a history of cocaine use, or three or more risk factors for coronary artery disease such as hypertension, diabetes, dyslipidemia, prolonged smoking history, or family history of premature coronary artery disease [35]. In the setting of left ventricular dysfunction, pulmonary artery catheter-directed management can maximize donor recovery. Knowledge of the patient's cardiac output and left ventricular filling pressures allows for optimal management of vasopressors and fluids. The role of adjunctive hormone therapy to improve cardiac function is discussed below.

Pulmonary System

Increased systemic pressures and left atrial pressures during the catecholamine surge can result in elevated pulmonary artery pressures and subsequent endothelial damage, leading

to direct pulmonary damage due to capillary leak. During cardiovascular collapse, intravenous fluid administration needed to maintain systemic blood pressure can cause further pulmonary damage due to volume overload, pulmonary capillary leak, and resultant development of pulmonary edema. Increased pulmonary capillary permeability as well as decreased pulmonary resistance makes the lungs particularly sensitive to increases in volume loading [36, 37].

Lung protective strategies commonly used in the intensive care unit should continue to be performed in the potential organ donor. In the brain-injured patient, hyperventilatory strategies are often employed, aimed at promoting hypocapnia and lower intracranial pressures through cerebral vasoconstriction. These same alkalinizing strategies can exasperate bronchospasm, airway edema, and pulmonary microvascular permeability [38]. High-minute ventilation strategies should be reversed after the declaration of neurologic death. Strategies to minimize atelectasis and promote alveolar recruitment should be employed. Protective modes of ventilation should be used to achieve a target PaO_2/FiO_2 ratio of >300. The protective strategies of the ARDSNET goals of low tidal volumes (6–8 mL/kg) and low plateau pressures (<30 cm H_2O) serve to minimize alveolar shear injury, volutrauma, and barotrauma [39]. Appropriate pressure control modes or newer modes such as airway pressure release ventilation can minimize lung injury and improve PaO_2/FiO_2 ratios [40].

Pulmonary toilet maneuvers such as chest percussion, postural drainage, recruitment maneuvers, and serial bronchoscopy can also improve lung function. Protocols with built-in lung recruitment maneuvers of brief periods of increased positive end-expiratory pressure to 30 cm H_2O have been shown to improve gas exchange and increase the number of suitable lungs for transplantation [41]. Bronchoscopy and lavage for microbiology is a routine part of the donation workup. Bronchoscopy allows for evaluation of individual lungs, as one may be suitable for transplant and the other injured from a process such as contusion or aspiration pneumonitis. Bronchial colonization or infection with bacteria or yeast is seen in up to 80 % of organ donors and correlates with lung recipient survival [42]. High endotracheal cuff pressures can minimize aspiration into the lungs, an important risk in this patient population with likely earlier neurologic injury and loss of cough reflex [40].

Other proposals for interventions to optimize organ function prior to potential donation include the use of high-frequency chest wall oscillation for pulmonary optimization and inhaled nitric oxide to support cardiopulmonary function [43, 44].

Renal System

Sympathetic storm and the subsequent cardiovascular collapse have a deleterious effect upon the renal system. Hypoperfusion of the juxtaglomerular cells of the kidney activates the renin-angiotensin-aldosterone axis, causing salt and water retention as well as vasoconstriction, which in turn can lead to compromised renal blood flow, glomerular and tubular injury, and ultimately renal insufficiency. This directly compromises kidney viability and post-transplantation function and underscores the need for active hemodynamic management in donors.

While dopamine administration is no longer recommended as a first-line vasopressor in the management of the DNDD because of its tachycardic and pro-arrhythmic effects, transplanted kidneys that come from donors treated with low-dose dopamine are better able to withstand ischemic damage during cold preservation and have better graft function post transplantation [45, 46]. The maintenance of urine output to a minimum of 0.5 cc/kg/h, while avoiding the massive diuresis of diabetes insipidus, is the goal of renoprotective resuscitation.

Hepatic System

While the overall inflammatory process of brain death takes its toll less on the liver, hypernatremia (sodium >155 mmol) has been associated with increased rates of transplanted liver allograft loss [47, 48]. It is theorized that hypernatremia promotes the influx of osmotic molecules into hepatocytes which then promote water influx and cell lysis when transplanted into a eunatremic recipient.

Coagulation and Thermoregulation Disorders

Disorders of coagulation are a direct consequence of the release of thromboplastin, cerebrogangliosides, and plasminogen-rich substrate from traumatized brain tissue [49]. Hypothermia and acidosis, along with the dilution of clotting factors, fibrinogen and platelets, can contribute to a state of disseminated intravascular coagulation and uncontrollable bleeding [50]. Massive transfusion protocols including the use of fresh frozen plasma, platelets, and cryoprecipitate are often required. Transfusion of packed red blood cells to a hematocrit >30 % for organ donors is recommended to maximize end-organ oxygen delivery [35]. Hypothermia should be proactively addressed with patient warming devices, including heated intravenous fluids and ventilated gases.

The Role of Protocols in Organ Donation

Because of the complexities involved in the caring for the critically ill patient and the numerous considerations for optimizing donation, it is useful to have written guidelines to

Table 38.1 Sample checklist of donor management goals

End points	Donor management goals
Mean arterial pressure	60–110 mmHg
Central venous pressure	4–10 mmHg
Ejection fraction	≥50 %
Arterial blood gas pH	7.3–7.55
PaO_2/FiO_2	>300
Vasopressors	≤1 at low dose
Serum sodium	135–155 mEq/L
Serum phosphate	>1.5 mEq/L
Blood glucose	≤150 mg/dL
Urine output	≥0.5 cc/kg/h over 4 h

direct the steps taken during the organ donation process. Most organ donors donate after neurological determination of death and may have been earlier managed with the goal of optimizing brain tissue outcome. Many intensive care units have catastrophic brain injury guidelines (CBIGs), which are useful in guiding patients with neurological injuries to recovery.

For the potential donor with severe irreversible neurologic injuries, however, care shifts from maximizing neurologic recovery to the maintenance of the remaining organ systems. Often, there are conflicts about which organ systems to prioritize as attempts to optimize one system may be deleterious to another. Unless the intensivist knows a priori that a particular organ will not be suitable for transplantation, one is faced with a delicate balancing act between the competing needs of several different organ systems. Therefore, the use of a checklist of standardized critical care end points, or donor management goals (DMGs), or aggressive donor management (ADM) protocols, will be beneficial in guiding care providers to optimize the number of organs suitable for transplant from donors. DMGs have been shown to lead to resuscitation of 92 % of organs that initially did not meet transplant criteria, and meeting DMGs prior to organ recovery is an independent predictor for achieving ≥4 organs transplanted per donor (OTPD) [51, 52]. In one center, adoption of a protocol of ADM was associated with an 82 % increase in the number of actual donors, a 71 % increase in the number of organs recovered, and an 87 % decrease in the number of donors lost from hemodynamic instability [53]. Because decreasing the number of donors lost from cardiovascular collapse increases the number of organs available for transplantation, the DMGs have been shown to be effective in improving donation outcomes. A sample checklist of donor management goals is shown in Table 38.1.

Aggressive Resuscitation of Potential Donors

Optimal and aggressive critical care of the potential donor begins long before the declaration of death. To ensure that the donor organs would be of utmost benefit to the recipients, efforts must be made to ensure optimal organ status through the process of referral, consent, and organ recovery. Because brain death is associated with profound physiologic alterations that result in diffuse regulatory disturbances and widespread cellular injury, severe alterations in metabolism, endocrine function, and coagulopathy are commonly observed in potential donors [54]. The following components of resuscitation would be useful in addressing some of these responses.

Hemodynamic Monitoring

In order to guide resuscitation and support, a recommended practice is to institute some sort of hemodynamic monitoring. Placement of a pulmonary catheter upon ICU admission has been recommended in the past and has been shown to improve donor outcomes including higher number of recovered organs [55]. This is attributable to the maintenance of optimal cardiac output through the donation process. Echocardiography is routinely used to assess the left ventricular function of a potential donor heart. In the setting of left ventricular dysfunction, pulmonary artery catheter-directed management can maximize donor recovery. It has been shown that properly managed younger hearts with left ventricular dysfunction can markedly recover function after transplantation [56].

Recently, the use of noninvasive methods that measure pulse pressure variations has been introduced to the care of organ donor [57]. The variations in pulse pressure have been used as a measure fluid responsiveness. A variation in pulse pressure of up to 20 % has been shown to be a very sensitive measure of fluid responders.

Aggressive Hemodynamic Management

Due to severe intracranial swelling, there is disruption of the function of the posterior pituitary leading to low or absent levels of vasopressin in up to 90 % of organ donors [58]. The consequence of this is cardiovascular collapse and hypotension with neurogenic diabetes insipidus (DI) occurring in nearly half of all DNDDs [31, 59]. Without adequate intervention, this could result in a massive hypoosmolar diuresis and electrolyte abnormalities. The loss of intravascular volume leads to profound hypotension. It is therefore a high priority to maintain optimal fluid status, through aggressive fluid management, in order to preserve perfusion.

Aggressive fluid resuscitation is recommended to maintain a CVP of 8–12 mmHg and a systolic arterial pressure of between 90 and 140 mmHg [60]. Of note, however, in lung donors, it has been shown that maintenance of a CVP between 8 and 10 mmHg may result in an increased alveolar

arterial oxygen gradient when compared with potential donors maintained between 4 and 6 mmHg [61]. The target mean arterial pressure should be maintained above 70 mmHg throughout resuscitation.

The Role of Vasopressin

After the achievement of adequate fluid resuscitation, vasopressin should be considered as the first choice hemodynamic therapy. Vasopressin (or antidiuretic hormone, ADH) acts upon its V1 subtype receptors found in vascular smooth muscle which are responsible for its vasopressor activity, as well as the V2 subtype found in renal collecting duct epithelia which increases water permeability and is responsible for its antidiuretic activity. 1-Desamino-8-D-arginine vasopressin (DDAVP) is highly selective for the V2 subtype alone and may be used as an adjunctive treatment for DI.

Administration of vasopressin acts to inhibit the diuresis of DI and the resultant hypotension due to its catecholamine-sparing effects and ability to counteract vasodilatation. Vasopressin is also usually seen to be deficient in donors who require catecholamine support [59]. It has replaced dopamine as the first-line of treatment in treating hypotensive patients and is associated with improved organ yield [62].

The Role of Thyroxine

The hemodynamic instability in DNDDs is partly due to low circulating levels of thyroxine. These low levels lead to diminished production of adenosine triphosphate, causing myocardial dysfunction, accumulation of lactate, and resultant circulatory collapse [29, 33, 54]. The etiology of this functional "hypothyroid state" is poorly understood, but may be a result of lower than normal thyroid-stimulating hormone levels caused by the irreversible damage to the hypothalamus and pituitary from ischemia. Another explanation is a decrease in the peripheral conversion of T4 to its more potent analog T3, similar to the euthyroid sick syndrome [63, 64].

Therapeutic replacement with T3 has been associated with complete reversal of anaerobic metabolism and subsequent stabilization of cardiac function when applied to DNDDs [48, 65]. It has been demonstrated that hemodynamically unstable organ donors require a significant decrease in, or complete lack of, vasopressor support after T4 administration [66]. In addition, the use of thyroid hormone has been associated with significant improvements in cardiovascular status, reductions in inotropic support, and decreases in donors lost from cardiac instability [33, 66]. In a study of DNDDs, T4 administration was associated with significantly more organs procured per donor group (3.9 ± 1.7 vs. 3.2 ± 1.7, $P = 0.048$) [67].

A "T4 protocol" is recommended in situations where there are increased vasopressor requirements. This protocol consists of one ampule 50 % dextrose, 2 g of Solu-Medrol, 20 units regular insulin, and 20 mcg of thyroid hormone (T_4), followed by a continuous infusion of 10 mcg/h [68].

The Role of Insulin

After the development of neurologic death, insulin levels have been measured to decrease to 50 % of baseline at 3 h, and even further to 20 % at 13 h [69]. The resulting hyperglycemia has profound effect on allograft function. Hyperglycemia is well known to impact renal function. Protein glycosylation from uncontrolled glucose levels promotes tissue damage. In addition, osmotic diuresis resulting from glucose spillage may overtax renal medullary function and contribute to the diuresis seen in brain death.

Inadequate glucose control among potential donors is associated with declining renal function prior to organ recovery [70]. This may be attributable to the up-regulation of glucose transporter 1 and 2 expression, impaired autoregulation of glomerular capillary pressure, and increased production of multiple inflammatory molecules [59, 71, 72].

Keeping glucose levels under 150 mg/dL using parenteral insulin yields renal allografts with lower creatinine levels [70]. Several studies have demonstrated concern for exceeding tight glucose control leading to hypoglycemic episodes, but in the setting of neurologic death, the concern for brain injury or stroke resulting from hypoglycemia no longer applies. Therefore, strict glucose control to attain levels from 80 to 110 mg/dL may lead to improved renal allograft function.

The Role of Steroids

The systemic responses known to follow brain death include a massive inflammatory response characterized by elevations in plasma levels of inflammatory mediators such as interleukin-6 and tumor necrosis factor. This increase in cytokine levels can be detrimental to the function and survival of grafts from potential organ donors [73]. Increased plasma levels of interleukin-6 have been shown to be associated with decreased graft survival [74]. Animal studies have demonstrated the effect of neurologic death upon ICAM-1 expression and leukocyte infiltration into peripheral organs, as well as a time-dependent progression of immune-mediated organ dysfunction [75].

Steroids exert anti-inflammatory effects by decreasing levels of serum cytokines [76]. Decreases in serum cytokines can lead to improved post-transplant organ viability [77]. Steroids also act to overcome a relative adrenal insufficiency as a result of the stress of traumatic brain injury [58]. The use of steroids has been shown to improve pulmonary function and lead to the utilization of lungs which

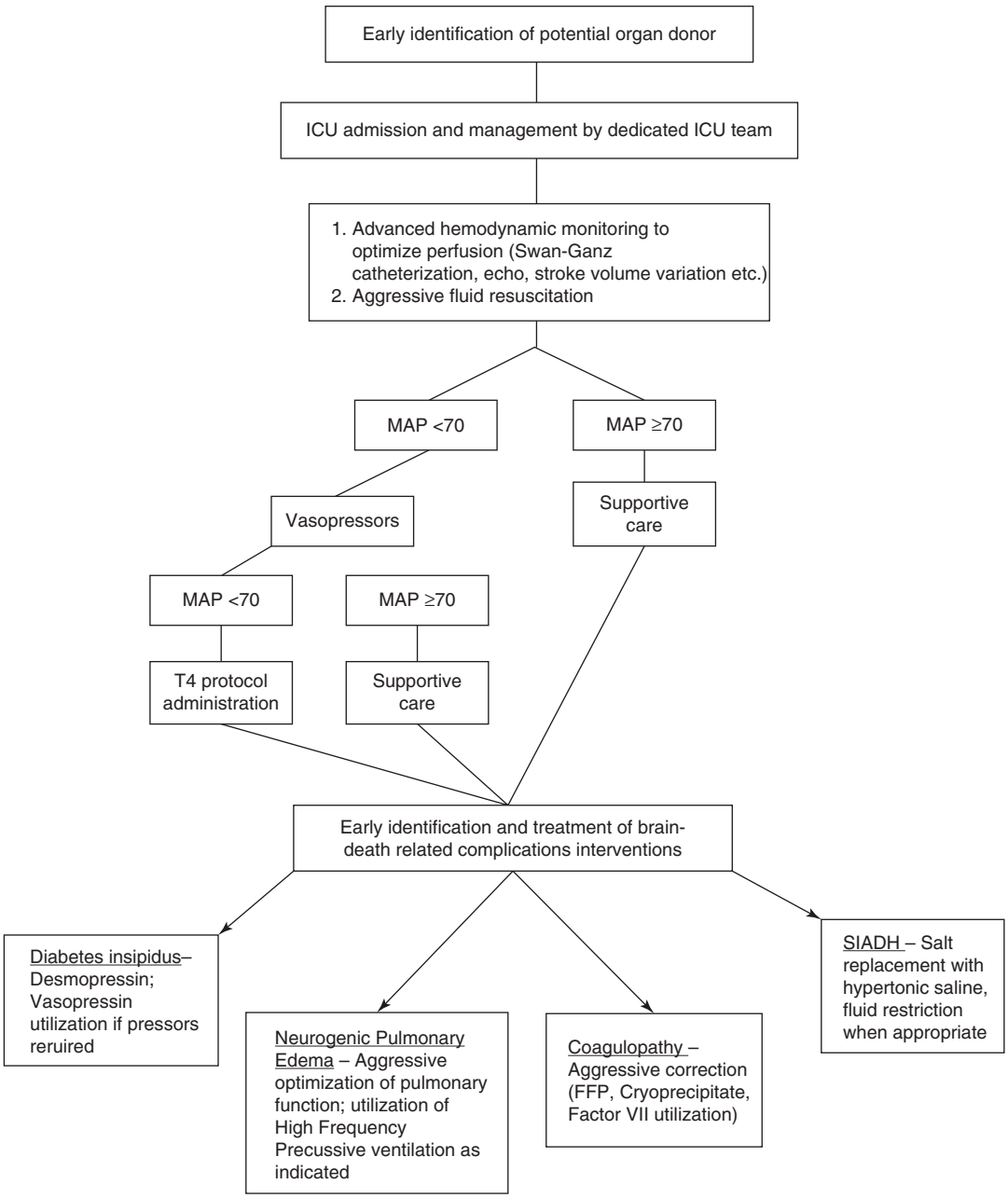

Fig. 38.1 Algorithm for optimal donor management

may have been previously deemed unacceptable for transplantation [78].

Managing Potential Complications

Brain death is associated with numerous complications such as disseminated intravascular coagulation (DIC), diabetes insipidus (DI), neurogenic pulmonary edema (NPE), hypothermia, and cardiac arrhythmias [68]. There are major swings in various hormones such as cortisol, vasopressin, thyroxine, and insulin. The effects of these hormones are sometimes synergistic and may cause dramatic changes in the physiological status of the potential donor. Understanding and anticipating these complications is important for the managing physician. Early identification of these complications coupled with adequate supplementation is necessary to maintain hormonal balance, hemodynamic stability, and organ perfusion. Figure 38.1 shows the complex interplay of all the various complications and interventions to ensure optimization of organ recovery.

Considerations During Organ Recovery

Once the declaration of death has been made and all necessary interventions have been taken to optimize the donor organs, it is important to put certain things into consideration during organ recovery.

Although individuals could be brain dead, they may still have hemodynamic responses to certain stimuli mediated by the spinal reflexes or adrenal medulla stimulation [79, 80]. Also, the determination of brain death does not preclude the possibility of spinal reflexes due to painful stimuli [14]. Therefore, chemical neuromuscular paralysis is usually administered to block muscle twitching.

All operating staff are expected to understand the need for timeliness in their operations and they will need to work simultaneously and efficiently. Except for cases of lung recovery where ventilatory support is needed, the anesthesiologist only needs to ensure aortic cross-clamping during the recovery process. Communication between all staff is necessary, and the leader of the operation should be well outlined in order to ensure smooth running of the procurement process.

Conclusion

Organ donation is an important process that ensures the availability of organs for individuals whose only opportunities for survival lie on receiving transplants. Efforts to ensure the success of every step of the process are therefore of utmost importance. Recommendations for all institutions that care for the critically ill patient include incorporating skilled team-driven approaches to the consent process, protocol-guided steps for the management of potential donors, and adequate balance of the physiological status of donors. Optimal hemodynamic management, multidrug hormone replacement therapy, and efficient organ recovery are strategies to improve organ yield and the viability of donor organs.

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Biostatistics for the Intensivist: A Clinically Oriented Guide to Research Analysis and Interpretation

39

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Introduction

Statistical analysis and interpretation of statistical results are vitally important components of medical research and clinical practice [1, 2]. Sound knowledge of relevant principles and practices provides healthcare professionals with tools to analyze and understand the ever-increasing number of contributions to scientific medical literature [3]. Whether one is examining the latest outcome trends for the intensive care unit or looking at the most recent randomized, controlled trial of a new antibiotic, statistics provide a standardized way to make sense of raw clinical data. Armed with an understanding of the meaning and significance of statistical findings, clinicians may benefit from practical application of key comparisons and treatment effects between different groups and/or treatments. In a way, this is the foundation of evidence-based medicine, as well as the equally important areas of healthcare quality, safety, and value. The most critical aspect of understanding the principles of statistical analysis is the ability to generalize and practically apply research conclusions to "the right patient population at the right time," thus guiding and informing critical steps in one's clinical decision-making. In this chapter, a practically oriented overview of essential statistics for the intensive care professional will be provided.

Our discussion begins with the basic principles and mechanics of a research study, including items such as hypothesis testing, statistical errors, statistical significance (e.g., *p*-values), statistical power, and various types of bias that may affect the validity and/or applicability of research conclusions. The chapter then highlights fundamental research study designs, followed by an overview of statistical testing that corresponds to the various study types. Finally, the chapter concludes with an important section on how to evaluate the integrity of diagnostic tests.

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The Basic Mechanics of a Research Study

Hypothesis Testing, Level of Significance, and *P*-Values

In order to conduct a study, a properly framed study question, or an experimental hypothesis, must be developed. First, researchers must determine their null hypothesis (H_0), which states that there is no observed trend, association, or difference in whatever is being measured [4]. Next, researchers formulate an experimental or alternative hypothesis (H_1) based on such factors as previous research and clinical observations that suggest a trend, association, or difference in outcomes. In conducting the research study, one then determines which of the two hypotheses is true based on the results and data.

Naturally, errors may occur when conducting a study. When the null hypothesis is accepted and the observed trend, association, or difference is missed, a type II error, or beta (β) (i.e., false-negative result), occurs [5]. When a null hypothesis is rejected, even though it is true, a type I error, α (i.e., false-positive result), results [5]. Consequently, the level of significance, or alpha (α), represents the probability that a type I error will be committed (i.e., the likelihood that the observed outcome is due to chance). The standard level of significance for conducting research is 0.05, meaning that only a 5 % chance (or 1 in 20 instances) is allowed that the observed outcome is due to chance, rather than reflecting true outcomes in the larger population of interest [6]. Having said that, the pre-determined

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level of significance can vary anywhere between 1 in 10 (or <0.10) and 1 in >100,000 (or <0.00001).

One then compares the test statistic's probability value (p-value) to the pre-established level of significance. A p-value accompanies each *test statistic* and is easily obtained using computer software, although it may also be calculated by hand using a table of pre-determined critical values. If the p-value is less than the pre-determined significance level, "α," of 0.05, one may conclude with greater confidence that the obtained outcome is indeed reflective of the larger population, rather than due to chance factors. However, given the potential for type I error in any given study, it is important to replicate and validate one's research in order to increase one's confidence in accepting or rejecting any particular hypothesis.

It is critical to examine statistical significance as expressed by p-values in the context of clinical relevance. As previously described, statistical significance occurs when the test statistic's p-value is less than the pre-established level of significance, typically 0.05 or 5 % (α). In contrast, clinical significance represents how the research may affect or change treatment or management practices. Not infrequently, a statistically significant result may not be clinically meaningful [7]. In a hypothetical example, for a large sample of patients, a difference of 3 % in total hospital stay may appear statistically significant, but when translated to less than 3 h of added hospitalization time, its clinical significance becomes less relevant. One way to help reduce the chance of the above-mentioned scenario taking place is to elevate the pre-determined level of significance from the standard $\alpha = 0.05$ to a more stringent $\alpha = 0.01$ (or any value defined a priori that determines the level of statistical significance needed to better reflect clinical discrimination).

Power and Sample Size

Statistical power represents a study's ability to effectively detect a trend, association, or difference in study outcomes while avoiding a type II error (β) [5, 8]. Therefore power can be calculated by subtracting the likelihood of type II error (1 – β). Generally speaking, the power of a study should be preset to a minimum value of 0.80, meaning that there is an 80 % chance of correctly detecting a difference in one's study sample that actually exists in the larger population (with a corresponding 20 % chance of committing a type II error or missing such a difference). Many studies fail to demonstrate statistical significance because their sample sizes are insufficient to effectively detect such a difference between groups, even though there may actually be a difference in the larger population [8–10]. Therefore, sample size is a critical component of achieving adequate statistical power. Effect size is another important factor, meaning the size of the difference clinicians expect to see, usually based on previous research, clinicians' own preliminary (pilot) study findings, and/or clinical observations. If clinicians want to detect a smaller effect size, a larger sample size will be required. In contrast, smaller sample sizes are generally sufficient to detect larger effect sizes [11]. Given the importance of statistical power, clinicians should always carefully examine the methodology section of study manuscripts in order to ascertain whether or not a formal "power analysis" was performed, particularly for the study's primary outcome(s). Lack of a formal power analysis should make clinicians more cautious about accepting the study's conclusions, especially if the study found no significant differences in outcomes (e.g., the presence of type II error).

Type III Error

On occasion, a study conclusion may appear to be inconsistent with study results. Here, a type III error is said to have occurred. In one definition, this type of error is attributed to asking the wrong question and using the wrong null hypothesis [12, 13]. In another definition, type III error occurs when one incorrectly concludes the directionality of the observed difference [13].

Bias

When analyzing a newly published study, it is important to be aware of biases that might preclude one from applying the study's conclusions to one's patient population. Bias represents underlying influences that may affect how information is analyzed, presented, and interpreted. There are many different types of bias [14], with only the major subtypes outlined in this section, largely due to the complexity and vastness of this important topic (Table 39.1).

Selection bias occurs when samples are chosen that are not representative of the larger population, such as choosing only females for one's sample when the larger population of interest consists of both males and females [15, 16]. *Observation* or *information bias* represents inherent characteristics that affect the outcome of interest [15, 16]. For example, *recall bias* is a type of observation bias whereby past events influence the recollection of an outcome of interest [17]. *Lead-time bias* occurs when early screening (e.g., mammography for breast cancer) appears to increase survival, when in reality, the disease course has not changed, but instead survival appears to increase simply because the disease is detected earlier [18]. Finally, *confounding bias* represents underlying factors that may obscure an outcome of interest (e.g., age, preexisting conditions, and other variables), which may diminish the validity of the study's conclusions [15, 17].

Because various forms of bias may become a significant issue when both sampling and analyzing data, there are multiple methods available to diminish these different biases. Such methods include randomization, masking, and matching. *Randomization* means that the intervention or treatment being studied is randomly assigned to individuals in the sample population (e.g., flipping a coin, using a computer-generated random number table), in order to diminish the effect of biases such as confounding variable influences [16, 17]. By randomly assigning subjects to study groups, any potential confounding factors are equally distributed, thus reducing the chance that the study outcomes will be unduly influenced by something other than the treatment or intervention being studied. *Masking*, previously known as *blinding*, prevents the study group members (and/or investigators) from learning study-related details or facts that could potentially influence the outcome of interest [16]. *Matching* tries to pair certain characteristics within sample groups that are comparable, such as age [17]. When matching occurs, the paired factor no longer affects the outcome of interest, as it is controlled among the two groups. Matching is usually performed in ratios and multiples of experimental-to-control group sizes (e.g., for each subject in experimental group, there are one, two, three, or more controls) [19]. Lack of well-matched groups may result in other types of biases, but it is important to mention that although increasing the matching ratio (e.g., 1:3 versus 1:1) does improve statistical power, the effect of each additional matched control beyond the ratio of 1:4 becomes less relevant [20].

Table 39.1 Types of bias in biomedical research

Type of bias	Definition
Selection bias (i.e., Berksonian bias)	Certain individuals are more likely to be selected for the study than others
Spectrum bias	Sensitivity and specificity of a diagnostic test are overestimated
Observation bias (i.e., information bias)	Inherent characteristics that affect the outcome of interest
Recall bias	Past events influence the recollection of an outcome of interest
Lead-time bias	Early screening appears to increase survival
Confounding bias	Underlying factors that obscure an outcome of interest
Detection bias	Certain findings are more likely to be detected in a particular subset of subjects
Funding bias	Study's financial sponsor is favored regarding study outcomes
Reporting bias	Certain observations are more likely to be recounted or presented
Exclusion bias	Subjects are omitted from participating in a study prior to statistical analysis
Attrition bias	Participants who leave a study or are lost to follow up

Study Types

Besides understanding the mechanics of designing and interpreting a study, one must understand the different types of studies commonly encountered in medical literature in order to recognize the strengths and weaknesses of each type. In general, there are two main study categories: *descriptive* and *analytical* studies.

Descriptive studies may show association(s) but no causation(s) (e.g., no cause-and-effect relationships can be demonstrated). Descriptive studies are generally used to describe a new phenomenon or an interesting observation that may serve to generate future ideas for potentially testable research hypotheses [21]. Beyond simple descriptive statistics, no further analyses or hypothesis testing is performed in such studies. The most basic form of descriptive study is a *case report*, where a description of an interesting or educational finding is presented in a single patient [21]. When a number of similarly themed cases are grouped into a single report, with more generalized and thematic descriptions of phenomena or intervention(s), the study is said to constitute a *case series* [21]. An example here might be identification of a new, previously unreported syndrome [22]. *Correlational* studies examine large series of patients to detect different associations and trends that may help generate research hypotheses. *Cross-sectional* studies are observational studies that collect information on a specific sample of population at one specific point in time [23]. Table 39.2 provides a quick overview of the basic types of descriptive studies.

In contrast to descriptive studies, *analytical* studies are used to test a *specific study question* (or *hypothesis*), and statistical tools are used to determine if any conclusions regarding relationship(s) beyond simple chance can be deduced [16, 23]. *Cohort studies* represent observations where various conditions of the study group are recorded as they occur, without any interventional changes or other types of manipulations by the investigator [16, 24]. Therefore, *cohort studies*

Table 39.2 Outline of different types of descriptive studies

Case report	Describes an interesting finding of a single patient
Case series	Describes similarly themed interesting finding(s) in multiple patients
	May identify disease patterns or syndromes
Correlational studies	Large studies that identify specific associations between different variables of interest
	Helpful in generating research hypotheses for future studies
Cross sectional studies	Group of patients observed at one specific point in time

may be conducted retrospectively or prospectively. A *case-control study* examines a sample of subjects who have a specific disease or finding of interest, and certain risk factors are identified that could be related to development of the disease or some other pre-determined outcome [16, 24]. A *prospective cohort* study observes healthy participants over time to identify risk factors that could have led to the development of a specific disease or pre-defined condition of interest [16, 24]. *Experimental studies* represent studies where the investigator actively intervenes to determine if there is a measureable outcome effect [16, 23]. A *randomized controlled trial* is the "gold standard" of interventional studies because it provides sufficient evidence to draw meaningful conclusions regarding effectiveness of treatments and/or interventions. This is so because subjects are randomly assigned to either treatment/intervention or control groups, bias is reduced to a minimum, and the study is conducted in such a way that an active intervention or manipulation is performed without the investigator's direct ability to direct patients to either the treatment/intervention or control group [25]. Table 39.3 provides a quick overview of major types of analytical studies.

One other study type is a *meta-analysis*, which is conducted by compiling data from other "source" studies to help provide a collective or "pooled" analysis that allows one to determine if certain treatment favors a specific approach to an outcome of interest. Such a study usually results in greater statistical power because the sample size has increased significantly. Ideally, a meta-analysis should synthesize high-quality prospective, randomized trials [26].

Table 39.3 Types of analytical studies

Cohort	*Case-control studies*	Retrospective
		Participants chosen with a specific disease being studied and risk factors are identified
	Prospective cohort studies	Healthy participants followed over a period of time
		Risk factors and onset of disease examined
Experimental	*Randomized control trials* (*with or without blinding*)	Intervention/manipulation performed to the experimental group
		Control group obtained for comparison
		Prospective
		Randomization
		Blinding performed
		Designed to reduce bias and confounding factors
		Best study to draw own conclusions

Measures of Disease Association

Relative Risk

In order to determine associations between risk factors and disease outcomes, there are different statistical approaches. *Relative risk* is a measure of the magnitude of the relationship between potential risk factor(s) and the development of particular disease, expressed as a ratio of probabilities. This type of calculation is typically used in prospective cohort studies [27]. Table 39.4 presents an example of relative risk calculation for breast cancer based on family history. If 50 patients have a "positive family history" of breast cancer, and 50 patients have "no family history of breast cancer," with 5 of 50 (10%) patients in the positive family history group developing breast cancer and only 1 of 50 (2%) patients in the negative family history group developing breast cancer, the *relative risk* of developing breast cancer with a positive family history is 5.00. With a relative risk of 5.00, a positive association is demonstrated between the risk factor to the development of disease. A relative risk of 1.00 means there is a 50–50 chance of disease development in either group, so values greater than 1.00 indicate a stronger association between the risk factor and the disease outcome, while values less than 1.00 suggest decreased risk (or possibly a protective influence, depending on what is being measured).

Odds Ratio

Many studies are conducted retrospectively based on previously collected data. In such cases, an *odds ratio* is generally used to measure the association between a disease and a pre-determined risk factor [28]. Patients with a particular disease state are selected, and risk factors that existed prior to the development of the disease are studied in order to demonstrate the odds of the disease given the presence of the risk factor [28]. Odds ratios represent the probability of the event occurring (P) versus the event not occurring ($1 - P$) in the identified risk factor group. Table 39.5 presents an example of odds ratio calculation for alcohol consumption

Table 39.4 An example of relative risk calculation

	Disease + (positive) e.g., breast cancer	Disease – (negative) e.g., no breast cancer
Risk factor + (positive), e.g., family history	a (5)	b (45)
Risk factor – (negative), e.g., no family history	c (1)	d (49)

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{5/(5+45)}{1/(1+49)} = 5.00$$

Table 39.5 An example of odds ratio calculation

	Disease + (positive), e.g., esophageal cancer	Disease – (negative), e.g., no esophageal cancer
Risk factor + (positive), e.g., alcohol	a (8)	b (30)
Risk factor – (negative), e.g., no alcohol	c (2)	d (90)

$$OR = \frac{a/b}{c/d} = \frac{8/30}{2/90} = 12$$

and esophageal cancer based on retrospectively collected data. If eight of the ten patients who developed esophageal cancer were determined to have history of heavy alcohol consumption, compared to only two of ten patients with no heavy alcohol consumption history, the odds ratio is 12.00, meaning there is a 12-fold increase in chance of developing esophageal cancer with heavy alcohol consumption. As with relative risk, an odds ratio of 1.00 means there is a 50–50 chance of the event occurring in either group, with values >1.00 indicating greater risk and values <1.00 suggesting decreased risk.

One must keep in mind that both *relative risk* and *odds ratio* are measures of disease association rather than indicators of cause and effect.

Statistical Testing

There are many different types of statistical tests available for analyzing study data, depending on variable characteristics, research objectives, and other consideration. However, the topic itself is so vast that this section is limited to essential information that will enable clinicians to understand how statistical tests may be applied within the practical context of clinical practice applications.

Regarding the use of statistical tests, the reader should also have general familiarity with major statistical software packages available both for general applications (e.g., data exploration, descriptive statistics) and for more advanced/specialized purposes (e.g., meta-analysis, multivariable analyses, survival analyses) [29, 30].

Statistical Testing and Types of Data: Discrete Variables

Discrete data (also known as categorical data) are variables that encompass a limited (and usually fixed) number of possible values, effectively assigning each discrete value to a particular group, subgroup, or category (e.g., patient gender, mortality status). By definition, discrete variables are not present in a continuous range [31]. A binary "yes/no" type variable is an example of a *dichotomous* variable. Variables with more than two possible values are called *polytomous* variables. Moreover, continuous data may be redefined under certain circumstances as categorical, which is called *data discretization* (e.g., creating an "age" variable based on <18 years old, 18–35 years old, and >35 years old). Converting a continuous or a polytomous variable into a binary variable is called *dichotomization*. Discrete variables are usually expressed with frequencies and percentages.

Statistical Testing with Discrete Variables

Among the simplest and most common statistical tests for analyzing discrete data are the *chi-square test* and *Fisher's exact test. The chi-square test* calculates the observed versus expected frequency of an outcome in a rows-by-columns table format in two or more independent groups [32]. For example, one may wish to examine whether the existence of type II diabetes (yes/no) is more common in patients with poor versus good nutritional status. For accurate results, the total number of cases should generally be greater than 50, with cell sizes of at least ten. If these sample size recommendations are not met, *the Fisher's exact* test may be used instead [33].

If one wishes to analyze the predictive relationship between one or more variables and a discrete outcome, *logistic regression* is the preferred approach. *Multivariate logistic regression* is used to determine how multiple variables (also known as covariates) contribute to a discrete outcome, as well as to assess the independent effect of each variable on the outcome after adjusting or controlling for the others. For example, one may wish to know how age, gender, BMI, family history, comorbid conditions, and other identified risk factors impact diabetes status [34].

Statistical Testing and Types of Data: Continuous Variables

Continuous data may take any value along a continuum within a specified range and are meaningfully expressed in mathematical terms (e.g., "John is twice as heavy as Sue"). Examples include values such as height, age, weight [31], and common laboratory output such as white blood count and fasting glucose. In contrast to discrete variables, which are usually expressed as frequencies and percentages, continuous data must be described and categorized in multiple ways to provide meaningful data.

Continuous Data: Mean, Median, Mode, and Related Concepts

The *mean*, *median*, and *mode* are important terms to describe the central tendencies of continuous data [35]. The *mean* represents the average value of the data and is calculated by taking the sum of the values in a dataset divided by the number of values in the dataset [36]. The *median* represents the middle value, or 50th percentile of the dataset, which is more appropriate than the mean when the data distribution is not normally distributed (i.e., does not follow a "bell-shaped" curve) [36]. The *mode* represents the most frequently occurring value in the dataset [36].

Data range refers to the difference between the highest and the lowest values in the dataset. The *interquartile range* [IQR] is a measure of variability commonly reported with the median and applicable mainly to non-normally distributed data with small sample sizes [37, 38]. To obtain the *IQR*, one divides a dataset into quartiles, or rank-ordered data in four equal parts, with reporting of 25th, 50th, and 75th percentiles [37, 38].

Continuous Data: Statistical Distributions

One essential component of statistical testing with continuous data is the *statistical distribution* of the data. A *normal distribution* (i.e., *bell-shaped* or *Gaussian)* occurs when the mean, median, and mode are all equal, and the central limit theorem states that with a sufficiently large sample of independent variables, the data will likely be normally distributed [39]. When the data are not normally distributed, they may be either positively or negatively skewed, depending on the directionality of the observed effect (Fig. 39.1). A dataset with positive skew occurs when the mean is greater than the median, which is in turn greater than the mode of the dataset [36]. Negative skew occurs when the mean is less than the median, which is in turn less than the mode [36].

Continuous Data: Standard Deviation (σ) and Standard Error of the Mean (SEM)

Measuring variability in a dataset is another important aspect of analyzing continuous variables. The most common measure of variability is the *standard deviation (σ)*, which represents the square root of the variance (or how much each value differs from the dataset's mean) (Fig. 39.2) [40]. *Standard error of the mean* (*SEM*) is the standard deviation of sample means over all possible samples of a given size drawn from the larger population of interest. In other words, SEM is the standard deviation of the sample mean's estimate of a population mean [40].

It is important to note that *standard deviation* and *SEM* are not interchangeable terms [41]. *SEM* estimates how far the sample mean is likely to be from the *true* population mean, if one were actually able to measure this value. In contrast, *standard deviation* describes the degree to which measurements within an actual sample differ from the mean of that sample.

Statistical Testing with Continuous Data

The *Student's t-test* is used to compare the means of two groups [4]. A *one-sample t-test* is conducted when the inves-

$$\sigma = \frac{\sqrt{(x-\bar{x})^2}}{n} \quad \text{SEM} = \frac{\sigma}{\sqrt{n}}$$

Fig. 39.2 Standard deviation (σ) and standard error of mean (SEM) calculations

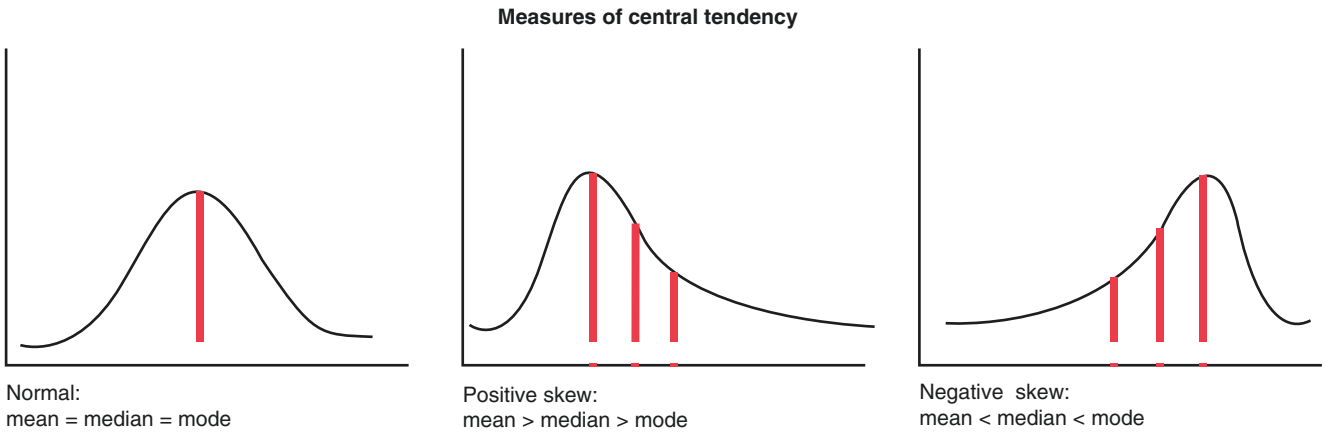

Fig. 39.1 Statistical distributions: normal, positive skew, and negative skew

tigator wants to compare a sample mean with a known mean in the larger population of interest [39]. In an *independent two-sample t-test*, two different means from two independent groups (e.g., males versus females) are compared [4]. A *paired t-test* is used when the samples are not independent of one another (e.g., "before-and-after" studies) [4].

The *Mann-Whitney U-test* is used to compare two independent groups when the variables of interest are either non-normally distributed or measured on an ordinal scale (e.g., patient satisfaction surveys, visual analog scales for pain) [42]. The Mann-Whitney U-test is considered "nonparametric" because it is applied to data that do not follow parameters such as having a large sample size, normally distributed outcomes, and/or continuous variables. Instead of comparing means, as the independent sample t-test does, the Mann-Whitney U-test compares the general distribution of ranked outcomes, and researchers typically report medians for their data. If there are more than two groups or categories being compared for nonparametric data, the *Kruskal-Wallis test* is conducted, and if there are repeated measurements within subjects for nonparametric data, the *Friedman's test* is used [43].

Analysis of variance (*ANOVA*) is an extension of the t-test when comparing the means for more than two groups or categories [44]. ANOVA models can include between-subject analyses, within-subject analysis (also known as *repeated measures ANOVA*), or some combination of both. If there is only one variable of interest (e.g., a group, or factor, based on weight, with normal, overweight, and obese categories), a *one-way ANOVA* is conducted. If there are multiple variables of interest, *factorial ANOVA* is conducted (e.g., in addition to the weight factor, one may wish to analyze age as a factor divided into the three categories of <18 years, 18–35 years, and >35 years). If there are multiple outcomes, a *multivariate ANOVA* (*MANOVA*) may be applied [45].

Correlational analysis allows researchers to evaluate associations between variables, as well as the strength of those associations. With normally distributed continuous data, the Pearson product-moment correlation coefficient is applied (symbolized by r). This coefficient ranges from −1 (inverse relationship between two variables, such as increasing exercise and decreasing weight) and +1 (positive relationship between two variables, such as increasing calorie consumption and increased weight gain), with a value of 0 representing no true linear relationship. The coefficient of determination (r^2 or the square of the correlation coefficient) further shows how much variance is shared in common between two variables. For example, a correlation coefficient of .90 (r) for the relationship between increasing calorie consumption and increased weight gain means that these two variables share 81 % (r^2) of variance in common, representing a strong association [46].

Note that the Pearson product-moment correlation coefficient is best suited to normally distributed continuous variables. If variables are ordinal and/or non-normally distributed, the Spearman's rank correlation coefficient (symbolized by ρ, the Greek letter "rho", or by r_s) is most appropriate [43].

While correlational analysis allows researchers to detect basic associations between two variables, *linear regression* is used to evaluate how one or more independent variables predict or determine a continuous outcome (also known as a dependent variable) [46, 47]. In *multiple linear regression*, many independent variables are analyzed simultaneously to determine the unique contributions of each while adjusting or controlling for the influences of the other variables. For example, one may wish to know how age, gender, BMI, family history, comorbid conditions, and other identified risk factors impact fasting glucose. In this context, the squared multiple correlation (*adjusted* R^2) reveals the proportion of variation in the dependent variable that is accounted for (or explained by) the best linear combination of independent variables [48].

Precision of the Data: Confidence Intervals

When reporting statistical outcomes, it is important to know the precision of these results in reflecting the larger population of interest, since one study sample obviously cannot capture an entire population. Such precision is expressed as a *confidence interval* (*CI*), or a range of values within which the true population outcome is likely to be found [49]. Generally, a *95 % confidence interval* (*95 % CI*) is accepted as the standard, meaning that researchers are 95 % confident that the range generated will capture the true value, and that with repeated sampling of the population, the means generated will be within that range 95 % of the time [35]. With normally distributed data, the 95 % confidence interval represents a range of values two standard deviations away from the mean in either direction [35, 49]. Therefore, when comparing means, if the 95 % confidence interval includes the value 0, the researchers can be 95 % confident that no true difference exists in the larger population of interest. For relative risk and odds ratio outcomes, if the 95 % confidence interval includes the value of 1.00, researchers can similarly conclude that there may be no actual population difference.

Less common confidence interval values include 67 % (i.e., one standard deviation) and 99.7 % (i.e., three standard deviations). The 67–95–99.7 "trio" of confidence intervals is also known as the "three-sigma" rule, indicating that in most datasets, nearly all measurements will fall within the calculated "three-sigma" interval (Fig. 39.3). The "67–95–99.7" rule can also be used as a crude determination of data normality as well as the presence of outliers [50].

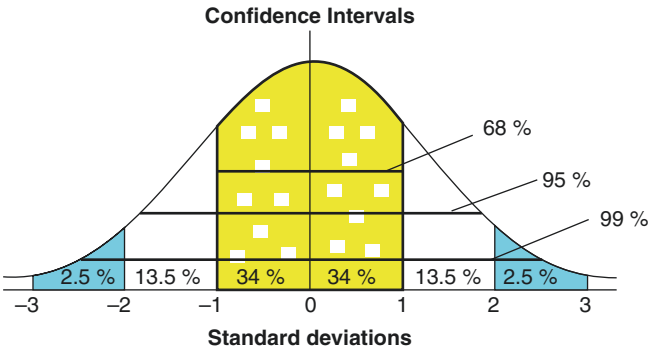

Fig. 39.3 Confidence intervals

Evaluating Diagnostic Tests

In certain research contexts, the primary outcome of interest is to determine diagnostic test characteristics. In other words, one must always question whether "the right test" was used for "the right indication."

First, a diagnostic test should have good *sensitivity* and *specificity*. When a diagnostic test is highly sensitive, it is a good screening test because it can detect a disease that is truly present (i.e., the true positive rate) [51]. Therefore, a diagnostic test with sensitivity close to 1.00 is used to rule out disease. When a diagnostic test is highly specific, the test is able to demonstrate no disease when it is truly absent [51]. Therefore, a diagnostic test with specificity close to 1.00 is used to rule in disease. Other concepts pertaining to diagnostic accuracy include the *positive predictive value* (PPV) (i.e., for all positive test results, the proportion truly having disease), the *negative predictive value* (NPV) (i.e., for all negative test results, the proportion truly not having disease) [51], the *positive likelihood ratio* (LR+) (i.e., the ratio of true positives to false positives or the probability of a person with disease testing positive divided by the probability of a person without disease testing positive), and the *negative likelihood ratio* (LR-) (i.e., the ratio of false negatives to true negatives or the probability of a person with disease testing negative divided by the probability of a person without disease testing negative). Test *accuracy* includes the true positive and true negative values as a measure of overall validity. Test *precision* indicates reliability, including consistency of a test over time [52]. An ideal test would both be accurate and precise.

In order to visualize a diagnostic test's sensitivity and specificity, researchers may create a *receiver operating characteristic* (*ROC*) curve or a graphical plot showing the performance of a diagnostic test across different cut-off points. The true positive rate (i.e., sensitivity) is plotted on the vertical axis against the false-positive rate (1 – specificity) on the horizontal axis. As displayed in Fig. 39.4, an excellent diagnostic test will have an ROC that rises sharply to the upper left corner. The test's diagnostic performance is measured

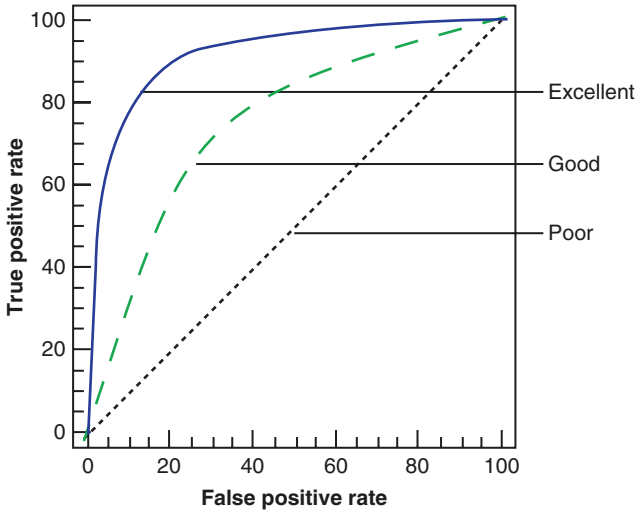

Fig. 39.4 A comparison of receiver operating characteristic (ROC) curves

mathematically as the *area under the curve* (*AUC*), with 1.00 representing a perfect test and .50 representing a worthless and poor test (i.e., one that performs no better than chance). Ideally, the researcher selects the cut-off point that maximizes sensitivity and minimizes the false-positive rate, with a corresponding high AUC [53].

Measuring Agreement

In a research context, the word "agreement" has different meanings depending on the study objectives. One could simply calculate the percentage of agreement between observers (i.e., the number of agreements divided by the total number of agreements plus disagreements, multiplied by 100) in order to get a general overview, but this approach fails to consider the role of chance in at least some of the observer agreement. Therefore, researchers often use the kappa coefficient to account for chance agreement [54]. There are different variations of the kappa coefficient depending on the type of outcome (e.g., categorical versus ordinal) and number of observers (two or more than two), but they all measure how much agreement is present between observers by subtracting out agreement that would be expected by chance alone [55]. The highest possible kappa value is 1.00. There is no universal standard for interpreting the results of kappa coefficients, but one common classification system defines values as follows [56]:

- Between 0.01 and 0.20 = "slight agreement"
- Between 0.21 and 0.40 = "fair agreement"
- Between 0.41 and 0.60 = "moderate agreement"
- Between 0.61 and 0.80 = "substantial agreement"
- Between 0.81 and 1.00 = "almost perfect agreement"

Table 39.6 Interobserver agreement measures and associated parameters

Type of data	# of observers	Agreement measure	Examples
Categorical	2	Cohen's kappa	Two radiologists review a set of mammograms to determine if breast cancer is present or absent
Categorical	>2	Fleiss' kappa	Ten trauma surgeons review a set of CT scans to determine if a pneumothorax is present or absent
Ordinal	Any number	Weighted kappa (*assigns subjectively defined weights to categories*; *less weight given to categories that are further apart*)	A group of pathologists rate a set of pathology report findings as "normal," "benign," or "cancerous"
Continuous	Any number	Intra-class correlation coefficient (ICC)	A group of orthopedic surgeons rate a set of video clips of anatomic structures during shoulder arthroscopy using an 11-point visual analog scale (0 = no visualization, 10 = perfect visualization)

It must be noted that kappa coefficients have limitations, including their extreme sensitivity to outcomes with low prevalence and/or small cell values [54]. Therefore, readers should use caution when interpreting results for kappa coefficients.

For measures of agreement involving continuous data, the intra-class correlation coefficient (ICC) is commonly applied. In general terms, ICCs are expressed as the ratio of the variance of interest divided by the ratio of the variance of interest plus error, with incorporation of either one-way or two-way analysis of variance (ANOVA) in the mathematical model. There are different types of ICCs depending on the study objectives, such as whether one wishes to assess absolute agreement or consistency of responses, whether it is more important to measure an individual rating versus the mean of several ratings, and/or whether the set of observers is the only group of interest or represents a random sample from a larger population of observers [57]. A practical summary of essential statistical methodologies for determining "agreement" is provided in Table 39.6.

Survival Analysis

Survival analysis measures time to a pre-specified event (e.g., mortality, readmission) as demonstrated in the calculation shown here [58]:

Survival analysis calculation

$$S(t) = \Pr(T > t)$$

T represents a random variable denoting the time of occurrence, Pr denotes "probability," and t is the time interval. If subjects have not experienced the outcome at the end of the study (e.g., for a time to death outcome, certain subjects are still alive), their exact survival times remain unknown, so these are considered censored observations. Other terms and concepts associated with survival analysis include lifetime distribution function, event density, hazard function, and cumulative hazard function [58], which are beyond the scope of this chapter. Survival is frequently plotted using

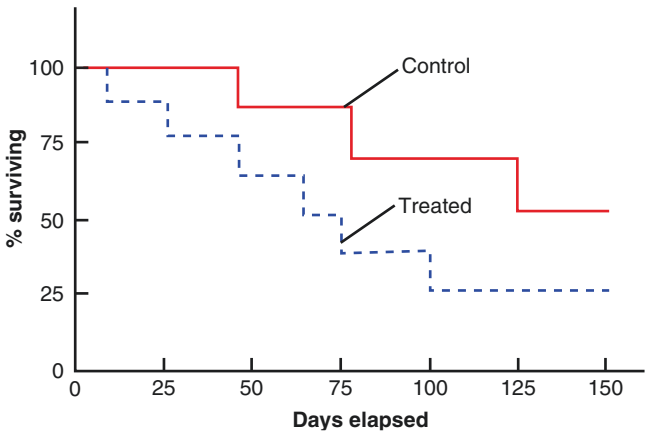

Fig. 39.5 Kaplan-Meier curve

Kaplan-Meier curves, with time on the horizontal axis and the survival distribution function on the vertical axis (Fig. 39.5). Statistical methods for analyzing survival data include the log rank test and the Cox proportional hazard model, which is a form of regression used when one wishes to determine how independent variables of interest predict the time-to-event outcome [58–60].

Brief Comment on Trends and Pattern Analysis

The derivation of actionable information in the clinical setting is heavily dependent on one's ability to understand and apply trend analysis or the performance of data over time [61]. In fact, the ability to recognize specific patterns and trends (e.g., changes in vital signs or laboratory parameters) is the cornerstone of clinical medicine. Modern computer-aided trend analysis of "big data" provides practitioners with a wealth of useful information [62]. The field of medical informatics provides a unique opportunity to not only identify trends and patterns [63–65] but to predict the future behavior of these trends and patterns [66]. A common statistical approach for analyzing trends and patterns in

medical research settings is some form of regression modeling with accompanying graphical output—a process that may be relatively simple or highly complex depending on the study objectives and types of data (e.g., normally distributed versus skewed, correlated errors requiring time-series analysis with moving averages, linear versus nonlinear relationships, no adjustment versus adjustment for independent variable, confounding, and/or interactional effects) [67].

Conclusion

This chapter described some of the key terms and concepts pertaining to research and statistical methodology, including important factors to consider in designing a study and/or analyzing the data. Interested readers should consult sources listed in the reference section for additional information. In addition, there are numerous online resources for readers who wish to pursue the topic further.

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Administration

40

Samuel A. Tisherman

Introduction

As medicine has advanced over the past 50 years, the need for high-quality, cost-effective critical care services has expanded exponentially. In the USA, one recent estimate was that five million patients are admitted to intensive care units (ICUs) every year, leading to 23 million ICU bed days [1]. The cost of managing these patients typically accounts for a large percentage of hospital costs.

The importance of high-quality care in ICUs cannot be underestimated. Major complications often occur in the ICU or lead to ICU admission. On the other hand, a strong critical care service that prioritizes quality care can demonstrate a high level of patient safety and allow the hospital to meet quality standards set by third-party payers and attract patients, who have now become more informed consumers of healthcare. Also, providing excellent critical care service can help attract and retain leading surgeons.

Though critical care may be provided to patients anywhere, including outside the hospital, in the emergency department, or in the operating room, this chapter focuses on the provision of care within an adult, surgical ICU, defined as a geographic space within the hospital with the equipment and personnel to support or prevent failing organ function in patients at high risk of death. The discussion includes the unit structure, leadership, personnel, development of policies and guidelines, performance and quality improvement, patient safety, and costs. The basic principles should also apply to medical and pediatric ICUs.

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Structure

The structure of ICUs varies depending upon the type of unit (e.g., mixed medical/surgical, general surgical, or subspecialty surgical) and local culture and politics. ICUs typically function as open or closed, depending upon which physicians are able to admit and discharge patients, as well as write orders. In a purely open model, any physician has the authority to admit and manage patients. In this model, there tend to be multiple consultants, each managing a single organ system. In contrast, in closed units, the intensivist team completely manages the patients, streamlining care and allowing for a more holistic approach to the patient. In semi-open units, the surgical team and the critical care team comanage the patient, each having the authority to write orders. The hospital may require intensivist consultation for each patient admitted to this type of ICU. Surgical ICUs tend to have a more open or semi-open structure, allowing the surgical team to maintain significant control of their patients' care. Both closed and semi-open models are referred to as "high-intensity" staffing. This model of care delivery is associated with improved mortality compared to a "low-intensity" staffing model [2]. Even in a functionally closed unit, it is critical for the surgical team to remain closely involved in the patient's care. The surgeon best knows the details of the operative intervention and the potential complications.

Nighttime, in-hospital intensivist coverage has been studied both retrospectively and prospectively. Wallace, et al. found that nighttime coverage did not improve outcome with high-intensity daytime coverage [3]. In contrast, however, there were improved outcomes with low-intensity daytime coverage. A subsequent, randomized, clinical trial of 24/7 staffing vs. daytime-only coverage with consultation at night by telephone did not demonstrate any differences in length of stay or mortality [4]. The recent Society of Critical Care Medicine (SCCM) guideline on the delivery of critical care recommended that high-intensity staffing "is an integral part of effective care delivery in the ICU and can lead to improved outcomes" [5].

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ICUs differ in their primary patient populations. Small hospitals may have only one ICU that manages both medical and surgical patients. At larger hospitals, in general, medical ICUs accept only critically ill medical patients, and coronary care units accept patients with acute coronary syndromes or heart failure, though there may be some other medical subspecialty units. These hospitals may have one dedicated surgical ICU. With the increasing sub-specialization of surgical services, however, large tertiary care hospitals or academic medical centers may have a variety of subspecialty surgical ICUs, including cardiothoracic, trauma, neurotrauma, and transplant. Neurocritical care has become a bona fide subspecialty of critical care. Depending upon the numbers of patients and local politics, tertiary care hospitals may have a dedicated neurosurgical, neurotrauma, neurologic, or neuroscience ICU.

Coverage of patients in subspecialty ICUs can also vary among hospitals. In some systems, the management is service based, e.g., the surgical ICU team follows all critically ill surgical patients, wherever they physically reside. The alternative strategy is that the critical care team manages all patients that are physically in their ICU. The latter approach can lead to managing "boarders," e.g., a medical patient in a surgical ICU. There is no clear evidence that boarders do any worse than if they were housed in their designated ICUs.

If possible, surgical patients who require intensive care should be taken directly from the operating room to the ICU. This may not be possible if a bed is not immediately available. In this situation, surgical patients may be taken to the postanesthesia care unit (PACU) postoperatively. Boarding patients in the PACU, in contrast to boarding them in another ICU, thus delaying ICU admission, may adversely affect mortality [6].

Critical events frequently occur outside of the ICU. Intensivists need to be involved in the development of a rapid response system to quickly provide critical care wherever it is needed in the hospital and to transport the patient to the appropriate ICU [7]. In some systems, the intensivist leads all responses. Other systems have a two-tiered system in which ICU nurses or advanced practice providers (APPs) initially assess the patient and then engage the intensivist when necessary.

The role of telemedicine in the ICU continues to evolve [8]. Advanced telemedicine systems combine the availability of an intensivist and APPs with an electronic health record (EHR) that provides real-time advice regarding best practices and longitudinal data collection for performance improvement. Such programs may be able to improve mortality and length of stay, particularly with low-intensity intensivist coverage. But even in academic medical centers with high-intensity intensivist staffing and in-house resident or fellow coverage, a telemedicine system may provide patient care benefits without diminishing the educational value of the ICU for the trainees.

Personnel

What ultimately separates an ICU from a standard medical/surgical ward in the hospital is the presence of a sufficient number of appropriately trained, highly specialized personnel working together to manage the most critically ill patients. These personnel include physicians, nurses, patient care technicians, respiratory therapists, and pharmacists. Physical and occupational therapists, speech therapists, social workers, and other administrative staff are critical to the ICU mission.

In the high-intensity staffing model, the intensivist is directly involved in the management of every patient in the ICU either as the primary physician (closed model) or a mandatory consultation (semi-open model). The ICU physician staffing standard of The Leapfrog Group [9] recommends that physicians managing patients in the ICU should be free from other responsibilities so that they can attend to patients' needs at any time. The optimal number of patients covered by a single intensivist is unclear, but 15 or more may be undesirable [10]. In addition to providing direct patient care, the intensivists should be responsible for developing diagnostic and therapeutic protocols, as well as admission and discharge criteria.

At large medical centers, trainees from a variety of specialties, including surgery, anesthesiology, internal medicine, emergency medicine, and neurology, provide direct patient care in the ICU. The staff intensivists are responsible for supervising and teaching the trainees. As the trainees progress through their training, they should have the opportunity to take on increasing responsibility.

As the need for critical care services have increased, concerns about a shortage of intensivists have been raised. Part of the solution is encouraging trainees to choose a career in critical care. Relatively new avenues to certification for emergency medicine physicians and neurologists have helped. In addition, APPs have become key providers at the bedside in ICUs. The number of intensivists, physician trainees, and APPs needed to run an ICU varies with the patient population and acuity.

Bedside nurses are the ones who spend the most time directly interacting with patients and implementing the plan of care. They need to have specialized critical care training to assure specific competencies needed for the specific patient populations they care for. Nurse trainees are often involved also. The number of nurses needed to provide appropriate care in an ICU is dependent upon the number of beds in the ICU and patient acuity. In the USA, the patient/nurse ratio is typically 2:1. However, some patients require very frequent, if not constant, attention, necessitating 1:1 staffing.

In the USA, certified respiratory therapy technicians manage ventilators. This paradigm is much less common outside the USA, where the physicians and nurses manage the

ventilators. In either system, it is critical that both physician and nursing personnel in the ICU are trained to assist the patients' ventilation in case of an emergency, either by adjusting the ventilator or using a self-inflating bag.

Bioengineering staff is needed to maintain the advanced monitors and devices that are used in the ICU. Administrative staff to stock supplies, manage paperwork, and answer phones can be invaluable for allowing the nursing staff to focus on direct patient care needs.

Guidelines

Managing critically ill patients can be very complex. There are multiple physicians, nurses, and allied healthcare team members involved. To optimize patient care, everyone must be "on the same page." ICU leadership is responsible for the development of policies (which reflect institutional principles or values) and protocols (which are specific management tools). These should be developed based upon the best evidence available.

Many national organizations have developed evidence-based guidelines for various aspects of the management of critically ill patients (Table 40.1). Some are developed for very specific diseases or procedures, e.g., guidelines for management of specific injuries in trauma patients. Others are more generic for critical illness, e.g., sepsis or mechanical ventilation.

Implementation of guidelines requires buy-in from all members of the ICU team. Representatives from all key professions and disciplines should be involved from the beginning. Protocols developed just by physicians can readily fail because nursing or respiratory therapy issues were not taken into account, making implementation impossible.

Once policies and protocols are developed, the practitioners at the bedside need to be aware of them. Educational programs should be developed so that they understand the details of the protocol. The choice of format for education, such as live in-services or web-based materials, depends upon the type of material, institutional support, and number of personnel to be trained. If possible, protocols, such as ventilator weaning protocols, should be embedded into electronic order sets. Policies, such as indications for transfusion, can be incorporated as prompts within the EHR. The EHR should provide data for the ICU leadership regarding policy and protocol compliance.

Quality Care

The goal of providing care to critically ill patients is to prevent or support major organ system dysfunction in order to minimize morbidity and mortality. To accomplish this, the critical care team needs data. Ideally, initiatives to improve the quality of patient care should demonstrate improvement in patient-centered outcomes, such as mortality, functional recovery, or major morbidity. Over the years, attempts to improve these types of outcomes have been fraught with non-statistically significant differences either between groups or before and after an intervention is implemented. Often it is just not practical or even possible to have enough patients to demonstrate a difference. Similarly, when one center seems to demonstrate a difference, replicating this effect at other centers has been difficult.

Donabedian described three aspects to quality care: structure, process, and outcome [11]. Structure refers to the organization of critical care services within the ICU. Process refers to how care is provided in the ICU. Outcomes refer to patient outcomes. Local infrastructure and politics often make changing the structure of care difficult. Demonstrating improvements in outcome, as noted above, is also difficult. Therefore, most projects focus on changing the process of care.

Process improvement projects have traditionally followed the plan, do, study, act (PDSA) paradigm. Curtis et al. have developed a more detailed guide to quality improvement projects [12]. Some key elements emphasized in this guide include (1) prioritizing projects based upon importance for patient care, level of motivation, and feasibility; (2) preparing for the project, including developing a plan and building support; (3) creating systems for collecting data and reporting it; and (4) introducing strategies for changing clinician behavior. Once initiated, it is important to review the data, potentially modify the strategy, and, if successful, develop a process for sustainability of the intervention.

Table 40.1 Resources for guidelines

Organization	Website
Society of Critical Care Medicine	http://www.learnicu.org/pages/guidelines.aspx
Chest	https://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-statements/CHEST-guidelines
American Thoracic Society	http://www.thoracic.org/professionals/clinical-resources/critical-care/statements-and-guidelines/
Eastern Association for the Surgery of Trauma	http://www.east.org/education/practice-management-guidelines
Western Trauma Association	http://westerntrauma.org/algorithms/algorithms.html
National Guideline Clearinghouse	http://www.guideline.gov/

Adherence to a protocol or a national guideline is a common starting place for quality improvement that is both doable and likely to improve the process of care and possibly the outcomes of care.

Bedside checklists can readily improve the processes of care [13]. Such a checklist could include spontaneous awakening trial, spontaneous breathing trial, need for urinary catheter, need for central venous catheters, deep venous thrombosis prophylaxis, stress ulcer prophylaxis, etc.

Though demonstrating that an intervention clearly improves outcomes is challenging and frustrating, we should not stop trying. Over time, even without obvious breakthrough treatments, outcomes for critically ill patients have been improving; the critical care system is doing something right. Mortality and complication rates should be tracked. Other straightforward outcomes to be followed include readmission to the ICU and unexpected extubations, particularly those that result in re-intubation. A "softer" outcome that is worthy of study is patient and/or family satisfaction with their experience in the ICU.

Obtaining data on ICU processes and outcomes can be challenging. If possible, the EHR should be able to generate much of the data. Asking staff (either nurses or physicians) to collect this data can be more problematic. All staff working in the ICU environment tend to be well motivated and hardworking. But asking them to add the additional burden of data collection may lead to pushback. On the other hand, with the right leadership and establishment of a culture of safety, it is possible to have clinicians' help with some of this data collection, as long as the workflow is as efficient as possible.

Outcomes for critically ill patients are dependent upon the severity of the patients' illness, as well as the processes of care within the ICU. Outcome data needs to be risk adjusted so that appropriate comparisons can be made between local ICUs and regional or national norms.

Beyond working with ICU staff, quality improvement and patient safety initiatives should be a high priority for hospital administration. This is particularly true in the era of hospital reimbursement based upon quality. For example, if the hospital stands to lose money if the frequency of healthcare-associated conditions reaches a certain threshold, then the hospital needs to provide the resources to gather data on the processes instituted to minimize these conditions.

Changing behaviors in the complex environment of the ICU can be challenging. Input and buy-in from all parties involved are critical. Some recommendations from the SCCM guideline on critical care delivery include (1) flow sheets posted in the ICU illustrating how new processes have been incorporated into daily workflow, (2) formal protocols for educating float staff, (3) inclusion of new processes into daily checklists completed during multidisciplinary rounds, (4) the use of auditors, and (5) staff evaluations that report how frequently staff comply with new processes [5]. Automatic triggers, such as via the EHR, and real-time feedback can help. Gurses et al. have developed a useful tool for identifying and eliminating barriers to compliance [14]. The tool involves assembling a multidisciplinary team, identifying barriers by observing the process and talking with staff, summarizing barriers, prioritizing barriers based upon severity and likelihood of causing noncompliance, and developing an action plan for each identified barrier.

Costs

The provision of critical care services absorbs a huge amount of hospital budgets. This can lead to tension between the hospital and ICU leadership. The hospital will try to contain costs. The ICU team wants to provide high-quality care, which takes resources. Personnel constitute the largest portion of the costs for providing critical care services. It is critical to have sufficient nursing staff and appropriate support staff to provide quality care while maintaining a high level of staff satisfaction and pride. When the staff feels overworked or undervalued, they will look elsewhere for employment, adding additional burdens on those left behind, who in turn become disgruntled. The ICU leadership needs to keep team morale as a high priority when negotiating staffing with hospital administration.

Other large components of ICU costs include laboratory tests, imaging studies, and medications, which the intensivist can, in part, control. It seems simple to suggest that the intensivist should only order laboratory or imaging tests that are clearly indicated, rather than ordering a series of tests on a daily basis. One part of the solution is to develop order sets that include only the minimum number of labs and imaging studies needed to safely manage a particular patient population. Another part of the strategy is to have the ordering of lab tests and imaging studies become a routine topic of discussion on rounds. Though intensivists can individually help control the use of expensive medications, the hospital pharmacy service (through the Pharmacy and Therapeutics Committee) has the ability to more directly limit certain medication use. Ideally, intensivists and pharmacists should work together to define appropriate indications for medication use based upon the best available literature. This can result in a range of approaches, from pop-ups in the EHR to direct control of the use of a certain medications by gatekeepers.

From the hospital perspective, there is a strong incentive to minimize the number of ICU days per patient since reimbursement from third-party payers is usually based upon the patient's Diagnosis Related Group, not per diem charges. From the perspective of optimizing care, transferring patients who need intensive care into the ICU should occur as rapidly

as possible. On the flip side, transferring appropriate patients out of the ICU should also be efficient. Yet, there are often downstream bottlenecks created by an inadequate number of intermediate care or telemetry beds. The ICU leadership needs to be able to present data to the hospital administration regarding how these delayed transfers affect ICU throughput and, ultimately, could lead to delayed transfers from outside hospitals, boarding of patients in the PACU, or even delay/cancelation of operative procedures.

Communication

Critically ill surgical patients typically have a number of physicians involved in their care, including the intensivist, the operating surgeon, and consultants. In addition, nurses, respiratory therapists, pharmacists, physical and occupational therapists, and others are involved. From the patient and family perspective, it is very helpful for a member of the team to explain everyone's role when the patient is admitted to the ICU.

Good communication among all these individuals is critical for providing high-quality care. Well-structured, multidisciplinary rounds go a long way toward setting the stage for communication. It is important for the intensivist to facilitate discussion on rounds so that all members of the team have input and feel engaged in the patient's plan of care. Using a checklist or goal sheet can help assure that the plan is clear to everyone and that small details are not missed. During afternoon or evening rounds, the goal sheet should be reviewed. If an item has not been accomplished, there should be documentation of why not.

Transitions of care, such as from the operating room to the ICU or from the ICU to a regular hospital floor, are points in time when various aspects of the patient's care may get lost. Development of handoff sheets and a structured reporting system can help assure that the continuum of care is maintained.

Role of the Surgeon

Whether or not the ICU is structured as a closed, semi-open, or open unit, the involvement of the operating surgeon is critical. It behooves the intensivist to be sure that the attending surgeon is involved in any major decisions affecting the patient's management. The surgeon best knows the operative findings, anticipated postoperative course, and potential complications. The surgeon has also developed a close rapport with the patient and the patient's family prior to the operation. Communication between the ICU and surgical teams needs to be open and collegial, both when the patient is doing well and when unexpected complications arise. If possible, developing protocols jointly can help keep everyone "on the same page."

The relationship between the surgeon and the intensivist can sometimes become contentious, particularly for the non-surgeon intensivist, when they have differing opinions regarding prognosis and end-of-life decision-making [15]. The surgeon may focus on defeating death, while the intensivist may focus on survival with good quality of life. Surgeons perform often complex and high-risk operations with the intent of curing the patient's underlying disease and achieving survival with a good quality of life. This has been described as the "covenant to cure." Because they have directly operated upon the patient, they feel a sense of responsibility and ownership that is different than that of the non-surgeons involved in the patient's care. As a consequence, they may not readily relinquish all or part of the responsibility for the patient's care to the intensivist. They also may feel a sense that their patients are somehow different than the typical patient studied in the ICU, such that general ICU or hospital protocols for administration of blood products or various medications do not apply. Discussion and education separated from the management of an individual patient can help, as can jointly developed protocols. Emotions can cloud judgment when discussing the care of a single patient.

Intensivists also want the patient to do well and have a good quality of life after ICU care. But intensivists tend to have a more holistic view of the patient's status, taking relief of pain and suffering into account.

When clear differences of opinion regarding prognosis exist, there is no easy way to come to consensus. Direct communication is always the best place to start. It is unfair to a family to ask them to make a decision regarding care of their loved one when the physicians involved cannot even agree on what to expect. That is not to say that medical uncertainty should not be part of the discussion with the family. It should. But giving them divergent messages only adds confusion. When there are differences of opinion between members of the healthcare team or between the healthcare team and the family, it can be helpful to engage the palliative medicine or supportive care service. These consultants, who are not expert in the medical issues involved and have no direct involvement in the patient's medical care, can help facilitate constructive conversations within the healthcare team and between the team and the patient's family. Although the discussion is often around continuing the "full court press" or shifting to comfort measures only, a middle ground of a time-limited trial of ongoing aggressive care is sometimes more palatable to everyone involved.

Leadership

Ideal functioning of the complex environment in the ICU requires excellent leadership, both medical and nursing. Leaders need to serve as role models for their staffs and

trainees. In addition, the leaders need to be excellent communicators. They need to listen to the concerns of their staff, as well as the concerns of the surgical teams. They also need to be very good at managing conflict. Keeping everyone focused on doing the right thing for the patient usually goes a long way.

Among intensivists, there may be significant variability in practice. The use of national guidelines can help the group come to consensus [16]. But much of the care delivered in the ICU is not covered by guidelines or randomized clinical trials. This does not preclude the development of local guidelines and protocols to provide more uniform care. Development of these guidelines in conjunction with other stakeholders, such as the nursing staff, pharmacy staff, and surgical services, will help.

For an ICU team to function well, it is critical that the medical and nursing leadership support each other. This synergy can enhance the quality of care and relationships with the surgical teams. All staff needs to be held accountable for their roles in providing quality care.

It is important for the medical leadership of ICUs to have a multi-professional forum for discussion of data on the quality of care for patients in the ICUs, quality improvement projects, and share best practices.

Leadership, both medical and nursing, needs to nurture the career development of members of the staff. This may involve modeling appropriate behaviors and communication skills, mentoring clinical skills and academic projects, and supporting career advancement, even when that means having a valued team member leave the ICU for a higher position in their profession.

The ideal functioning of an ICU requires a number of people in leadership positions that answer to the medical director and nurse manager. There may be several important committees, including process improvement, education, and equipment/resources. A social (or "retention") committee can serve an important role in developing team camaraderie. The leaders of these committees should be appropriately mentored for their current and future leadership roles.

Intensivist Compensation

Intensivist staffing for an ICU has a significant impact on compensation. Staffing can become complex because the size of an ICU and the average census of the ICU are not designed around the intensivist workload. The optimal number of patients for an intensivist to manage on a daily basis is difficult to define. Within the pulmonary critical care medicine community, one survey suggested concerns about the quality of care if one intensivist needed to manage 15 or more patients [10]. If an ICU has ten beds, can an intensivist generate sufficient billing to justify appropriate salary support? As the size of the ICU increases beyond 15, the covering intensivist may become increasingly stressed. At what size of unit is it viable to have two intensivists? How readily do residents and fellows allow intensivists to cover more patients? Advanced practice providers may also allow a single intensivist to cover more patients. In addition, they can bill independently, though they typically are reimbursed at 85 % of that of the physician. If the APPs are part of the same billing unit or practice corporation as the intensivist and they capture billing that would otherwise have been lost, their reimbursement can help with the group's financial viability.

Like other hospital-based specialists, intensivists have little control over the number of patients they see on a daily basis. Clinical income for intensivists is usually limited by the number of patients in the ICU. Efforts to optimize this billing within the Centers for Medicare and Medicaid Services guidelines for critical care billing are worthwhile. The use of critical care codes (e.g., 99291 and 99292) is reimbursed at a significantly higher level than the subsequent hospital visit codes (e.g., 99231–99233). Intensivists need to learn the nuances of critical care documentation and coding in order to appropriately maximize billing. In addition, all procedures, such as intubation, bronchoscopy, and central venous catheter placement that are not bundled within the critical care codes, should be captured.

Some critical care groups have taken on responsibility for patients outside the ICU. This may take the form of participation in rapid response systems or a critical care consultation service. These initiatives can add to practice income, though the more important impact may be on the quality of patient care outside the ICU, helping to decrease the need for ICU transfer and for readmission.

Compensation for availability is important for an intensivist group to negotiate with the hospital [17]. Whether this availability is from home or in the hospital at night, it benefits the hospital in terms of quality patient care. Therefore, the hospital should financially support the group for providing this service.

Incentive plans within private practice or academic groups vary considerably. Some offer "carrots" for compliance with regulatory paperwork, quality improvement initiatives, education, or research. Such an approach encourages individuals to go "above and beyond" the minimal workload and can increase the quality and quantity of scholarly activities. Others use a "stick" approach, e.g., placing a certain percentage of salary at risk for failure to comply with various requirements or not participating in various activities.

Effective ICU leaders are able to demonstrate the value of critical care services to the hospital [17]. Providing quality care can decrease complications, readmissions, and length of stay. In addition, because critical care costs are such a large part of the hospital's budget, critical care teams have the potential for providing considerable savings to the hospital by limiting the use of expensive therapies to patients who

would most benefit from them and decreasing unnecessary lab and imaging tests. In some circumstances, the savings can be substantial, giving the intensivists an opportunity to ask the administration for a percentage of those savings.

Measuring Success

The success of an ICU team can be measured in a variety of ways. Patients' clinical outcomes may be the most important, but, as discussed above, improving outcomes via changes in the process of care can be difficult to demonstrate. On the other hand, successfully following protocols and other processes of care is a valuable measure of success. Other parameters include patient/family satisfaction and respect of the surgical services. Finally, retention of high-quality, dedicated staff is a sign of successful ICU structure and leadership.

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Practical Pharmacokinetics and Pharmacodynamics

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Abbreviations

α	Distribution half-life
AUC	Area under the curve
β	Terminal half-life
Cl	Clearance
Cmax	Maximum concentration
Cmaxss	Steady-state maximum concentration
Css	Steady-state concentration
CYP	Cytochrome P450
F	Bioavailability
*f*T>MIC	Free concentration time above minimum inhibitory concentration
ICU	Intensive care unit
Ke	Elimination constant
LD	Loading dose
LOS	Length of stay
MIC	Minimum inhibitory concentration
PD	Pharmacodynamics
PK	Pharmacokinetics
PK/PD	Pharmacokinetics and pharmacodynamics
TDM	Therapeutic drug monitoring
T1/2	Half-life
T>MIC	Time above mean inhibitory concentration
Vd	Volume of distribution

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Introduction

The physiological responses to surgery, critical illness, and subsequent resuscitation can alter both pharmacokinetics (PK) and pharmacodynamics (PD) [1]. As a result of these changes, pharmacotherapy may need to be altered to produce the desired outcomes. A basic understanding of the principles of pharmacokinetics, or the movement of drugs in the body, and pharmacodynamics, the cells responses to drugs, is needed to maximize pharmacotherapy [2]. This chapter will review basic pharmacokinetic and pharmacodynamic principles and some changes in the critically ill surgical patient.

Pharmacokinetics

Pharmacokinetics is the process by which drugs are absorbed, distributed, metabolized, and eliminated by the body. It relates to the concentration of drug in the blood and various body parts and how drug moves through the body over time. These principles dictate drug dose and dosing interval, and understanding them will aid the clinician in medication selection, dosing, and appropriate monitoring. The four main pharmacokinetic parameters used in PK models are bioavailability (F), volume of distribution (Vd), half-life (t1/2), and clearance (Cl). In simple PK modeling, the one-compartment model assumes a drug enters into a compartment with a given volume of distribution to achieve a homogenous concentration and is subsequently eliminated based on an elimination rate constant (ke). Vasoactive catecholamines such as epinephrine and norepinephrine follow one-compartment PK model. The two-compartment model aligns better with what actually occurs in the body clinically. It accounts for a second compartment mimicking tissues and organs. A drug enters into a central compartment and distributes between the central and peripheral compartments [3]. For some very lipid soluble drugs, such as amiodarone, there are three or four compartment PK models that also account for adipose tissue. Despite underlying assumptions to simplify these

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Table 41.1 Basic pharmacokinetic equations

	Equation
Half-life	0.693/ke
Elimination constant	$(\ln C1 - \ln C2)/(t1 - t2)$
Maximum concentration	C1/[ê - ke(t1)]
Minimum concentration	$Cmax\left[\hat{e} - ke(\tau - t')\right]$
Volume of distribution first dose	Dose/Cmax
Volume of distribution steady state	$D\left(1 - \hat{e} - ke(t')\right)/\left[t'ke\left(Cmax - Cmin * \hat{e} - ket'\right)\right]$
New maximum concentration steady state	$D\left(1 - \hat{e} - ket'\right)\right]/\left[t'keVd\left(1 - \hat{e} - ke\tau\right)\right]$

C1 concentration one, *C2* concentration two, *Cmax* maximum concentration, *Cmin* minimum concentration, *ke* elimination constant, *t1* time one, *t2* time two, *t'* infusion duration, τ (*tau*) dosing interval

models, they are clinically useful in predicting drug concentrations (Table 41.1).

The bioavailability of a drug is the fraction of the administered dose that reaches systemic circulation of the patient. A drug with 100 % oral bioavailability achieves a systemic concentration comparable to that of the intravenous route when the drug is administered at the same dose. Drug properties such as the chemical and dosage form impact absorption as well as patient factors. An oral solution, for example, may have greater bioavailability than a solid formulation such as a capsule or tablet as it has already undergone the dissolution phase. The first-pass effect, metabolism by enzymes in the liver or gut wall occurring prior to the drug entering systemic circulation, will also affect bioavailability. Medications which undergo extensive first-pass metabolism will have a lower bioavailability, although it could also be increased in the setting of liver impairment [4]. Sublingual administration of some medications, such as tacrolimus, has enhanced bioavailability since first-pass metabolism is bypassed. Medications with low oral bioavailability either need to be dosed higher or administered using alternate routes. Physiologic factors such as ileus may be another reason for use of alternate routes in the critically ill population. These alternate routes including rectal, subcutaneous, or transdermal administration are not without disadvantages such as unpredictable serum concentrations. Dosing conversions between intravenous and alternate formulations depend on the bioavailability. Medications with high bioavailability such as levetiracetam have a one-to-one conversion from intravenous to oral, whereas it is generally accepted to dose oral furosemide twice that of the intravenous form because of its lower bioavailability. Most PK studies are conducted in young healthy males, and as a result there are little data on how bioavailability may or may not be affected in critically ill surgical patients.

Volume of distribution (Vd) is a theoretically derived PK parameter that corresponds to the lipophilicity of a specific drug. Typically, drugs with higher Vd are more fat-soluble. The amount of bound and unbound (free) drug in the plasma versus tissues relates not only to bioavailability but also to Vd. Only the unbound drug has a pharmacologic effect. It is a hypothetical volume relating the total amount of drug in the body to plasma concentration, but is not associated with a true physiologic space. Apparent Vd could be a greater value than what is physiologically reasonable. A large Vd thus indicates extensive tissue distribution [3]. For example, amiodarone has a Vd of 60 L/kg due to it being extremely fat-soluble. A small volume indicates that a large proportion of drug is confined to the plasma and does not readily distribute to tissues. Vasoactive catecholamines are examples of drugs with small Vd. The degree and rate of distribution depends on tissue perfusion and protein binding among other factors. For example, amiodarone is typically loaded when used for atrial arrhythmias because it has a large volume of distribution. A continuous infusion is typically started after the loading infusion because amiodarone rapidly distributes out of the plasma into tissues. Another example of extensive distribution is midazolam. Although it readily crosses the blood-brain barrier and therefore has a quick onset of action, it also has a shorter duration of action rendering it useful for procedures. On the other hand, aminoglycosides are hydrophilic and have a small volume of distribution and the VD may be affected by total body water. Volume of distribution should be considered when determining dosing weight for weight-based medications, especially in obese patients where there is a large disparity between actual body weight and ideal body weight. There are numerous factors affecting Vd, and some factors include age, total body water, acid-base imbalances, and protein binding [5].

Medications with a large Vd may warrant a loading dose (LD) in order to achieve adequate serum concentrations. Amiodarone is one such example as well as vancomycin. Typically loading doses are used to quickly fill up the volume of the space. They do not need to be altered due to problems with elimination such as renal failure with vancomycin [4]:

$$LD = Css \times Vd$$

Digoxin is the exception to the "rule." A typical loading dose is 15 mcg/kg, but in critically ill patients or those with renal insufficiency, there is altered protein binding leading to a decreased volume of distribution and thus increased plasma drug concentration. Typically half the normal loading dosage is sufficient in these patients [6].

The elimination of a drug by the body is called clearance and the main routes of clearance are renal, hepatic, and biliary. Other routes of clearance include the reticuloendothelial system and plasma enzymes. Clearance is measured by the amount of drug cleared over a unit of time. In first-order kinetics, which a majority of drugs follow, clearance is proportional to drug concentration. In other words, the rate of elimination will proportionately increase with increases in drug concentration. Total drug clearance is the sum of all routes of clearance such as renal clearance, hepatic clearance, and biliary clearance. Depending on the extent of each type of elimination for a particular drug, dose adjustments may be warranted in the setting of organ impairment. For example, digoxin is primarily renally excreted, necessitating a decrease in dose with renal impairment. In contrast, diltiazem has negligible renal excretion, so the dose does not need to be adjusted in the case of renal impairment. Cisatracurium and remifentanil are considered to have organ-independent metabolism since cisatracurium relies on nonenzymatic degradation in the blood for metabolism, and remifentanil is rapidly metabolized by blood and tissue esterases.

Clearance also estimates the drug concentration over time or area under the curve (AUC) based on the dose. Dosing strategies used may have the same AUC with different peak effect. It is influenced by bioavailability, dose, dosing interval, and clearance:

$$AUC = Dose / Cl$$

For example, intravenous acetaminophen was shown to have the same AUC as oral acetaminophen despite reaching a higher peak concentration.

Half-life is the period of time required for the amount of drug in the body to be reduced to one-half of a given concentration. It is dependent on volume of distribution and clearance:

$$t1/2 = \left(0.693 \times Vd\right) / Cl$$

The half-life is directly proportional to Vd and inversely proportional to Cl. Drugs with very fast clearance such as norepinephrine have very short half-lives because they are metabolized by the blood enzymes, monoamine oxidase, and carboxy-O-methyltransaminase. It has a short half-life of 2–2.5 min and therefore has a small Vd. Amiodarone, on the other hand, is very lipid soluble and has a long half-life of approximately 60 days based on its large Vd. Half-life is clinically relevant in determining dosing interval since it indicates how quickly drug concentration decreases over time. Generally, drugs with shorter half-lives are dosed more frequently or continuously. Critically ill patients may develop renal impairment, so the dosing interval would be extended to account for the longer half-life. In some cases, drugs with short half-lives such as esomeprazole may not be dosed as frequently due to the longer pharmacodynamic effects that persist.

As a general rule, a drug is at approximately 90 % of its steady state at 3.3 half-lives and at approximately 100 % of steady-state concentration at five half-lives. A drug is completely eliminated from the body in approximately five half-lives irrespective of dosage itself. It takes this same amount of time to reach a steady-state concentration whereby peak and trough concentrations converge and the amount of drug entering the body matches the amount being eliminated over a period of time. Peak concentration is the highest concentration within one dosing interval and trough concentration is the lowest. A loading dose may be administered to maintain therapeutic concentrations prior to the steady state being reached.

Some drugs such as vasopressors follow the one-compartment model, but most drugs follow the two-compartment model including antibiotics. These drugs with more than one compartment have both a distribution phase (α), or distribution half-life, and an elimination phase (β), or terminal half-life. The distribution phase generally consists of a shorter half-life, but the drug will be nearly entirely distributed throughout the body after five half-lives also [3, 4]. In the case of amiodarone, because of its lipophilicity, a bolus dose will be distributed into the tissues rapidly in contrast to its long terminal half-life, necessitating a continuous infusion to maintain an adequate serum drug concentration.

The liver plays a major part of metabolism and drugs that are metabolized by the liver can undergo a variety of pathways. Phase 1 metabolism occurs via the cytochrome P (CYP) enzyme system and phase 2 metabolism occurs via glucuronidation. Glucuronidation is a more fundamental process than oxidation by the complex CYP enzyme system. There are numerous CYP enzymes responsible for drug metabolism. Common enzymes include CYP3A4, 2D6, 2C9, and 2C19 [7]. The CYP3A4 enzyme metabolizes over 50 % of medications [8]. Medications may be metabolized through more than one pathway. There is a higher risk of drug-drug interactions for medications that are substrates, inducers, or inhibitors of common enzymes. There is potentially a major drug-drug interaction between carbamazepine and phenytoin. Carbamazepine can induce CYP2C9- and CYP2C19-mediated phenytoin metabolism, and phenytoin can induce CYP3A4-mediated carbamazepine metabolism. Interactions based on enzyme induction may have a delayed onset

compared to inhibition because of the time needed for enzyme synthesis.

Genetic polymorphisms and other factors can also affect function of the CYP enzyme system. The resulting phenotypes are defined as poor, intermediate, extensive, and ultrarapid metabolizers [8]. In the case of patients who are deficient in CYP2D6, they would have inadequate analgesia with codeine, a prodrug whose activity is dependent on its conversion to the active metabolite, morphine. Ultrarapid metabolizers, on the contrary, may develop serious side effects from codeine based on excessive morphine plasma concentrations. Warfarin has a multitude of drug-drug interactions as well as altered metabolism based on variations of the CYP2C9 and VKORC1 genes. Genetic polymorphisms can impact response to clopidogrel therapy, a platelet P2Y12 receptor blocker, resulting in clopidogrel treatment failure. Hypo-responsiveness, or platelet resistance, may result in a patient being switched to a more potent thienopyridine such as ticagrelor or prasugrel. There are assays available to determine the degree of platelet inhibition from the use of P2Y12 inhibition drug therapies [9].

Another source of drug interactions can arise based on altered protein binding. Drugs that are highly protein bound at the same sites may compete with one another for the limited binding sites. This is the case with phenytoin and valproic acid in which concurrent use may result in altered levels. In addition this partially explains why the interaction is unpredictable.

Changes in Pharmacokinetics in Surgical ICU Patients

The physiological response to surgery and critical illness and the resultant fluid resuscitation can alter the pharmacokinetics of drugs in critically ill surgical patients [1]. The resultant trauma from surgery and response to critical illness may lead to changes in renal, hepatic, and cardiovascular systems and significant changes in protein binding and intravascular volume. As a result, patients are often fluid resuscitated and may require many liters of fluid. In these patients there may be an increase in total body fluid and for drugs that have small volumes of distribution and distribute to the extracellular space, such as aminoglycoside and beta-lactam antibiotics, a result increase in Vd with a decrease in concentrations [1]. Therefore larger dosages may be required during this acute phase. As the patients get better and mobilize the fluids and diuresis, the volume of distribution will return to normal and the dosage may need to be modified especially with the aminoglycosides. In addition there are changes in plasma protein homeostasis that may affect distribution especially of unbound drug. Albumin in particular is decreased during critical illness, and drugs that are highly protein bound such as phenytoin may have altered pharmacokinetics. Conversely there can be a relative increase in acute phase proteins such as alpha-glycoproteins which may affect drugs such as morphine and lidocaine [1].

There are little data describing the absorption of drugs in critically ill surgical patients. Changes in gastric motility, intestinal permeability, and motility are thought to affect drug absorption. Critically ill surgical patients are affected by these and surgical complications such as fistula development or short gut syndrome. In general, most drugs are absorbed in the small bowel but a few drugs such as warfarin are absorbed in the stomach and can be administered to patients with short gut. As it is hard to determine if the gut is working, one may have to determine this based on clinical response. For example, a patient that is both tachycardic and on high end of normal blood pressure, the addition of enteral diltiazem to intravenous metoprolol may result in a significant decrease in heart rate and signify that the diltiazem is being absorbed.

The clearance of drugs may also be significantly altered in the critically ill. Most drugs are eliminated either hepatically or renally, and in states of shock blood is shunted away from these organs potentially decreasing elimination. Furthermore, hypoxia can decrease hepatic enzyme activity, especially the cytochrome P450 system. Finally the use of renal replacement therapies, which are common in the ICU setting, can increase clearance of some drugs.

Pharmacodynamics

The relationship of the drug concentration and pharmacologic responses is termed pharmacodynamics [2]. It is also been defined as *what the drug does to the body* [10]. Although this is somewhat similar to pharmacokinetics, it differs in that the change in drug effect is usually not proportional to the change in drug dose or concentrations [2]. Since pharmacokinetics and pharmacodynamics are related, it may be difficult to explain the difference. Using loop diuretics, such as furosemide, as an example, there can be both a pharmacokinetic and pharmacodynamic reason to diuretic resistance [11]. Furosemide is secreted into the nephron by the organic acid pathway. To be actively secreted into the nephron, a threshold concentration of furosemide needs to be achieved, and if there is significant gut edema present, this may not occur with oral administration of furosemide. This is the pharmacokinetic reason for diuretic resistance and it can be overcome by giving intravenous furosemide that should result in diuresis. In cases where intravenous furosemide does not achieve adequate diuresis, there may be a pharmacodynamic change in the patient that may be the cause of diuretic resistance. With chronic use of loop diuretics, there is a higher sodium concentration than normal in the distal tubules, and as a result there is hypertrophy of the distal tubules causing more sodium and in turn water reabsorption than normal. This pharmaco-

dynamic response can be overcome by administration of concomitant thiazide diuretic that works in the distal tubules.

The most basic pharmacodynamic concept is the pharmacologic response produced by a drug as a result of the drug's binding to the receptor. This explains why a pharmacologic response may lag behind the drug pharmacokinetic concentrations. Take the sedative dexmedetomidine as an example. Dexmedetomidine is an alpha-2a agonist that produces "cooperative sedation" in the critically ill patient by decreasing norepinephrine concentrations [12]. Dexmedetomidine has a half-life of 2–3 h. Although the product labeling suggests the use of a loading infusion followed by a continuous infusion, clinical studies have shown that the use of loading infusion does not increase onset of sedation. By understanding the pharmacology of dexmedetomidine and its pharmacodynamics this makes sense. As dexmedetomidine binds to the alpha-2a receptor, it blocks norepinephrine reuptake, and thus the norepinephrine is inactivated by plasma enzymes to produce a decrease in norepinephrine concentrations. Since the half-life of norepinephrine is between 2 and 5 min, it will take four to five half-lives for the norepinephrine to be metabolized or approximately 20 min, which happens to be the onset of dexmedetomidine. As dexmedetomidine does not by itself metabolize norepinephrine, it does not matter if initially there is a high or low concentration of dexmedetomidine at the alpha-2a receptor; it is the pharmacodynamic response that is needed.

Pharmacodynamics is often applied by the use of sophisticated models, especially during the development phase to help determine drug-dosing regimens [2, 13]. These models are often complex and may contain many linked mathematical sub-models [13]. Although used in the drug development process, these models are often not used in clinical practice. The use of complex pharmacokinetic and pharmacodynamic (PK/PD) modeling is being increasingly used to help maximize and individualize pharmacotherapy. Basically PK/PD models have been developed to combine both principles of PK and PD to describe the effect-time course directly resulting from administration of a fixed dose of the drug [13]. The main value of the PK/PD modeling is to extrapolate relation between the effect-time course from existing data [13]. Many studies are now using complex PK/PD modeling, most notable with antibiotics to help improve efficacy in this time of increasing antibiotic resistance [14]. Pharmacokinetic and pharmacodynamic modeling is also being applied to other classes of medications such as antifungals and analgesics [13, 15, 16].

The ultimate goal of PK/PD is maximize a drug-induced effect or changed in physiologic parameter [13]. Especially in critically ill surgical patients, the physiologic baseline values are not constant. It is often difficult to quantify efficacy based on PK/PD models and surrogates often are used [13]. As a result it is necessary that the surrogate parameter needs to correlate with the desired effect. Using dexmedetomidine again as an example, the sedation effect is a result of decreased norepinephrine concentrations in the synaptic cleft between the presynaptic and postsynaptic neuron. As it is very difficult to measure this, so surrogates are often used, most notably mean arterial pressure and heart rate. Although heart rate typically correlates with the decrease in norepinephrine concentrations, mean arterial does not. As the concentration of dexmedetomidine increases, it loses selectivity for the alpha-2a receptor, a vasodilator, and also binds to the alpha-2b receptor, a vasoconstrictor. As it is very difficult to measure this, surrogates are often used, most notably mean arterial pressure and heart rate. Although heart rate typically correlates with the decrease in norepinephrine concentrations, mean arterial does not. As the concentration of dexmedetomidine increases, it loses selectivity for the alpha-2a receptor, a vasodilator, and also binds to the alpha-2b receptor, a vasoconstrictor. This results in higher mean arterial blood pressure from baseline so use of mean arterial as a surrogate of efficacy would not be useful in PK/PD modeling for dexmedetomidine.

There are four common PD modes used based on steady-state concentrations [13]. They are fixed effect model, linear model, log-linear model, and E_{max} model. In the fixed effect model, it relates a certain concentration of a drug with the statistical likelihood of a predefined effect (Table 41.2). An example of this model would be the development of ototoxicity with gentamicin therapy when the trough concentration exceeds 4 mcg/mL for greater than 10 days [13, 17]. In the linear model, there is a direct correlation between the drug concentration and drug effect. In this model doubling the dosage of a drug and thus the concentration would double the effect seen. The linear model is most intuitive, but it rarely applies to most drugs [13]. More common than the linear model is the log-linear model where the desired effect is linear when compared to the logarithm of the drug concentration. With all things being constant, this was used to relate synthesis of prothrombin complex activity with the concentration of warfarin [13, 18]. When the curve produced by the log-linear model is hyperbolic in shape, then one has the E_{max} model. This model is based on the receptor theory relationship and explains when a concentration of a drug is below the EC50; increasing the dosage typically increases the effect. An example of this is increasing the dosage of amlo-

Table 41.2 Pharmacodynamic model equations

Model	Equation
Fixed effect model	$E = E_{\text{fixed}} \text{ if } C > C_{\text{threshold}}$
Linear model	$E = m \times C + E_0$
Log-linear model	$E = m \times \log C + b$
E_{max} model	$E = (E_{max} \times C)/(E_{50} + C)$

C concentration, E effect, E_0 baseline effect without any drug, E_{50} 50 % of the maximal effect, E_{max} maximal effect of drug

dipine from 5 to 10 mg and then seeing an increase in the blood pressure-lowering effect. When the concentration exceeds the EC50, increasing the concentration of the drug only produces small changes in the effect. This can be seen when increasing amlodipine from 10 to 20 mg, as the changes in blood pressure are minimal.

Pharmacokinetic/Pharmacodynamic Modeling

With the decrease in new and novel antibiotics being developed and available for use worldwide, complex PK/PD modeling is increasing being used to help maximize antibiotic therapy (Table 41.3) [14]. The PK/PD modeling takes into account the concentration-time response achieved in a patient and the effect in this case is on the bacteria [14]. With antibiotics the minimum inhibitory concentration (MIC) is used to determine susceptibility to an antibiotic. It is the minimum concentration that inhibits visible growth of a microorganism. Although the use of broth dilution is the gold standard for determining MIC, it is labor intensive and not routinely used in clinical practice. Automated systems such as Vitek-2 or Microscan are commonly used. Since these are commercially available, they cannot be modified and may estimate the MIC. *E*-test is a less labor-intensive method than broth dilution to assess exact MIC by using a test strip that is impregnated with an exponential gradient of the antibiotic. Use of *E*-test is restricted to those antibiotic strips supplied by the *E*-test manufacturer, and since the MIC is based on ocular inspection it may be subjective. As a result, there may be differences in reported MIC by various testing methods, therefore the MIC may not be a good PD parameter to characterize concentration-effect relationships.

In general antibiotics are bactericidal or bacteriostatic [14]. Bactericidal antibiotics kill bacteria, while bacteriostatic agents stun bacteria to prevent growth and allow the patient's immune system to kill the bacteria. Beta-lactams and aminoglycoside are examples of bactericidal agents, while linezolid is an example of a bacteriostatic agent. Bactericidal agents can also be broken into two subgroups: time-dependent killing and concentration-dependent killing. Time-dependent antibiotics effectively kill bacteria at the same rate as long as the concentration is above the MIC. Beta-lactam antibiotics are an example of time-dependent killing, and it does not matter if the concentration is at the MIC or 1,000 times the MIC. For concentration-dependent antibiotics, there is more effective or faster killing of the bacteria with high concentrations of antibiotics. Examples of antibiotics that are concentration dependent include the aminoglycoside or fluoroquinolones. Area under the curve, AUC, and maximum concentrations, Cmax, are often used with these concentration-dependent antibiotics and are represented by AUC/MIC and Cmax/MIC [14].

The use of simulations with PK/PD modeling is a potential powerful tool to select the optimum dosing regimen to maximize the efficacy of antibiotics [14]. In 2001, Drusano and colleagues introduced Monte Carlo, a stochastic, simulation to antibiotic PK/PD modeling [19]. In these simulations the probability of target attainment above the MIC is simulated from a large population and is simulated, and the proportion of subjects above the identified target is computed form a range of MIC and dosing regimens [14, 19]. Based on the results, the probability of target attainment based on the MIC and dosing regimen is determined. The use of simulation with PK/PD modeling, such as Monte Carlo, has increased dramatically since the turn of the century, and it is even used by the European Committee on Antibiotic Susceptibility Testing to set clinical breakpoints for antibiotics susceptibility [14, 20].

Based on these PK/PD models and simulation changes, many alternative antibiotic dosing regimens have been developed [21]. For time-dependent antibiotics, such as beta-lactams, efficacy is optimized when the free concentration above the MIC (*f*T>MIC) for 60–70 % of the dosing regimen (Table 41.4) [22]. In most cases antibiotics are either administered as a loading infusion followed by continuous infusion (e.g., nafcillin 2 g over 60 min followed by 0.5 g/h) or extended infusion (e.g., cefepime 2 g over 3–4 h every 8 h). Although these alternative regimens are based on population parameters, it is unknown if they truly improve clinical outcomes. In 87 patients with *Pseudomonas aeruginosa* bacteremia or pneumonia where 63 % were in the ICU at the onset set of infection, Bauer and colleagues reported the use of extended-interval cefepime regimen (2 g over 4 h every 8 h) versus traditional cefepime (2 g over 30 min every 8 h) was associated with significant lower mortality (3 % versus 20 %, $p = 0.03$) and median ICU length of stay (8 versus 18.5 days,

Table 41.3 Basic pharmacokinetic and pharmacodynamic models for antibiotics and antifungals

Model	Equation
Area under the inhibitory curve (AUIC)	AUC/MIC
Concentration-dependent model	Cmax/MIC
Time-dependent model	$T >$ MIC
Free concentration time-dependent model	fT > MIC

AUC area under the curve, *Cmax* maximum concentration, *fT* free concentration over time, *MIC* minimum inhibitory concentration, *T* time

Table 41.4 Pharmacokinetic and pharmacodynamic effects of beta-lactam antibiotics

Drug class	Time > MIC for bacteriostatic effect	Time > MIC for bactericidal effect
Penicillins	30 %	50 %
Cephalosporins	40 %	70 %
Carbapenems	20 %	40 %

MIC minimum inhibitory concentration

$p = 0.04$) [22]. More studies are needed especially with pathogens with higher MIC organisms and ICU patients to determine the true efficacy of these alternative dosing regimens.

For concentration-dependent antibiotics such as aminoglycosides (amikacin, gentamicin, and tobramycin), the use of high-dose extended-interval dosing (i.e., 7 mg/kg tobramycin q24–28 h based on renal function) has been promoted [23]. This is based on the PK/PD models with the goal to obtain a Cmax/MIC >10 with the first dose. This parameter has been demonstrated to have a quicker resolution of infection in the general population with less nephrotoxicity than traditional dosing. In ICU patients due to changes in volume of distribution and variability in clearance, the target attainment (Cmax/MIC > 10) may be difficult to achieve. In addition it will be harder to attain this goal for pathogens with higher MICs, and they are more likely to occur in the ICU than the general units.

Not only has PK/PD modeling been used to maximize antibiotic therapy, it also is being used to maximize antifungal therapy [16]. Most of the data are with the triazole antifungals (e.g., fluconazole) with *Candida* infections. Studies have demonstrated that triazole have time-dependent killing that is optimized at one to two times the MIC and that there is a prolonged suppression of growth following therapy. The best PK/PD model for the triazole is AUC/MIC [24–26]. In this case for *Candida* species with higher MICs, a higher dosage is required [24–26]. As AUC is the concentration over time curve, increasing the dose will increase the AUC, and dose/MIC has been used when describing the effect of triazole on candidemia as the AUC/MIC and dose/MIC correlate to each other. In a study of 77 patients with candidemia including 29 ICU patients, treated with fluconazole, those that survived had significant higher dose/MIC ratio and a trend to higher AUC/MIC ratio suggesting that maximizing them improves mortality [26]. This explains why higher dosages, such as 800 mg a day, are used in *Candida* infections in which there is a higher MIC (e.g., 8–16 mg/L). It is also thought that for triazoles active against *Aspergillus* species, such as voriconazole, the PK/PD is best described by AUC/MIC [16]. In a study of 51 patients with invasive mycoses, there was a significant reduction in lack of response when the trough level exceeded 1 mg/L compared to those with a trough less than 1 mg/L (12 % versus 46 %, $p = 0.02$) [27].

Similar to aminoglycosides, the echinocandins (anidulafungin, caspofungin, and micafungin) and amphotericin B formulations exhibit concentration-dependent killing. They are also best described by Cmax/MIC in which large doses are given less frequently [16]. These agents also produce a significant prolonged suppression of growth. Unlike the triazoles, there is little PD data with these agents in humans. With amphotericin B studies have demonstrated that there is increased killing when concentrations are two to ten times above the MIC. Unfortunately infusion-related adverse effects and toxicities are a problem with amphotericin B formulations, especially the deoxycholate formulation.

Drug Classes

Nondepolarizing Neuromuscular Blockers

Nondepolarizing neuromuscular blocking agents are used during procedures and as continuous infusion in the critically ill [28]. They are competitive antagonist of the nicotinic receptor and block acetylcholine from binding to the nicotinic receptors. They are divided into two classes the aminosteroid compounds and the benzylisoquinoliniums. The aminosteroid compounds include pancuronium, vecuronium, and rocuronium. These agents have significant renal and hepatic elimination and can accumulate in renal or hepatic insufficiency [28]. The benzylisoquinoliniums include atracurium and cisatracurium which are eliminated in by plasma hydrolysis and Hofmann elimination. These agents are the preferred agents for continuous infusions in critically ill with hepatic or renal insufficiency [28].

Opiates

Intravenous opioids are the mainstay for analgesia in the surgical ICU and are considered first-line therapy [29]. The most commonly used opiates include morphine, hydromorphone, and fentanyl, while methadone and remifentanil are occasionally used. With the exception of remifentanil that is metabolized by ester hydrolysis in the plasma, all opioids are metabolized in the liver and some have active metabolites. Morphine and hydromorphone are glucuronidated, but morphine has active metabolites that are eliminated renally. Morphine can accumulate in hepatic or renal insufficiency. Meperidine has an active metabolite that is eliminated renally, normeperidine, and is known to lower seizure threshold and limits it use. Fentanyl has no active metabolites but undergoes dealkylation and accumulates in hepatic failure. With prolonged use fentanyl can accumulate in adipose tissue and have prolonged elimination. Methadone has dual mechanism of action on both the mu and N-methyl-D-aspartate receptors. It also has unpredictable PK/PD and elimination half-life of 15–60 h. Conversely due to its rapid clearance, remifentanil has an elimination half-life of 3–10 min.

Sedatives

Sedatives are also commonly used medications in the surgical ICU, and like opioids there are PK differences among them [29]. The most commonly used agents are propofol,

benzodiazepines, and dexmedetomidine. Propofol is a sedative-hypnotic that is highly lipid soluble. As a result it is has an extremely short onset of action, 1–2 min, as it readily crosses the blood-brain barrier. It has a large Vd due to its lipid solubility and therefore a prolonged half-life. With short use its half-life is 3–12 h and with prolonged use it has a half-life of over 50 h.

The common used benzodiazepines include lorazepam and midazolam and to a lesser extent diazepam. Both midazolam and diazepam are highly lipid soluble, oxidized via the cytochrome P450 system, and have a quick onset of action of 2–5 min [29]. They also have active metabolites, which are eliminated renally. Midazolam has a shorter half-life of 3–11 h, while diazepam is 20–120 h. Due to accumulation from their high VD, the half-life is longer with prolonged use. Conversely, lorazepam is less lipid soluble and has a longer onset of action of 15–20 min. It is glucuronidated in the liver and does not have any active metabolites. It has a half-life 4–15 h. Similar to lorazepam, dexmedetomidine is glucuronidated and does not have any active metabolites. Its half-life is 2–3 h [12].

Anticoagulants

Heparin and low molecular weight heparins, such as enoxaparin and dalteparin, are commonly used anticoagulants for both prophylaxis and treatment of venous thromboembolism in the surgical ICU [30]. Heparin is a large molecular and is eliminated by the reticuloendothelial system with a volume of distribution closely mirrors that of total blood volume [31]. Obese and morbidly obese critically ill patients required higher dosages of therapeutic heparin than the non-obese critically ill patients [31]. Conversely low molecular weight heparins and fondaparinux, a pentasaccharide, are smaller than heparin and eliminated predominately renally [30]. Their use in patients with renal insufficiency may lead to accumulation and increased bleeding. Recently, newer oral anticoagulants are available in the United States and include the direct thrombin inhibitor, dabigatran, and the anti-Xa inhibitors, apixaban, edoxaban, and rivaroxaban. Dabigatran cannot be crewed or crushed. At the time of writing, there are not good laboratory markers for anticoagulation or a reversal agent available. All these newer anticoagulants are eliminated between 25 and 40 % unchanged in the urine, and clinical studies excluded the use in patients with creatinine clearance less than 30 ml/min. Therefore the agents should be used with extreme caution or not at all in most surgical ICU patients.

The parenteral direct thrombin inhibitors, argatroban and bivalirudin, are often used as anticoagulants for patients with suspected or confirmed heparin-induced thrombocytopenia [32, 33]. Argatroban is mainly metabolized in the liver and eliminated in the feces through the biliary system, although the half-life is short in healthy males (39–51 min) but is unpredictably prolonged in patients with hepatic or renal insufficiency and during critical illness [33]. In a study of 73 critically ill patients, 21.9 % developed bleeding complications including 9.6 % with major bleeding. Risk factors included major surgery, total bilirubin 3 mg/dl, weight >90 kg, and baseline platelet <70,000/mcL [33]. Bivalirudin has a half-life of 25 min in healthy volunteers and is eliminated predominately through serum proteases (80 %) and unchanged in the urine (20 %) [32]. Studies have demonstrated that as renal function worsens, the dosing of bivalirudin decreases linear fashion, and it is removed by hemodialysis by approximately 25 % [34, 35]. The use of a bivalirudin nomogram in 65 critically ill patients demonstrated a similar rate of bleeding as the argatroban study of 30 % with 10.7 % developing a major bleeding [32]. Caution should be used with the use of either agent in critically ill surgical patients. Initial dosages may need to be decreased, and frequent monitoring may be required.

Proton Pump Inhibitors

Proton pump inhibitors are commonly used medications in the ICU for both prevention and treatment of gastric bleeding. Critically ill patients typically have more acid secretion than healthy patients and have potential for altered pharmacokinetics such as gut edema, luminal stasis, and decreased blood flow [36, 37]. The half-life of proton is relatively short, 2–3 h, but they bind irreversibly to gastric proton pump, which allow daily dosing for prevention of stress-related mucosal bleeding. Olsen and Devlin demonstrated that the use of enteral lansoprazole compared to IV was associated with lower bioavailability (76 %); probably for the reasons above, the PD effects demonstrated significantly higher average gastric pH over 24 h and average time for pH to be greater than 4 [37].

Levetiracetam and Lacosamide

In recent years, the use of levetiracetam and lacosamide for the treatment of seizures has increased. This is partially due to some favorable effects such as minimal drug interaction and linear pharmacokinetics, unlike fosphenytoin or phenytoin [38]. Levetiracetam and lacosamide are both relatively small molecular weight that have small Vd and low protein binding. They have excellent bioavailability and are eliminated unchanged in the urine. In a PK study in 12 neurocritical care patients, levetiracetam was demonstrated to have faster clearance and shorter half-life than studies in healthy volunteers. Therefore higher dosages administered every

12 h (1,500–2,000 mg) or smaller dosages (100 mg) every 8 h may be needed [39]. Although PK studies with lacosamide are currently lacking, it is expected to have similar PK profile as levetiracetam. In addition both of these medications are expected to be significantly removed by continuous renal replacement therapy.

Therapeutic Drug Monitoring

The therapeutic range of a drug is based on the minimum therapeutic concentration and the minimum toxic concentration observed. Not all drugs have an established therapeutic range, limiting drug monitoring using drug levels in some cases. Drugs with an established narrow therapeutic window such as phenytoin may be more closely monitored to ensure safety compared to those with a wider therapeutic window. In fact, some drugs with narrow therapeutic windows such as theophylline, a methylxanthine, are no longer used in favor of ones with wider therapeutic windows, such as caffeine for apnea of prematurity. Selective serotonin reuptake inhibitors (SSRIs) may be favored over tricyclic antidepressants for this same reason.

Therapeutic drug monitoring (TDM) can be used both for efficacy and safety purposes. It is the monitoring of medication concentration in the plasma. Most drug levels measure total drug concentration, including both bound and unbound drug. Some drugs that are highly protein (albumin) bound, such as phenytoin, may also be measured as an unbound or free level. In many cases TDM is relevant for medications with narrow therapeutic windows to ensure efficacy and prevent toxicity. There may be an increased need for TDM in critically ill patients due to physiologic changes such as acute kidney injury as well as fluid shifts that would affect medication concentrations differently than expected.

Not all medications have interpretable levels. For example, it is not clear at what level levetiracetam has optimal efficacy and may differ among patients. Some levels may take time to return if the assay is not available at the particular institution. Monitoring of low molecular weight heparin involves drawing an anti-Xa level 4 h following dosage administration. However, it may take several days for the result to return, at which time a clinical decision may be made whether a dosage change is needed.

Therapeutic drug monitoring does not replace overt clinical monitoring such as signs and symptoms of bleeding or clotting. Most drugs require peak and/or trough levels for TDM. Vancomycin is a commonly monitored antibiotic that requires trough levels to be drawn. It is important to recognize that TDM relating to pharmacokinetics does not necessarily correlate with the pharmacodynamics. Regardless of therapeutic vancomycin trough levels, if a patient is exhibiting persistent signs and symptoms of infection despite perceived adequate therapy, vancomycin therapy failure should be considered in the differential.

Conclusion

A basic understanding of PK and PD principles is necessary in critically ill surgical patients to help maximize efficacy and minimize adverse effects. In the complex environment of the surgical ICU, alterations in PK parameters can be multifactorial and be constantly changing. Likewise PD changes frequently occur. As a result of these alterations in PK and PD parameters, development of alternative dosing methods may be needed to optimize drug therapy.

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Ethics and the ICU

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Christine C. Toevs

Introduction

Ethical issues continue to exist in the ICU and in many ways are becoming more complex. Despite years of bioethicists and increased attention to the challenging situations in the ICU, the issues do not get easier. As advances in technology increase in medicine and the application of this technology to prolong life, we deal with more and more ethical conundrums. As a society, we are increasingly independent and demand autonomy. As healthcare providers, we feel obligated to honor autonomy. As humans, we often want to avoid conflict, and it is easier to just "do everything" than take the time and energy to explain why that may not be beneficial to the patient. The purpose of this chapter is to review several ethical principles and situations common in the ICU and hopefully offer guidance and potential solutions.

Withdrawing and Withholding

One of the most important ethical principles is withdrawing/withholding potentially life-sustaining therapy (LST). Withdrawing LST is stopping therapy that has already been initiated (e.g., withdraw of mechanical ventilation, discontinuing dialysis). Withholding is not starting potentially LST (e.g., do not resuscitate/do not intubate DNR/DNI, not initiating dialysis). Legally and ethically, they are both equal; there is no moral difference between withdrawing a therapy and withholding a therapy. We tend to consider them different, and withdrawing therapy can often be more difficult emotionally on the patients, the family, and the healthcare providers; in which case, it is even more crucial than ever that we have the difficult conversation with the patient and the family and determine goals of care prior to initiating LST.

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In the past, the term euthanasia has been used. Passive euthanasia was used to describe the withdrawing of LST. However, this term has fallen out of favor as the intent of withdrawing therapy was never to kill the patient, but rather to focus on comfort, recognition of limitations of specific therapies to extend life, and acknowledging wishes of patients and families regarding goals of care. Active euthanasia is death of the patient caused by an action of the healthcare provider with the intent of ending the life of the patient (giving paralytics at time of withdraw of mechanical ventilation; high-dose potassium given to cause cardiac arrest). In several European countries, active euthanasia is legal.

DNR

"Do not resuscitate" is a common order in the hospital setting. DNR creates limitations to LST and is considered a form of withholding medical therapy. It is important to realize that code status really should exist in only two forms: full code and DNR. Unfortunately, we often create conflict in the ICU by asking patient to choose from a long list of therapies. Do you want chest compressions, cardioversion, vasopressors, intubation, noninvasive ventilation, etc.? This laundry list of medical interventions can be very difficult for the patients and the families; as a result, they seem to choose "do everything" rather than have to understand and make a decision on each option. Perhaps it is better if we as healthcare professionals think about CPR in another way: we code dead people, we treat alive people. Therefore, CPR is performed when a patient has no pulse; vasopressors and cardioversion are used on patients with a pulse. These options should not be presented to patients as treatment along a spectrum, but rather what to do once the heart has stopped.

A term that is perhaps a better option and clearer in terms of patients defining their wishes is "Allow Natural Death (AND). Patients seem to understand that term as "not being hooked to machines" and it can be used to define goals of care. AND seems to eliminate much of the confusion that

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can occur with the "limited resuscitation" menu of options. Most importantly, a DNR order does not mean "Do Not Treat." DNR means that we do not try to restart a heart that has stopped. We continue to treat the patient with appropriate medical therapies and discuss options regarding further treatments.

Futility

Futility is a term that all understand, but few can define, thus creating much of the conflict and ethical issues in the ICU. One definition of futility is treatments successful in less than 10 % of the patients. Futility has also been dismissed as a term, since many treatments are physiologically beneficial, even if those treatments do not change outcome or restore the patient to health. An example would be dialysis in the dying patient in the ICU; the patient will still die, but dialysis does what it is designed to do, which is clean toxins and fluid from the body.

Healthcare professionals often consider many medical treatments in the ICU as futile, which we tend to define as "inability to survive outside of the ICU." The new term to describe these patients is "the hospital-dependent patient." For some families, the fact their loved one is alive is sufficient. The traditional "quality of life" argument often does not work in discussion with many families. Discussions of goals of care and ability for their loved one to participate in activities that are important to them are often a more beneficial conversation and may help families define the limits of treatment in the ICU. Another term that may be more helpful than "futile" is "non-beneficial treatment." We need to help the patient and family define non-beneficial in terms of what the patient would consider beneficial related to the context of their lives; again, a goal of care discussion is indicated. Several critical care organizations have composed a consensus statement regarding futility in the ICU, and they recommend the term "potentially inappropriate" rather than "futile."

Most importantly, healthcare professionals are not obligated to provide nonmedically beneficial treatment regardless of patient and family demands. Examples of this would include CPR in a patient with uncontrolled bleeding and an inability to stop the bleeding, liver transplant in stage 4 cancer, and surgical feeding tubes in advanced dementia. The Choosing Wisely campaign by the ABIM Foundation is meant to offer guidelines in nonmedically beneficial tests and treatments (www.choosingwisely.org). Autonomy is a negative right, not a positive right. Patients have the right to refuse medical treatments, even if it would save their life. Patients do not have the right to demand non-beneficial treatments.

Advance Directives/POLST

In an ideal world, everyone would write down his or her wishes for treatment near the end of life. These wishes would be clear, concise, and leave no scenario undefined, making ethical dilemmas rare. Regrettably, few of us ever write down our desires, and even less likely do we ever discuss them with our families. The lack of planning for the end of our lives has created a huge burden on families, healthcare providers, and the healthcare system. Despite an increased effort to encourage people to fill out an advance directive (AD), few do so. (Do you have one?).

One problem with AD is they tend to be vague. "If terminal or permanent unconsciousness" is often the clinical scenario included. In the ICU, very few patients are declared "terminal" or "permanently unconscious." Families and healthcare providers are then tasked with trying to define what exactly the person wanted in this particular clinical situation. Including families in the discussion in the creation of the advance directive is critical to its implementation. Physicians tend to preferentially honor family requests over what is written on the patient's AD, therefore making it crucial for the family to be involved in the advance directive discussion. Several states are considering legislating advance directives over surrogate decision making, potentially resolving some of this conflict. However, given the generic nature of AD, discussion regarding treatment options with family is still necessary.

One potential solution to the AD is the use of physician orders for life-sustaining therapy (POLST, www.polst.org). POLST has been adopted by many states and has several variations on the name (MOLST, POST). The goal is the same: to define goals of care in patients with a terminal condition. POLST is generally on a bright pink card stock, designed to be immediately visible to EMS and healthcare providers. POLST defines treatment in terms of full treatment, limited treatment, or comfort care as the goal. POSLT also includes options for antibiotic use, DNR, artificial nutrition and hydration. These are actual healthcare provider orders that cross the spectrum of healthcare settings, preventing multiple DNR discussions as the patient is, for example, transferred to the hospital from the nursing home or from home to the hospital. If the patient signs POLST, it cannot be overruled or changed by the surrogate decision maker. The patient can change their mind and void the orders. If a member of the family signs the POLST form, the signer can change the orders. There are legal protections for healthcare providers for honoring a POLST. The major limitation of POLST is that the patient must be terminal (usually stage 4 cancer, advanced dementia, end-stage COPD, or CHF).

Artificial Nutrition and Hydration

Nutrition and early use of enteral feedings has made a huge difference in the outcomes of patients in the ICU. There are few ethical issues regarding the use of enteral feeds in the ICU. The controversy arises in the placement of surgical feeding tubes (PEG or gastrostomy tube) in select patient populations. As the population ages and dementia becomes more common, many of these patients come to the ICU for treatment of injuries from falls, sepsis, pneumonia, etc. Their swallowing difficulties become quickly apparent and often trigger a series of events resulting in a speech therapy evaluation which documents the dysphagia, then a consult for PEG tube placement. Often this medical pathway takes on a life of its own and occurs without a discussion of goals of care and whether artificial nutrition and hydration are beneficial in these patients in changing survival. Both the American Academy of Hospice and Palliative Medicine (AAHPM) and the American Geriatrics Society (AGS) have position statements on ANH in advanced dementia. Generally, the recommendation is not to offer feeding tubes to these patients. Since this pathway often begins in the ICU, we need to be aware of the need to start discussions early with the families.

Dialysis

Dialysis in the ICU can be lifesaving, especially in cases of drug overdose or rhabdomyolysis. Dialysis can be less helpful in cases of multisystem organ failure or the very elderly. As it is a technology that we have, we often have difficulty limiting offering it to patients. The nephrology literature has begun to recommend that nephrologists be involved with the goals of care discussions with patients and their families prior to initiating dialysis. The literature also makes specific recommendations for decision making and conflict resolution in cases of dialysis.

One strong recommendation from the ethics literature and palliative medicine literature is to consider time-limited trials. Although the best option may be not to initiate therapies that may not be beneficial and with the difficulty of stopping treatments, one consideration is to offer a time-limited trial. Offering a therapy to a patient for a limited period of time (usually 72 h) to see if improvement occurs is one way to help the patient and the family as they wrestle with options regarding care. Time-limited trails offer an opportunity to see if the treatment is beneficial without the commitment of indefinite continuation. When the trial is over and no improvement is seen, the treatment stops automatically. A time trial allows more time for ongoing discussions regarding goals of care and a plan for withdrawal of therapy that is often easier emotionally on the family and the healthcare team.

Organ Donation

The goal of organ transplantation to save lives is an admirable goal. The ICU is often involved in the care of potential organ donors. As the technology increases to preserve organ function until donation can occur, ethical issues seem to be increasing rather than decreasing. One ethical issue regarding organ donation is driver's license assent; checking the box "yes" (or in some states "no" is not an option, only "skip the question") is considered first person consent for organ donation and by federal law overrides the family wishes if they do not want to donate. The issue of "opt-out" vs. "opt-in" is currently being debated in the literature, but more and more states are going to an "opt-out" model, meaning the default is the patient is an organ donor unless explicitly written somewhere, usually in an AD.

Another ethical issue regarding organ donation is organ preservation protocols. Prior to the patient being considered for organ donation, or being declared dead by neurological criteria (brain death), a variety of procedures and treatments are given not for the benefit of the patient but for the preservation of the organs. These treatments can include resuscitative thoracotomies to restore circulation for organ retrieval in the trauma bay, hormonal therapy to preserve organ function, placement of lines, use of vasopressors, transfusions, and several others. In some hospitals, these protocols are the default for all patients who are potential organ donor candidates, potentially shifting the focus from caring for the patient to caring for his organs.

In order to increase the donor pool for solid organ transplantation, death by neurological criteria (brain death) is not the only option. Many hospitals are performing donation by circulatory death (DCD), where the withdrawal of LST occurs in the operating room and organ retrieval occurs once the patient progresses to cardiac standstill. DCD continues to be controversial in the ICU and the ethics literature.

Ethics Consultation, Palliative Medicine, and Conflict Resolution

Most hospitals have an ethics consultation service that often involves a single provider obtaining the necessary information and the ethical issue at hand and speaking to the family, healthcare team, and patient if possible. The ethical issues will then be presented to an ethics committee that tends to be

multidisciplinary (social worker, chaplain, physician, nurse, administration, and others). They will discuss the case, discuss the ethical principles involved, and often write a recommendation regarding what is ethically permissible in this particular case. Focusing on what is ethically permissible rather than providing a direct solution to the ethical issue can be frustrating for everyone involved hoping for an answer. Standards regarding ethic consultations have been developed, and it is recommended that the team leader have a master's degree in ethics.

Given the limitations of ethics consultation, many hospitals have asked the palliative medicine service to assist with these ethical issues. Many of the ethical dilemmas in the ICU arise from application of medical technologies that may not be beneficial for the patient. In a busy ICU, it can be very difficult to take the time necessary to explain all options to the family and to put these technologies into perspective regarding the patient's wishes. These discussions are often called "goals of care" discussions. A palliative care team consisting of a physician, nurse practitioner, social worker, chaplain, and potentially other members can often help the families walk through the process of this decision-making process. Some have suggested that including palliative medicine as part of the ICU multidisciplinary team may improve the outcomes and experiences for patients and the families, as well as avoiding much of the conflict that can occur in the ICU.

Since many hospitals and ICUs have not integrated palliative medicine into the ICU team, and we tend not to be proactive in preventing conflict, a conflict resolution team has been suggested as the next step for dealing with the unresolved conflict in the ICU. The primary goal of this mediation is to actually mediate the conflict; they do not have a vested interest in the outcome, just that an outcome suitable to all can be reached. There are two methods of conflict resolution: one in which the mediator reads the chart, talks to the healthcare providers, and gathers information before meeting with all parties involved. The second method involves the mediator coming to the table with the interested parties (usually family and the ICU team) and listens to the issues at the time. The mediator can then choose to interact with individuals or small groups of the people involved before helping all come to a consensus. This process tends to be very labor intensive and time consuming, not only for the mediator but also for the ICU team. Given the extensive time commitment required for conflict mediation to be successful, it is often not a technique that is utilized. However, it can be a great resource for the ICU team and families when an impasse in the ICU is reached.

Conclusion

In an ideal world, the patient will have an advance directive, POLST orders if appropriate, a family who is in complete agreement with the wishes of their loved one, and a clearly communicating and realistic ICU team regarding the benefits and limitations of the ICU. Communication can solve many of these ethical dilemmas, but we also have a responsibility to recognize that increasing use and development of technology creates new challenges and can sometimes solve existing ones. General recommendations for prevention of ethical dilemmas in the ICU, which usually are conflict with the family, are early, and frequent communication, a consistent message from the ICU team, goals of care discussions, integration of palliative medicine in the ICU, and conflict resolution/mediation as needed.

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Disaster Management and Preparedness

43

Susan Miller Briggs

Introduction

Mass casualty incidents (MCI) are events causing numbers of casualties large enough to disrupt the healthcare services of the affected region. This is in contrast to multiple casualty events in which medical resources are strained (prehospital and/or hospital resources) but not overwhelmed. Demand for resources always exceeds the supply of available resources in a mass casualty incident. Disaster surgical care is not the same as conventional surgical care. The objective of conventional surgical care is the "greatest good for the individual patient." The objective of disaster surgical care is the "greatest good for the greatest number of victims" [1–5].

Epidemiology of Disasters

Disasters may be natural or man-made or a combination of the two. Natural disasters may be classified as sudden-impact (acute) disasters or chronic-onset (slow) disasters [6]. Sudden-impact disasters include:

- Earthquakes
- Tsunamis
- Tornados
- Floods
- Tropical cyclones, hurricanes, and typhoons
- Volcanic eruptions

Chronic-onset disasters include:

- Famine
- Drought

Sudden-impact natural disasters generally cause significant morbidity and mortality immediately as a direct result of the primary event (e.g., traumatic injuries, crush injuries, or drowning) [7], whereas chronic-onset disasters cause mortality and morbidity through prolonged secondary effects (e.g., infectious disease outbreaks, dehydration, or malnutrition).

Man-made disasters may be unintentional or intentional (terrorism) [1, 8–10]. The spectrum of agents used by terrorists is limitless and includes conventional weapons, explosives, and biological, chemical, and radioactive agents (Fig. 43.1). In addition to the possibility of a large number of victims, responders must be aware of the potential for secondary strikes directed at harming emergency personnel. More than 70 % of terrorist attacks involve the use of explosive weapons and are a significant challenge for surgeons due to the complexity of injuries (primary, secondary, tertiary, and quaternary blast injuries) [1, 7–11]. Terrorists do not have to kill people to achieve their goals. They just have to create a climate of fear and panic to overwhelm the healthcare system (e.g., sarin/anthrax attacks).

Disasters involving weapons of mass destruction (biological, chemical, or radioactive agents), whether accidental or man-made, are a significant challenge for critical care providers for three reasons:

1. Weapons of mass destruction have the greatest potential to produce numbers of casualties large enough to overwhelm the medical infrastructures. Such agents will also produce a category of victims known as "expectant" victims, a particular challenge for critical care providers. This denotes a category of victims not expected to survive due to the severity of injuries or underlying diseases and/or limited resources. This term was first used in conjunction with chemical warfare. Appropriate triage of "expectant" victims is a particular challenge for critical care providers given limited ICU capacities in most mass casualty incidents. Weapons of mass

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Fig. 43.1 World Trade Center bombing (2001)

destruction produce significant numbers of "psychogenic" casualties, greatly complicating medical providers' rescue efforts. During the sarin attack in Tokyo (1995), 5,000 casualties were referred to local hospitals. Fewer than 1,000 individuals were actually suffering from the effects of the gas.

2. Weapons of mass destruction will produce "contaminated" environments. Surgeons must be able to perform triage and initial stabilization, operative care, and critical care outside traditional hospital facilities. The necessity for decontamination prior to surgical care interventions further complicates resuscitative efforts.

Biological Agents

Biological terrorism is the intentional use of microorganisms or toxins to kill or injure humans. Exposure to biological agents may be accidental or intentional (terrorism) [1, 10].

Routes of Exposure

The route of exposure of most concern with biological agents is inhalation of the agent. Oral exposure to biological agents may occur directly or secondarily after an aerosol attack. Agents with the highest potential for person-to-person transmission (pneumonic plague, smallpox, and viral hemorrhagic fevers) constitute the greatest hazards. The most effective and important protection against biological agents is physical protection. Removal of clothing will eliminate greater than 85 % of the agents. Any dermal exposure should be treated immediately by gross decontamination with soap and water.

Prophylaxis and Therapy

Medical defenses against some biological agents are limited. Vaccines are available to protect against some biological agents (anthrax, smallpox), and antibiotics may be effective against bacterial agents such as anthrax, plague, and tularemia if given early enough. Disasters involving biological agents have a significant impact on the healthcare system for the following reasons:

- Terror in affected populations and medical care systems
- Overwhelming casualties and significant ICU/special medication needs
- Problems with handling dead victims

Chemical Agents

Chemical agent release may be unintentional (industrial accidents) or intentional (terrorism) [1, 10, 12]. Many chemical agents, especially warfare agents, are liquids and must

be dispersed to be maximally effective. There are three general methods of dispersion:

- Aerosolizing with an aerial sprayer
- Aerosolizing the liquid with an explosion (improvised explosive device (IED) + chlorine tanker)
- Allowing the liquid to evaporate (Tokyo sarin attacks)

Time is of the essence in the decontamination and treatment of chemical agent casualties. Treatment areas should be upwind and uphill from the contamination site. It is important that decontamination facilities be SEPARATE from the emergency department.

Specific Chemical Agents

Nerve Agents

Nerve agents are toxic relatives of organophosphate insecticides. They cause effects by disrupting the normal mechanism by which nerves communicate with muscles, glands, and other nerves. Nerve agents enter the body either percutaneously (through the skin) or by inhalation (through the lungs). The most important nerve agents are GA (tabun), GB (sarin), GD (soman), GF, and VX.

Treatment of nerve agents: [1, 10, 12].

- Atropine – Antidote for smooth muscles and exocrine glands.
- Pralidoxime (2-PAM) – Antidote for skeletal muscle sites.
  - Atropine-sparing effect.
  - Timing of 2-PAM administration is critical. Binding of nerve agents to cholinesterase can become irreversible with time.

Valium (diazepam) is used as an anticonvulsant as needed. The traditional Mark 1 Kit contains two spring-loaded injectors of atropine and 2-PAM. A new product, DuoDote, contains atropine + 2-PAM in a single auto-injector. Antidotes may be given by medical personnel in appropriate protective gear prior to decontamination.

Vesicants

Vesicants are agents that cause erythema and vesicles on the skin as well as injury to the eyes, airways, and other organs. Key to treatment of these agents is thorough decontamination as soon as possible. Sulfur mustard has no specific antidote. BAL is the specific antidote for Lewisite [1, 10, 12].

Hydrogen Cyanide

Hydrogen cyanide has a long history as a deadly poison as it causes death within minutes of exposure. The antidote is hydroxocobalamin 5GM IV (preferred) or cyanide antidote kit.

Pulmonary Agents

Pulmonary agents cause pulmonary edema which can be exacerbated by exertion. Phosgene and chlorine are the most common agents. The pulmonary edema caused by phosgene and chlorine causes dryland drowning to the point that the casualty can become hypoxic and apneic.

Riot Control Agents (Tear Gases or Lacrimators)

Treatment is symptomatic with copious irrigation of eyes and skin with water or normal saline.

Radioactive Agents

Release of radioactive material would most likely involve the following scenarios: [1]

- Detonation of a nuclear device
- Meltdown of a nuclear reactor – melting of the nuclear fuel within a reactor with release of radioactive materials into the environment (Fukushima nuclear accident)
- Dispersal of material through the use of a conventional explosive (radiological dispersal device (RDD) or "dirty bomb")
- Nonexplosive dispersal of radioactive material

Radiation types include nonionizing radiation (no tissue damage) and ionizing radiation (tissue damage). Electromagnetic radiation and particle radiation ("radiation dust") are the two types of ionizing radiation seen in disasters. Radiation exposure may be external irradiation (whole body or localized) and/or contamination (radiation debris) – internal and external contamination. Responders must assume *both external and internal contamination* when responding to disasters involving radiation agents.

Medical Effects of Ionizing Radiation

- Focal tissue damage and necrosis
- Acute radiation syndrome (result of whole body exposure)
- Long-term effects (thyroid cancer, leukemia, etc.)

Treatment of Radiation Casualties

- Removal of clothing in victims with external contamination eliminates more than 90 % of the contamination.
- Radiation effects are delayed – trauma triage is done according to conventional trauma protocols.
- Decontamination: Before, during, or after initial stabilization, depending on severity of injury.

- Emergency surgery, as well as closure of surgical wounds, should be performed early.
- Know the limitations of your radiation detection devices. Protect yourself until victim is free of all radiation contamination.

Decontamination

The basic principles in response to any hazardous-material incident are the same regardless of agents involved. Removal of clothing and jewelry may reduce contamination by up to 85 %. It is important for medical providers to protect themselves during decontamination with the appropriate level of personal protective equipment (PPE).

Principles of Disaster Response

Principle #1

Medical providers cannot utilize traditional command and control structures when participating in disaster response. The Incident Command System (ICS) is a modular/adaptable system for all incidents and facilities and is the accepted standard for all disaster response. The Hospital Incident Command System (HICS) is an adaptation of the ICS for hospital use, allowing effective coordination in disaster preparedness and response activities with prehospital, public safety, and other response organizations. The trauma system is an important component of the ICS.

Functional requirements, not titles, determine the ICS hierarchy. The organizational structure of the ICS is built around five major management activities (Incident Command, Operations, Planning, Logistics, and Finance/Administration) [1, 10, 11]. The structure of the ICS is the same regardless of the nature of the disaster [1, 10, 11]. The difference is in the particular expertise of key personnel.

An important part of disaster planning is the identification of the Incident Commander and other key positions *before* a disaster occurs (24 h/day–7 days/week). Each person within the command structure should supervise only three to seven persons. This is quite different from conventional hospital command structures. All medical providers must adhere to the structure of the ICS in order to integrate successfully into the disaster response team and avoid many negative consequences including:

- Death of medical personnel due to lack of safety and training
- Lack of adequate medical supplies to provide care
- Staff working beyond their training or certification
- Lack of coordination

Principle #2

A single emergency operations plan for many different situations is more effective than multiple separate disaster plans (*ALL HAZARDS APPROACH*) [1–4, 11]. The difference in disasters is the degree of disruption of the medical and public health infrastructures and the amount of outside assistance (regional, national, international) that is needed to meet the needs of disaster victims.

Principle #3

Effective "surge capacity" is not based on well-intentioned and readily available volunteers. Disaster responders must understand the basic principles of disaster response (ICS, disaster triage, gross decontamination) to be effective members of the disaster teams.

Disaster Medical Response

Disaster response includes basic medical concerns that are the same in all disasters. The difference in disasters is the degree of disruption of medical capacity and the amount of outside assistance needed to meet disaster needs. Rapid assessment by experienced disaster responders will determine which *functional capacities*, *including critical care capacity*, are needed to meet the demands of the *acute* phase of the disaster.

Search and Rescue

Many disasters, both natural and man-made, involve large numbers of victims trapped in collapsed structures. Many countries, including the United States, have developed specialized search-and-rescue teams as an integral part of their national disaster plans [1, 13, 14]. Members of these teams, which receive specialized training in confined space environments, generally include the following:

- A cadre of acute care specialists, including surgeons
- Technical specialists knowledgeable in hazardous materials, structural engineering, heavy equipment operation, and technical search-and-rescue methodology
- Trained canines and their handlers

Disaster Triage

Triage is a dynamic decision-making process of matching patients' needs with available resources. Triage is the most important and psychologically challenging aspect of disaster

medical response, both in the prehospital and hospital phases of disaster response. This is especially true in disasters occurring in austere environments where resources, especially critical care capacity and evacuation assets, are limited.

Surgical disaster triage is significantly different from conventional triage. The objective of conventional surgical triage is to do the "greatest good for the individual patient." Severity of injury or disease is the major determinant of triage priority as adequate resources are available for the care of the patient. The objective of disaster triage is to do the "greatest good for the greatest number of victims." The major objective and challenge of surgical triage is to identify the small minority of critically injured patients who require urgent life-saving treatments, including damage control surgery, from the larger majority of noncritical casualties. Review of the literature from major disasters estimates that 15–25 % of victims are critically injured. The remainder of victims are noncritical casualties [1, 4, 7, 11]. In a mass casualty event, the critical patients having the greatest chance of survival with the least expenditure of time and resources (equipment, supplies, personnel) are prioritized to be treated first.

Levels of Triage

Three levels of disaster medical triage have been defined. The level of disaster triage utilized at any phase of the disaster will depend on the ratio of casualties to capabilities. Many mass casualty incidents will have multiple levels of triage as surgical patients move from the disaster scene to definitive medical care [1–4, 12, 15, 16].

Level 1: Field Triage

Field triage is the rapid categorization of victims who potentially need immediate medical care "where they are lying" or at a casualty collection center. Victims are designated as *acute* or *nonacute*. Color-coding may be used. One effective way to begin Level 1 triage on a large number of victims is to instruct people to get up and move to a designated location. This will separate ambulatory (noncritical) individuals from nonambulatory (critical) victims.

Level 2: Medical Triage

Medical triage is the rapid categorization of victims by experienced medical providers at a casualty collection site or fixed or mobile medical facility, including deployable field hospitals [15, 17]. Medical personnel performing triage must have knowledge of various disaster injuries and illnesses. Victims are classified into the following categories:

- *Red (urgent)*: Lifesaving interventions (airway, breathing, circulation) are required.
- *Yellow (delayed)*: Immediate lifesaving interventions are not required.
- *Green (minor)*: Minimal or no medical care is needed or psychogenic casualties.
- *Black*: Deceased victims.
- *Expectant category*: Victims not expected to survive.

The "expectant" category of victims is unique to mass casualty incidents. Victims are classified as "expectant" if they are not expected to survive due to the severity of injuries (blast injuries, massive crush injuries or burns or exposure to large quantities of chemical, biological, or radioactive agents) or underlying diseases and/or limited resources. The "expectant" category of triage was first developed during military conflicts given the threat of weapons of mass destruction (biological, chemical, radioactive) but is now utilized in all disasters. Traditionally, this category of disaster casualties has been classified as "yellow or delayed" category. Currently, most triage systems classify "expectant" victims as a separate category with a different color designation.

Classification of the expectant category of disaster victims is challenging and controversial, especially for critical care surgeons. The challenge for critical care providers is to delineate red category victims who are expected to live with the resources available versus expectant victims. Many models have been proposed based on severity of injury, age, underlying diseases, and hemodynamic stability of victims at time of rescue [1, 2, 5, 7]. Criteria that are currently utilized as guidelines for the "expectant" category are:

- Cardiac arrest on scene
- Severity of comorbid diseases
- Requirement for intubation and ventilation on scene
- Head injuries
- Age
- Massive burns (greater than 80 % total body surface area)

Level 3: Evacuation Triage

Evacuation triage is often a neglected area of disaster preparedness. Priorities for transfer to medical facilities are assigned to disaster victims using the same color classification as medical triage. Victims are matched to available receiving facilities. Critical care facilities are usually overwhelmed with surviving casualties in a MCI (Fig. 43.2). Often victims with minor injuries can be sent to more distant facilities, keeping closer facilities available for higher-priority victims. Rapid evacuation of critical casualties expected to survive allows more time and resources for caring for the larger majority of noncritical victims.

Triage Errors

Triage errors, in the form of *under-triage* and *over-triage*, are always present in the chaos of mass casualty events. Under-triage is the assignment of critically injured casualties requiring immediate care to a "delayed" category. Under-triage leads to treatment delays with increased mortality and morbidity. Over-triage is the assignment of noncritical survivors with no life-threatening injuries to immediate urgent care. The higher the incidence of over-triage, the more the medical system is overwhelmed. In mass casualty incidents, especially explosions, triage errors more commonly involve over-triage than under-triage. Children are often over-triaged due to the emotional impact of injured children on medical responders. The level of acceptable over-/under-triage in a mass casualty incident and the best method for evaluation of triage effectiveness in mass casualty incidents is still controversial. Various triage systems exist, and, unfortunately, there is no universally accepted triage system for mass casualty incidents.

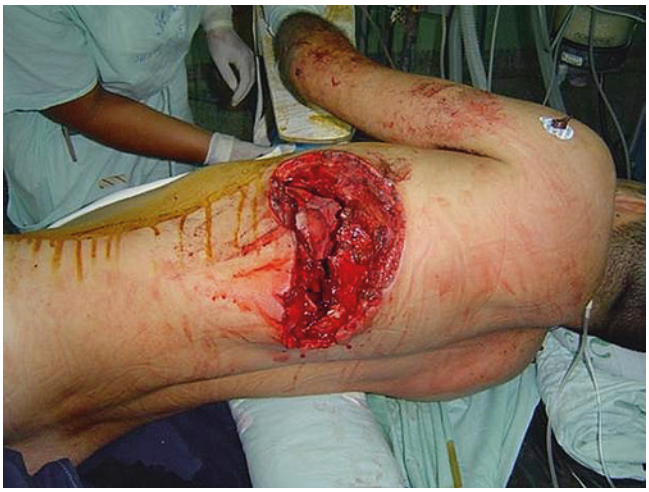

Fig. 43.2 Crush injury to chest

Definitive Medical Care

Definitive medical care refers to care that will improve, rather than simply stabilize, a casualty's condition. Maximally acceptable care for all surgical patients is not possible in the early stages of the disaster given the large number of victims in a mass casualty incident. In the initial stage of the disaster, minimally acceptable surgical care (crisis management care or altered standards of care) to provide lifesaving interventions is necessary to provide the "greatest good for the greatest number of victims" [1, 14–16].

Damage control surgery is an important component of crisis management care. In many disasters, local hospitals are destroyed, transportation to medical facilities may not be immediately feasible, or the environment may be contaminated. Mobile surgical facilities with the capacity for operative interventions and critical care can provide a graded, flexible response to the need for surgical care in mass casualty incidents (Fig. 43.3).

Damage control surgery limits trauma interventions to control of hemorrhage and contamination. Damage control surgery was initially developed for abdominal trauma with uncontrolled hemorrhage but has expanded to all other trauma specialties in disasters [18–20]. Spinal and regional anesthesias, as well as intravenous sedation and intraosseous infusions, are important adjuvants to surgical care in disasters.

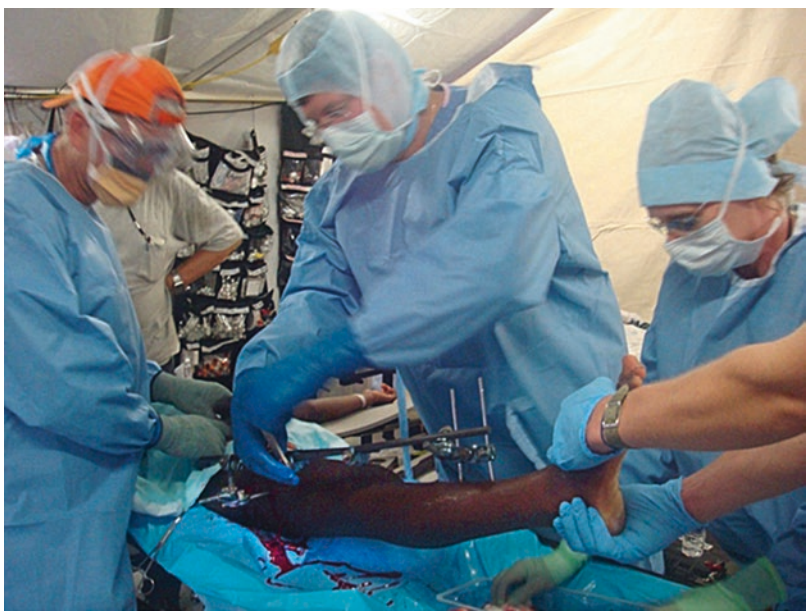

Fig. 43.3 Damage control surgery (Haiti earthquake 2010)

Evacuation

Evacuation may be useful in a disaster to decompress the disaster area and provide specialized surgical care for specific casualties, such as those with major burns and crush injuries. Surgeons with expertise in critical care are increasingly valuable evacuation resources in disasters. In most disasters, the large number of victims needing evacuation, especially in austere environments, will mandate the use of unconventional medical transport aircraft. Special considerations during evacuation include [1]:

- A decrease in cabin pressure occurs as altitude increases. Trapped gas in any body cavity can cause serious complications as it expands on ascent. Special attention must be paid to trapped gas within the thorax, cranium, eye, and the gut in the presence of an ileus. Patient care appliances, such as endotracheal tube cuffs, are also susceptible.
- The partial pressure of oxygen in the ambient air decreases with increasing altitude. Monitoring with pulse oximetry is important.
- Takeoffs and landings present unique challenges, especially with head injury patients.
- Young children, burn patients, and postsurgical casualties are particularly susceptible to temperature changes during evacuation.

Disaster Management Teams

Clinical competencies, not titles, determine the roles of medical providers in disaster response. Disaster management teams are designed and trained to provide specific "functional" areas of disaster care such critical care, pediatrics, obstetrics, and acute and trauma surgery, especially when the casualty load is unknown. The complexity of today's disasters demands civilian and military partnerships as key to effective disaster response. Critical care teams must be equipped to take care of both pediatric and adult patients in a mass casualty incident.

Disaster Drills

Disaster preparedness must include practical drills to ascertain the true magnitude of system problems, not just tabletop exercises. Mass-casualty drills must include three phases: preparation phase, exercise management phase, and patient treatment phase. The preparation phase must include clear definition of functional areas of responsibility that can be evaluated objectively, not subjectively, during the disaster drill. The exercise management phase includes objective evaluation of all key functional roles in the ICS. The patient treatment phase includes objective evaluation of well-defined functional capacities such as triage, operative interventions, critical care, and evacuation [1, 11, 21].

Summary

The mass casualty incident response is a consistent approach to disasters based on an understanding of the common features and the response expertise they require in all phases of the disaster response. The goal of disaster medical response is to reduce the critical mortality associated with a disaster. Critical mortality rate is defined as the percentage of critically injured survivors who subsequently die [1, 8]. Numerous factors influence the critical mortality rate, including:

- Triage accuracy, particularly the incidence of over-triage of victims
- Rapid movement of patients to definitive care
- Implementation of damage control procedures
- Critical care interventions
- Coordinated regional preparedness and response

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Postoperative Complications Following Surgery Abroad

44

Nicole Lucas and William A. Walters

Introduction

Caring for another surgeon's complication can be a common, albeit unpleasant, part of any surgical practice in a tertiary care facility. It comes with the territory and can define key differences between academic and community practice. Typically, the patient was cared for in a modern hospital, by a surgeon that was appropriately trained, equipped with modern and sterile equipment, and assisted by competent nursing professionals. In essence, the presenting complication could just as easily have developed in any hospital, and the care plan is understandable and predictable.

As societies broaden their reach, and an individual patient is able to avail themselves of unprecedented opportunities for global travel, the issue of surgical complications takes on a different light. With increasing frequency, patients are presenting to tertiary care medical centers with previously undiagnosed or untreated postoperative complications after either elective surgical care abroad or emergency surgery in an austere environment following a natural or man-made disaster. In either case, the surgeon is left with little written accounting of the surgical procedure, postoperative course, or rehabilitation. Furthermore, the patient's condition may be directly related to the geographic location of the first hospital or the process of travel itself.

Elective Surgery Abroad

Elective surgery abroad, often referred to as "medical tourism," represents a recent development in healthcare economics, involving purposeful travel of patients to a nation other than their own for the expressed purpose of receiving care that is either unavailable, prohibitively expensive, or illegal in their own country. According to Patients Beyond Borders, a consumer medical tourism resource, around 11 million patients go abroad for medical treatment every year. Although these numbers vary, the organization believes the market size is an estimated US $38.5–55.0 billion, with the average patient spending $3500–5000 per visit [1]. Reviewing 2008 data, the cost of individual procedures has been an estimated 20–80 % lower in less developed countries compared to a private hospital in the United States [2, 3]. Furthermore, the medical tourism market is only expected to grow, as healthcare shortages and costs to patients increase in western countries, and surgical technology costs decrease to an affordable level in less developed countries. Although millions of Americans are now newly enrolled into health insurance under the Affordable Care Act, an estimated 71 % of the new insurance arises through Medicaid [4]. And, with 55 % of American doctors already refusing new Medicaid patients, according to a 2014 Merritt Hawkins study by Miller and colleagues [5], the American public is still not immune to the pressures of healthcare austerity.

An Unregulated Industry

Marketing of surgical services overseas is regulated at the host nation level, where legal restrictions regarding medical practice and quality of care may differ greatly from the patient's expectations. While no registry or formal means of tracking patients has been established, published studies show a significant percentage of these patients seek bariatric, dental, and cosmetic surgery due to cost savings. Many also have a specific predilection toward transplant surgery, driven by the availability of donor organs. Because quality of care varies greatly by institution, it is difficult to make meaningful generalizations about risks outside the United States [6]. Information asymmetries are particularly pronounced by a lack of comparative quality and safety data, reduced knowledge of infection rates for overseas institutions, and insufficient reporting of adverse events [7]. The World Health Organization issued a

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2014 report on antimicrobial resistance, noting that very high rates of resistance for common bacteria have been recorded in all regions. Overall, surveillance of resistance is neither coordinated nor harmonized [8], but must be considered carefully by the surgeon managing an imported surgical catastrophe.

Just as there is no registry of patients that seek medical care abroad, there are no international standards that tie to outcome measures for hospitals catering to the medical tourism market. Several international organizations are available to accredit hospitals in foreign countries, each with their own methods and standards, but given the migratory nature of the medical tourist, this specific patient population is almost universally lost to follow-up. Overall, little is known about the relative clinical outcomes for particular treatments, institutions, clinicians, and localities associated with medical tourism, partly because follow-up is rare once patients return to their home countries after a procedure [7]. Overall, this lack of information obstructs a patient's ability to make informed, evidence-based judgments about the quality of care and safety in medical travel [8].

Nosocomial and Travel-Related Postoperative Infection

Postoperative infection is an ever-present risk that, in the United States and other highly developed healthcare systems, involves significant investment in broad reaching systems within each hospital. From dedicated personnel for surveillance, materials and supplies at each bedside to reduce transmission, and rigid inspection criteria tied to third-party reimbursements, great effort is paid to reducing the financial burden of postoperative care. Lacking the same focus and resources, the prevalence of healthcare-associated infections in developing countries is substantially higher than in Europe and the United States. Many countries with robust medical tourism programs have high background rates of tuberculosis, antibiotic resistance, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) [9].A recent meta-analysis showed that intensive care units in developing nations had infection rates at least three times higher than those reported in the United States. Surgical site infection rates were also comparatively increased (5.6 vs. 1.6–2.9 per 100 surgical procedures) [10]. Many countries with robust medical tourism programs lie in tropical and subtropical regions where malaria, dengue fever, enteric fever, and other endemic infections exist [9]. And, although blood and blood products used in hospitals certified by International Joint Commission (IJC) require screening for common blood-borne pathogens, they do not necessarily require screening for these region-specific agents. As a result, dengue and West Nile viruses, for example, which cause rare infections after transfusion, are not a part of routine screening in most countries and have a higher chance at being transmitted [11].

Postoperative infections are not limited to hospital-acquired pathogens. The transit involved with medical tourism may also put patients at a greater risk of infection because passengers are typically confined to close quarters for many hours when using commercial aircrafts [12]. In an interesting surveillance study from 2010, the extended-spectrum beta-lactamase colonization rate in traveling Australians increased from 7.8 % pretravel to 49 % posttravel, with resistant *E. coli* isolated from 50 to 79 % of travelers to Asia (excluding Japan), South America, the Middle East, and Africa. At 6 months posttravel, 18–24 % remained colonized [13]. This demonstrates that at any point in the circular migration of patients traveling for medical care, microbes may also travel from one location where they constitute a harmless bacteria, or at least a known and treatable infection, to another where they are unknown, making diagnosis and treatment much more problematic [12]. Therefore, surgeons treating an imported postoperative infection do well to discuss the case early with infectious disease and pathology colleagues to provide sufficiently broad consideration during the laboratory workup.

Transplant Tourism

Perhaps the most popular and most risky procedures sought by consumers in medical tourism involve solid organ transplants. In 2007, the World Health Organization estimated that 10 % of organ transplants worldwide are the result of transplant tourism [14], due in part to the practice of solid organ sales and the relative affordability of the surgery itself. In one study in the Philippines, upward of 3 % of the population in a single community had sold a kidney for transplant [15]. However, evidence again suggests increased complication rates. In a 2009 meta-analysis, patients that travel internationally in order to receive their transplant had a lower 1-year graft and patient survival rate compared to those domestic kidney transplant recipients described by United Network for Organ Sharing (UNOS) [16]. In addition, transplant tourists had an increased requirement for postoperative surgical intervention and were more likely than domestic kidney transplant recipients to develop cytomegalovirus (12 %), hepatitis B virus (7.1 %), HIV (4.1 %), and wound infections (8.6 %) [17]. A 2006 study of patients evaluated at University of Minnesota Medical Center or Hennepin County Medical Center after undergoing kidney transplantation overseas concluded that there was inadequate communication of information concerning immunosuppressive regimens and preoperative information. In the majority of cases, vital information on induction therapy, immunosuppression, and posttransplant course were missing. In three cases within the study period for this single center, postoperative patients were sent back to the United States in the midst of a crisis (active severe wound infection, seizure, and acute rejection),

and in all of these situations, documentation of the posttransplant course was lacking [18].

Cosmetic Surgery

Based on available data and marketing efforts by international medical tourism "hubs," elective cosmetic and aesthetic surgery represents the majority of the medical tourist surgical caseload. A 2007 national study conducted by the Australian Society of Plastic Surgeons evaluated female patients returning from Asia after surgery, a majority of which underwent breast enlargements, breast reductions, or facelifts. Of the 68 surgeons surveyed, 40 (59%) reported seeing patients with complications or poor results, and 15 (22%) reported treating more than one patient that had traveled abroad for their cosmetic procedure. The majority of procedures were reportedly performed in Thailand, followed by Malaysia [19, 20]. In an audit of the pan-Thames region of the UK, 60% of National Health Services (NHS) consultants in plastic surgery units had seen complications of returning patients after completed procedures abroad, including abdominoplasty, breast augmentation, and breast reduction. The majority of these cases (66%) were emergencies that required inpatient admission [21]. In a survey of the British Association of Plastic, Reconstructive and Aesthetic Surgeons members, 37% of consultants report having seen patients in the National Health System with complications arising from overseas cosmetic surgery. The most popular procedures included breast augmentation, abdominoplasty, breast reduction, and face/neck lift. The majority (88%) were referred to these plastic surgeons by primary care and emergency department colleagues and required treatment in an outpatient setting (i.e., wound management) or elective surgical revision for cosmetic reasons. Twenty-five percent of patients required emergency surgery [22]. Finally, in a 2011 survey of the American Society of Plastic Surgeons (ASPS), 83.9% of surgeons reported treating patients with complications who had undergone cosmetic procedures abroad by noncore practitioners. A majority of the noncore providers performing procedures abroad were otolaryngologists, but also included general surgeons, oral surgeons, OB-GYNs, and ophthalmologists. The largest percentage of reported complications (31%) in this study were postoperative infections, followed by dehiscence, contour abnormality, and hematoma [23].

Surgical Complications in the Context of Disaster Medicine

In contrast to medical tourism, where procedures are planned and researched by patients in advance, surgical resuscitation following critical injury abroad occurs in the most remote locations, where the untouched beauty of nature is usually accompanied by an undeveloped or completely absent medical infrastructure. In a retrospective database review of American citizen deaths worldwide from October 2002 through June 2012, authors found the total number of Americans traveling abroad annually was approximately 58.7 million, with the majority traveling to Mexico, Canada, the United Kingdom, France, and Italy. Only one accidental death of an American occurred during the 10-year study period in those highly traveled areas. In travelers visiting less common destinations, however, the story is quite different. There were 7,963 American citizen nonnatural deaths abroad during this study period, and of these 163 (2%) were due to disaster-related deaths. These deaths occurred as a result of 19 disasters in 15 countries, with the only disasters causing greater than 2 deaths being the 2010 earthquake in Haiti (resulting in 121 deaths) and the 2004 tsunami in Thailand (causing 22 fatalities) [24].

In a 2013 meta-analysis focusing on acute traumatic injuries requiring surgical intervention following earthquakes abroad, Missair and coworkers found that major earthquakes result in the highest casualty rates, between 1 and 8% of the at-risk population [25]. Though many injuries are fatal, 69% of earthquake-related injuries requiring urgent surgical intervention involved survivors with limb trauma and survivable traumatic injuries including bone fractures, soft tissue lacerations, and crush injuries to various parts of the body. In humanitarian disaster and conflict, amputation is often hastily performed as a way of removing significant amounts of damaged tissue and saving a life, without consideration for more conservative techniques. This strategy requires multiple surgical revisions and results in complicated postoperative management and prolonged rehabilitation periods for patients.

The Haitian earthquake of 2010 provides a good example of surgical management following a large-scale disaster that destroys what little medical infrastructure may exist. Many patients received amputations as a primary intervention for complex severe wounds and fractures which could potentially have been salvaged. Amputations as secondary treatment for infected wounds and compartment syndromes were also reported in high numbers even though this is not the standard of care. Significant volumes of guillotine amputations were performed as a "lifesaving intervention" or when technical expertise was limited, subsequently requiring revision at higher levels. These patients' rehabilitation potential was negatively affected by poor surgical indication, timing, and technique [26]. In the end, Haiti's earthquake left approximately 1,500 amputation survivors relying on a healthcare system whose baseline, pre-earthquake surgical, anesthesia, rehabilitation, and prosthetic services were already severely limited [27]. Many survivors were evacuated to the United States on humanitarian grounds for continued treatment.

Surgical Infections in Disaster Response

Emergency surgery following a natural or large-scale man-made disaster safely assumes that the deliberate care and processes associated with modern surgical technique break down, if only for the sake of expediency in saving the greatest number of lives. Given unhygienic conditions, gross wound contamination, and delayed presentation of patients following a building collapse, catastrophic bombing, or flood, it is no surprise that surgical infections are common causes for operation in low- and middle-income countries, particularly during a crisis. Infections, in general, require greater than expected surgical resources given the frequent need for serial operations, especially in these areas with limited resources. Because survival and quality of life after severe surgical infection depends on prompt resuscitation, antibiotics, and operative intervention, a large proportion of individuals with surgical infections may be left with disability or not survive. Subsequently, the surgical disease burden, condition for condition, is significantly greater in poorer countries than the rest of the world, and early efforts to evacuate patients to western medical facilities should be expected in an effort to spread the load across a wider and better prepared healthcare base.

In a review of procedures performed in operating rooms managed by Medecins Sans Frontieres/Doctors Without Borders–Operations Centre Brussels from July 2008 through June 2014, investigators found that operations for skin and soft tissue infections were the most common surgical infection (64 %), followed by intra-abdominal (26 %), orthopedic (6 %), and tropical infections (3 %). Return trips to the operating room for serial washouts, debridement, and "second looks" were more common after procedures for orthopedic (38 %) and skin and soft tissue infections (33 %) than for intra-abdominal infections. In reviewing resource utilization patterns, it is clear that the pattern of operations for infections is related to nature of the crisis. Resources necessary for the treatment of skin and soft tissue infections (e.g., dressing supplies) are disproportionately higher during natural disasters, while resources necessary for intra-abdominal infections (e.g., closed suction drains, temporary abdominal closure systems) are needed more during hospital support missions. Lastly, resources necessary for the management of orthopedic infections (e.g., surgical sepsis care, ultrasound-guided drainage procedures) are critical during support to areas of armed conflict [28, 29].

Strategies in Patient Management

Assumptions remain the greatest barrier to management of a patient treated abroad that presents with a postoperative complication. When treating patients in one's own city or country, it is said that "when you hear hoof beats, think horses." But, the astute clinician treating an imported postoperative complication must first ask to which ground he has placed his ear before defining the probability of horses versus zebras.

The investigation starts with a carefully obtained history, developing a comprehensive picture of the patient's preoperative state of health. Then consider the location and setting of the surgical procedure. Early consultation with infectious disease colleagues with specific knowledge of tropical disease is essential, and frank collaboration with laboratory medicine colleagues will yield early benefits in identifying unusual pathogens. Early imaging is critical in identifying deep tissue abscesses and retained instruments or materials as the source of postoperative infection. For the critically ill patient that is unable to provide a detailed history, evaluation of the location and type of surgical wound is critical and must be compared to both modern surgical approaches and outdated approaches that may still be in use in less developed countries.

Perioperative management of the critically ill medical tourist may require a more protracted period of empirical therapy, allowing for offsite testing of samples for unusual or exotic pathogens. Early consideration must be given to fungemia, parasitemia, and viral etiologies that are typically prevented in western surgical practice. Finally, it is important to account for the psychological impact of a debilitating or disfiguring postoperative complication, ranging from regret in having accepted the risk of an elective procedure abroad to frank post-traumatic stress disorder related to the disastrous etiology for their original injury.

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Post-intensive Care Syndrome (PICS)

45

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Introduction

More than five million patients are admitted to intensive care units (ICUs) in the United States annually, and almost 90 % are surviving to discharge [1, 2]. The long-term consequences of critical illness are growing in importance and gaining more attention as demand for critical care grows and the short-term mortality after critical illness decreases. The number of survivors living with chronic critical illness has increased, and, unable to care for themselves, these patients are often discharged to long-term care facilities. Between 2001 and 2012, the percentage of ICU survivors discharged to these facilities rose from 15 to 25 % [3–6].

Both physical and psychiatric sequelae of critical illness can persist for years after discharge (see Table 45.1) [2]. Up to 85–95 % of ICU survivors struggle with persistent weakness, 50–70 % have difficulties completing activities of daily living, 30–80 % have cognitive impairment, and more than 50 % manifest various forms of psychiatric morbidity [2]. The presence of impairment in survivors' mental health, cognitive function, or physical function has been termed post-intensive care syndrome (PICS) (see Fig. 45.1) [3]. Psychiatric morbidity affects not only the surviving patient but their caregivers as well. This phenomenon has been termed post-intensive care syndrome-family (PICS-F) (see Fig. 45.1) [3, 7]. The impairments of PICS and PICS-F lead to an inability for survivors and family members to return to the workforce and increased healthcare utilization [2, 8].

It is becoming clear that discharge from the ICU no longer represents the end of critical illness. The ongoing physical, cognitive, and psychiatric suffering of survivors and the psychiatric suffering of their caregivers can last for years [2, 9]. The number of studies on this topic has greatly increased between 2010 and 2015 compared with the 5 years prior [10]. Familiarity with the physical, cognitive, and psychiatric challenges (see Table 45.1) faced by patients and families not only during but after their ICU stay and the interventions that can mitigate the sequelae of critical illness will help clinicians better serve their patients and their patients' families.

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Physical Impairment

A 2005 review of over 7,000 ICU survivors found that most survivors experienced a significant reduction in quality of life (QOL) in the months following ICU discharge, including impairment in role functioning due to physical problems [11]. Post-ICU long-term physical impairment is therefore an increasing public health concern and encompasses general physical dysfunction, pulmonary dysfunction, and neuromuscular dysfunction.

Physical Dysfunction

Physical dysfunction is commonly reported in ICU survivors. Outcome measures such as performance of activities of daily living and 6-min walk distance (6MWD) are almost universally impaired at hospital discharge and frequently persist at the 1-year mark [12–14]. Severe disability occurs in almost one-third of survivors at 1-year follow-up [14, 15]. Studies of ARDS survivors have identified several potential risk factors, including exposure to systemic corticosteroids, development of illness acquired within the ICU stay, and slow resolution of lung injury and multi-organ dysfunction [16]. Treatment strategies generally favor the implementation of early structured and individualized rehabilitation in concordance with sedation lightening [17–19]. In fact, patients exposed to early mobilization are able to ambulate further at hospital discharge. One study of mechanically ventilated patients found that those subjected

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Table 45.1 Selected potential long-term patient and family outcomes after intensive care

Complication	Description	Selected risk factors	Natural history
Patient outcomes			
Pulmonary	Impairment in spirometry, lung volumes, and diffusion capacity	Diffusion capacity: duration of mechanical ventilation	Generally mild impairment with improvement during first year, but can persist 5 years or more
Neuromuscular/ICU-acquired weakness	Includes critical illness polyneuropathy and myopathy	Hyperglycemia	Polyneuropathy may recover more slowly than myopathy; can extend to 5 years
Physical function	Disuse atrophy	Immobility/bed rest	Some improvement in ADL within months, but impairments may be seen in ADL at 1 year and in IADL at 2 years
	Impairment in activities of daily living (ADL/IADL) and 6-min walk distance	Systemic corticosteroids	
		ICU-acquired illnesses	
		Slow resolution of lung injury	
		Age	
		Preexisting IADL impairment	
Psychiatric	Depression	Traumatic/delusional memories of ICU, sedation, psychiatric symptoms at discharge, impairment of physical function	May decrease over first year
	Post-traumatic stress disorder	Sedation, agitation, physical restraints, traumatic/delusional memories	Little improvement in first year
	Anxiety	Unemployment, duration of mechanical ventilation	May persist past first year
		Overall risk factors: female gender, younger age, less education, and pre-ICU psychiatric symptoms, and personality	
Cognitive	Impairments in memory, attention, executive function, mental processing speed, visuospatial ability	Lower pre-ICU intelligence	Significant improvement during first year, with residual deficits up to 6 years later
		ICU delirium	
		Sedation	
		Hypoxia	
		Glucose dysregulation	
Family outcomes			
Psychiatric	Depression	Overall risk factors: female gender, younger age, less education, pre-ICU psychiatric symptoms, personality, distance to hospital, restricted visiting	Depression and anxiety decrease over time, but are higher than population norms at 6 months
	Post-traumatic stress disorder	Dissatisfaction with communication, ICU physician perceived as "uncaring," passive preference for decision-making, mismatch between involvement in decision-making and preference	Post-traumatic stress disorder and complicated grief can persist 4 years or more after death or discharge and may not decrease over time
	Anxiety	Severity of illness not associated with development of symptoms	
	Complicated grief	Complicated grief is worse when family does not have knowledge of patient's wishes	
		In pediatric ICU, paternal stress after discharge is associated with child stress in pediatric ICU	

From Needham et al. [3]

ADL activities of daily living, *IADL* instrumental activities of daily living, *ICU* intensive care unit

to early mobilization ambulated a mean of 30.4 m, compared with a median of 0 m in control patients [17]. Specifically, quality improvement measures which focus on reducing the use of continuous administration of benzodiazepines, increasing ICU staffing for physical and occupational therapy, and updating consultative guidelines to

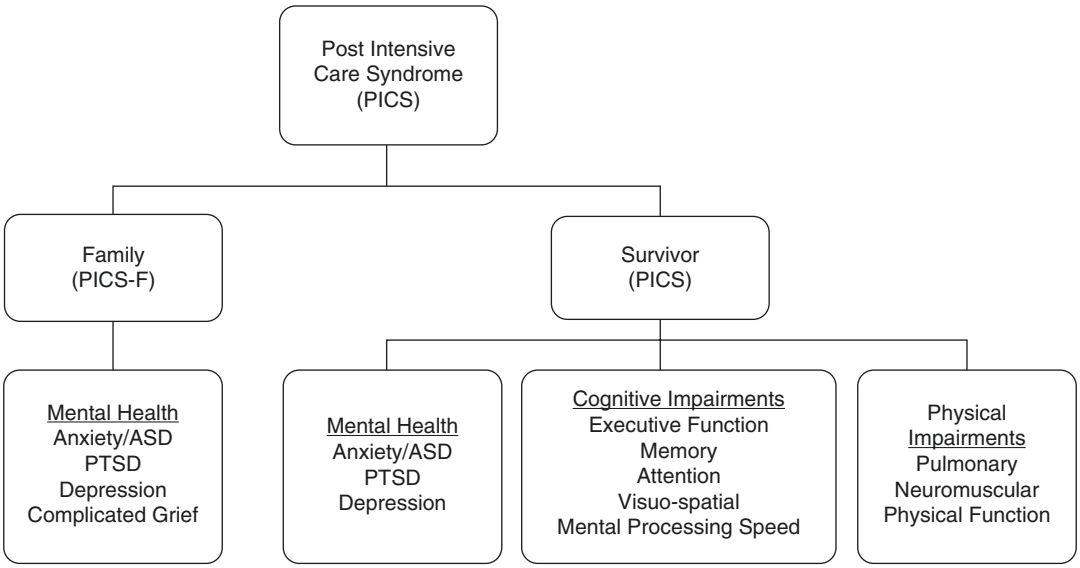

Fig. 45.1 Post-intensive care syndrome (PICS) conceptual diagram. *ASD* acute stress disorder, *PTSD* post-traumatic stress disorder (From Needham et al. [3])

facilitate early rehabilitation have been shown to improve the functional mobility of ICU patients and reduce both ICU and hospital length of stay [59].

Pulmonary Dysfunction

Most data regarding pulmonary dysfunction comes from that of long-term ARDS survivors. When present, dysfunction is usually mild and may present as impairment in diffusion capacity, obstructive lung disease, or restrictive lung disease [20, 21]. Impairment in diffusion capacity is the most common type of pulmonary dysfunction and may persist in up to 80% ARDS survivors at the 1-year mark [16, 21]. Obstructive and restrictive defects typically normalize by 1 year [16]. Multiple indicators of poor pulmonary function, such as forced expiratory volume in 1 s (FEV1), ratio of FEV1 to vital capacity, and diffusion capacity for carbon monoxide, have been shown to correlate with a decline in overall health-related quality of life [22, 23]. Pulmonary dysfunction and diffusion capacity in particular may be associated with the duration and mode of mechanical ventilation [22, 24]. In addition, prolonged diaphragmatic inactivity seen with extended duration mechanical ventilation is known to precipitate diaphragmatic atrophy and subsequent dysfunction as the diaphragm thins and undergoes a change in curvature [46].

Neuromuscular Dysfunction

Neuromuscular dysfunction has long been observed in conjunction with critical illness and can be thought to comprise a syndrome with the hallmarks of generalized weakness and inability to separate from mechanical ventilation [25]. Weakness is increasingly prevalent, occurring in up to 50% of patients with sepsis, multi-organ failure, or protracted mechanical ventilation [25]. Consequences are significant both in the acute-care setting, as well as in the long-term recovery period, affecting mortality, ICU length of stay, hospital length of stay, duration of mechanical ventilation, and duration of post-ICU rehabilitation [25–27]. Patients with critical illness-associated weakness often experience persistent physical deficit and disability, impeding activities such as independent walking and spontaneous ventilation [28]. Furthermore, physical disability has been noted to persist in follow-up periods for as long as 5 years [29].

ICU-Acquired Weakness

The term ICU-acquired weakness (IAW) was developed in an effort to standardize nomenclature used for describing clinically apparent weakness in ICU patients [3, 30]. It embodies several distinct but overlapping entities, including critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and critical illness neuromyopathy (CINM), which occur when features of both CIP and CIM are present. There are several modalities of testing which can aid in the diagnosis of IAW. These include clinical assessment, electrophysiologic testing (needle EMG, nerve conduction studies, neuromuscular junction testing), and morphologic investigation (nerve histology and muscle biopsy). Diagnosis is often challenging due to the high prevalence of altered mental status in ICU patients and inability to elicit voluntary muscle contraction, as well as the common presence of tissue edema, which can impair accurate needle EMG or nerve conduction study. Clinical assess-

ment is done by manual muscle testing in concordance with the previously validated Medical Research Council scoring system in which three muscle groups of each extremity are scored from 0 to 5 for a maximal strength score of 60 and a score <48 qualifying for IAW [30, 31]. Recent research also explores the use of biomarkers, such as CK level, and ultrasound measurement of muscle thickness to detect the presence of and quantify the extent of IAW, but these methods have yet to be fully delineated [32–35]. Ultimately, however, the diagnosis of IAW must be made by exclusion, and a careful history and physical examination is an essential part of the initial investigation (see Table 45.2).

Critical Illness Polyneuropathy

CIP is manifested by proximal extremity and respiratory muscle weakness, with sparing of facial and ocular muscle groups (see Table 45.3). Respiratory weakness may be significant enough to prolong weaning from mechanical ventilation [36]. Sensory deficits are less common and usually involve distal extremity loss of pain, temperature, and vibratory sensation. Deep tendon reflexes may be absent or depressed. CIP occurs following secondary nerve axonal injury in the absence of demyelination. When present, it carries a poorer prognosis for recovery compared with CIM [37]. Nerve conduction studies demonstrate a reduction in compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) with preservation of nerve conduction velocities (NCVs) [30]. Repetitive nerve stimulation of the neuromuscular junction does not produce a decline in muscle response. The pathophysiology is likely multifactorial, and proposed mechanisms include reduction of sodium ion channel excitability, nerve ischemia, and impairment of the nerve microcirculation, which may be exacerbated by local hypoxia or hyperglycemia and downstream dysregulation of nerve mitochondria [38–42]. Supporting studies demonstrate increased expression of E-selectin proteins in the peripheral nerve vascular endothelium, which may be responsible for microvascular leak and the strong association between CIP and sepsis [25, 42].

Critical Illness Myopathy

CIM describes a primary myopathy, without involvement of the sensory system [28]. Clinically, it can be very difficult to distinguish from CIP by simple bedside examination since both entities may be manifested by respiratory and limb muscle weakness (see Table 45.4). In CIM, nerve conduction studies demonstrate reduction of CMAPs, with preserved NCVs and SNAPs, direct muscle stimulation reveals reduced excitability, and histology is consistent with myopathy [30]. Mechanisms of pathophysiology include skeletal muscle wasting from an overall catabolic state often present in critical illness and sepsis, systemic inflammation and oxidative injury, mitochondrial dysfunction, and sodium channelopathy [41, 43–45]. Muscle atrophy is likely precipitated by prolonged immobilization and diaphragmatic inactivity, which in turn leads to protease activation, muscle protein breakdown, and proteolysis by the ubiquitin-proteasome pathway [46–48]. Support for disuse atrophy is demonstrated by the loss of diaphragmatic thick filaments and increase in proteolysis observed after diaphragmatic inactivity for as little as 16 h [48].

Risk Factors

Clear risk factors for the development of IAW include sepsis, states of persisting systemic inflammation, catabolic state, and multi-organ failure. Prolonged immobilization, long duration of mechanical ventilation, and long ICU length of stay, in addi-

Table 45.2 Diagnostic criteria for ICU-acquired weakness

1. Generalized weakness developing after the onset of critical illness
2. Weakness is diffuse (involving both proximal and distal muscles), symmetric, flaccid, and generally spares cranial nerves[a]
3. MRS sumscore <48 or mean MRC score <4 in all testable muscle groups noted on ≥2 occasions separated by >24 h
4. Dependence on mechanical ventilation
5. Causes of weakness not related to the underlying critical illness have been excluded
Minimum criteria for diagnosing ICUAW: 1, 2, 3 or 4, 5

From Stevens et al. [30]
ICUAW intensive care unit-acquired weakness, *MRC* Medical Research Council
[a]For example, facial grimace is intact

Table 45.3 Diagnostic criteria for CIP

1. Patient meets criteria for ICUAW
2. Compound muscle action potential amplitudes are decreased to <80 % of lower limit of normal in ≥2 nerves
3. Sensory nerve action potential amplitudes are decreased to <80 % of lower limit of normal in ≥2 nerves
4. Normal or near-normal nerve conduction velocities without conduction block
5. Absence of a decremental response on repetitive nerve stimulation

From Stevens et al. [30]
CIP critical illness polyneuropathy, *ICUAW* intensive care unit-acquired weakness

Table 45.4 Diagnostic criteria for critical illness myopathy

1. Patient meets criteria for ICUAW
2. Sensory nerve action potential amplitudes are >80 % of the lower limit of normal in ≥2 nerves
3. Needle electromyogram in ≥2 muscle groups demonstrates short-duration, low-amplitude motor unit potentials with early or normal full recruitment with or without fibrillation potentials
4. Direct muscle stimulation demonstrates reduced excitability (muscle-nerve ratio >0.5) in ≥2 muscle groups
5. Muscle histology consistent with myopathy
Probable CIM: criteria 1, 2, 3 or 4; or 1 and 5
Definite CIM: criteria 1, 2, 3 or 4, 5

From Stevens et al. [30]

CIM critical illness myopathy, *ICUAW* intensive care unit-acquired weakness

tion, have independently been shown to increase risk [25, 48, 49]. In addition, the presence of hyperglycemia has been associated with the development of CIP and CIM. The treatment of hyperglycemia by intensive insulin therapy may lead to a greater frequency of hypoglycemic events, although this may not carry clinical significance and thus is not associated with IAW [40, 49–51]. The use of corticosteroids and neuromuscular blocking agents has inconsistently been associated with the development of weakness [16, 40, 43, 50, 52]. Combined use of aminosteroid neuromuscular blockers and corticosteroids in patients with status asthmaticus has been strongly linked to the development of weakness, yet neuromuscular blockers used for short periods in severe ARDS patients resulted in improved survival without significant weakness [53–55].

Goals of Therapy

Physical dysfunction and weakness are substantial in ICU survivors and can persist for years following ICU discharge [29, 56]. Efforts to prevent or minimize IAW should therefore begin during the ICU phase of care and center around the optimization of early physical activity. A necessary first step is the paradigm shift toward sedation lightening despite critical illness, allowing for improvement in patient participation in rehabilitation. Several trials have demonstrated that reduction in sedation levels leads to improved activity levels and prevention of activity-limiting pressure sores [57–59]. Early, aggressive mobility should be considered in all ICU patients, even those requiring extracorporeal mechanical circulation [60]. Large trials have shown consistently that early physical therapy results in improved survival, shorter hospital and ICU length of stay, lower readmission rates, and improved short- and long-term post-ICU physical function and functional dependence, without a significant rate of adverse events [17, 19, 61, 62]. Specifically, mechanically ventilated patients randomized to receive early rehabilitation within 72 h of intubation were more likely to return to a state of functional independence at hospital discharge and experience a lower rate of ventilator-free days [17]. In addition, in patients who are unable to cooperate with active participation in physical therapy, passive range of motion accomplished by other rehabilitation technologies such as neuromuscular electrical stimulation or cycle ergometry can still improve strength and physical function by the time of hospital discharge. Cycle ergometry, in particular, has been shown to improve strength, with treatment patients achieving an average 6MWD of 196 m (29 % predicted) versus 143 m (25 % predicted) achieved in controls [61].

Cognitive Dysfunction

Cognitive impairment is common in survivors of critical illness, often presenting as an acquired dementia spanning multiple domains, especially those affecting memory, attention, and executive function [63, 64]. Brain dysfunction may manifest as a new deficit, exacerbation of preexisting deficit, or delirium. The prevalence of brain dysfunction is most commonly studied in survivors of ARDS and severe sepsis. Among long-term survivors of ARDS, 73 % were diagnosed with cognitive impairment at hospital discharge, with a significant reduction by 1 year and unchanged at 2 years [29]. Similarly, survivors of severe sepsis are more likely to experience severe cognitive impairment, and these deficits may be long-lasting, persisting for up to 8 years in elderly patients [56]. A recent review of ICU survivors of respiratory failure or shock revealed a 74 % rate of delirium within hospital stay, 40 % rate of cognitive impairment <1.5 SD below the population mean at 3 months, and 26 % with scores comparable to those of Alzheimer's' patients or survivors of traumatic brain injury at 12 months [67]. Long-term brain dysfunction is a growing public health problem, as it is likely tied to reduced quality of life, institutionalization, and increasing healthcare costs seen with the care of elderly patients with dementia [68, 69]. In addition, delirium itself has been independently shown to increase risk for short-term mortality in mechanically ventilated patients [70].

Mechanisms

The pathogenesis of long-term cognitive dysfunction is not well elucidated, but is likely multi-factorial. One model describes a process of accelerated neurodegeneration

occurring in susceptible patients. Common exposures in critical illness, such as hypoxemia, hypotension, anemia, fever, glucose dysregulation, systemic inflammation, the use of pharmacologic agents, or hepatorenal disease, may ultimately result in acute brain injury. Furthermore, certain patient populations may be particularly vulnerable, such as those with advanced age, low cognitive reserve, or predisposition for dementia [63]. Interestingly, abnormal neuroimaging and histopathology of ICU survivors have been shown to correlate with neurocognitive impairment. Brain atrophy and ventricular enlargement have been reported in ARDS survivors and patients known to have had delirium [71, 72]. Similarly, hippocampal lesions and disruptions of white matter tracts in the corpus callosum and internal capsule have been found in ICU patients with cognitive impairment [72, 73].

Risk Factors

The development of delirium is perhaps the strongest risk factor for long-term cognitive dysfunction in ICU survivors. Furthermore, the duration of delirium was recently shown to predict impaired global cognition and executive function, or the ability to integrate visuospatial information and make decisions, in mechanically ventilated ICU patients [74]. Other potential risk factors include the use of sedatives/analgesics, poor ICU recall, lower pre-ICU intelligence, older age, severity of illness, and global disturbances such as hypoxia and hypotension [65, 75–77]. Blood glucose dysregulation demonstrated by either hyperglycemia or hypoglycemia has also been shown to increase risk for long-term neurobehavioral impairment as well [78, 79].

Management

There appears to be a link between exercise and cognitive function. Theories of improved cerebrovascular flow have been proposed [80]. Treatment and prevention of cognitive dysfunction therefore targets the management of delirium, as well as the implementation of early rehabilitation. Strategies to prevent and treat delirium include minimization of sedation, restoration of normal sleep-wake cycling, avoidance of deliriogenic agents such as benzodiazepines, and treatment of metabolic disturbances, predominantly hypoglycemia [63]. Therapies investigated for early rehabilitation support the use of ICU protocols designed to lighten sedation, perform daily awakening and breathing trials, and implement early physical and occupational therapy [81, 82]. Early results indicate overall improvement in long-term cognitive outcomes without a significant rate of adverse events. Similarly, efforts to provide intensive home rehabilitation may provide improvement in long-term executive functioning in ADL performance [82]. Strategies to prevent and treat delirium include minimization of sedation, restoration of normal sleep-wake cycling, avoidance of deliriogenic agents such as benzodiazepines, and treatment of metabolic disturbances, predominantly hypoglycemia [63].

Mental Health

ICU survivors are at risk for psychiatric sequelae that can affect their quality of life for years after discharge. More than 50 % of ICU survivors have psychiatric morbidity related to their ICU stay [83, 84]. Critical illness places them at risk for developing post-traumatic stress disorder (PTSD), anxiety, and depression (see Fig. 45.1) [3].

Post-traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is an acute anxiety disorder following exposure to an extreme stressor that causes injury and threatens life or physical integrity with an immediate response involving intense fear, helplessness, or horror. Sufferers experience intrusive recollections of the event, symptoms of hyperarousal and avoidant behaviors related to the event persisting over a month and causing distress or impaired functioning [2, 85]. More than 60 % of ICU survivors experience symptoms of PTSD at some point after their ICU stay with 22–25 % experiencing clinically significant and lasting symptoms. This compares to the rate of PTSD following acute coronary syndrome at 12 % and is similar to rates of PTSD in survivors of wartime combat and the World Trade Center attacks [10, 86–90].

Risk Factors

Acute stress during the ICU stay is a risk factor for later development of PTSD. This stress is exacerbated by noxious experiences such as the presence of an endotracheal tube, inability to speak or effectively communicate, endotracheal suctioning, family worries, noise, pain, sleep deprivation, physical restraints, and thirst [2, 91]. Indeed, the ICU has been described as being full of noxious stimuli that providers become desensitized to leaving them unable to recognize how the stimuli are affecting patients [92].

One significant effect of these constant stimuli on critically ill patients is interference with normal sleep patterns. Sleep disturbance during the ICU stay is associated with the development of PTSD and impaired recovery from psychiatric illness [93, 94]. Furthermore, severe sleep deprivation can lead to psychotic behavior and paranoia that are worse at night [95]. This may lead to increased use of sedatives which are also associated with increased risk of PTSD.

Sleep disturbance is common in the ICU with most patients experiencing only stages 1 and 2 of sleep, and therefore they do not experience the restorative benefits of deeper sleep [96]. Fifty percent of survivors report their sleep disturbance as having been moderate or severe and say that it remained a problem for up to 6 months after hospital discharge. The most common factor associated with the loss of normal sleep patterns is the use of psychoactive medications [2].

The use of sedatives, especially benzodiazepines, is associated with the development of PTSD with increasing dose of benzodiazepine sedatives associated with increasing risk. While it was once thought that providing sedation was a humane intervention that would protect patients from psychiatric sequelae, it is now clear that this is not true. In fact, it appears that there is no increase in psychological morbidity in mechanically ventilated ICU patients randomized to receive no sedation compared to patients receiving sedation with daily sedation interruptions [97, 98].

The use of high-dose opiates has been shown to be associated with PTSD, while the overall duration of exposure was associated with a reduced risk, perhaps suggesting that sufficient pain control may be protective while analgesics used in excess for the purpose of sedation are harmful [99].

The early post-discharge development of memories of frightening ICU experiences, whether factual or not, is highly associated with PTSD [10]. It may be that the memories of hallucinations and delusions from the ICU stay may be more traumatizing than factual experiences. Thus, patients may suffer from, in essence, a post-psychosis PTSD [100]. Memory impairments, from partial lack of recall to complete amnesia, of what happened in the ICU are often severe and are augmented or filled in unconsciously by confabulation. Delusional memories are experienced by up to 75 % of ICU survivors, are associated with increased sedative use while in the ICU, and are consistently reported as risk factors for psychiatric sequelae. Whether delusional or factual, the specific memory of being distressed due to a lack of control was a strong predictor of PTSD as well as anxiety and depression [84, 101, 102].

Other risk factors associated with the development of psychiatric sequelae include anger, nervousness, and confusion in the ICU, a pessimistic attitude, and lower education level. Women, parents with children younger than 18, and the unemployed are at higher risk regardless of the degree of injury. Survivors who develop anxiety, depression, or substance abuse post-discharge are at higher risk for developing PTSD [2, 10, 85, 103, 104].

Factors not associated with an increased risk of PTSD include admission diagnosis, steroid administration, severity of illness, ICU length of stay, duration of mechanical ventilation, and presence of or duration of in-ICU delirium [10].

Interventions

Early physical therapy and mobilization in the ICU can reduce anxiety and possibly the subsequent development of PTSD as well as ICU length of stay, mechanical ventilation, and depression. Nonetheless, early physical rehabilitation in the ICU is rare despite demonstrated safety and feasibility [2, 105–107]. Daily sedation interruptions have been shown to reduce PTSD, and, as mentioned above, the complete avoidance of sedation did not increase PTSD [97, 108].

ICU diaries consisting of a detailed log of events during the ICU stay filled out jointly by patients, families, and providers have been shown to reduce the incidence of PTSD at various time points post-discharge up to 1 year. These diaries have become standard of care in some European ICUs [2, 10, 108–113].

Patient-directed music therapy and noise-canceling headphones reduced patient anxiety. Non-pharmacologic interventions such as earplugs, eye masks, relaxation techniques, daytime mobilization, and avoidance of medications that interrupt sleep can reduce psychiatric sequelae. A perception of active social support and clinical counseling of ICU patients by psychologists also shows promise as does post-ICU discharge telephone interventions [10, 114–118]. However, therapist-guided prolonged exposure therapy, the mainstay of treatment for PTSD in other populations, has not been studied in ICU survivors [10].

Limitations

Prior to 2012, there was no formal definition of PICS, and thus reviews and meta-analyses must pull together studies without a common overarching search term limiting their comprehensiveness. Additionally, studies are limited by the lack of standardized assessment tools for measuring PTSD and other psychiatric sequelae in this population. The gold standard is considered to be clinician interviews, but the vast majority of studies are done using questionnaires, and few studies use the same forms. In some countries, ICU follow-up clinics provide a way to follow patients and families over time; however, there is still no such system of clinics in most countries including the United States. Finally, in this patient population, the most vulnerable patients often do not survive long enough to take part in mail surveys or are unable to walk and therefore cannot take part in early post-discharge physical therapy [3, 10, 119, 120].

While patients may benefit from interventions that are known to be effective in other patient populations with psychiatric morbidity such as stroke and post-MI patients, ICU survivors don't carry a recognized unifying diagnosis and therefore often don't qualify for insurance coverage for rehabilitation services. While a diagnosis of PTSD or depression might qualify them for insurance coverage for counseling, it will not help them attain the full spectrum of rehabilitation, physical and mental, that they need [121].

Anxiety and Depression

Feelings of anxiety are reported by up to 85% of ICU patients, and of these, up to 44–62% had symptoms persisting at 1 year post-discharge. These feelings include apprehension, agitation, increased motor tension, autonomic arousal, and fear. Anxiety symptoms are associated with worse physical functioning and lower health-related quality of life (HRQOL) [2, 122].

Depression is also common in ICU patients especially those requiring prolonged mechanical ventilation. Of patients being discharged to a ventilator weaning facility, 42% meet DSM4 criteria for depression, and these patients have higher rates of weaning failure and mortality. ARDS survivors discharged home have rates ranging from 17 to 43% depending on the assessment used. The percentage of ICU survivors discharged to long-term care facilities increased from 15 to 25% from 2001 to 2012. These individuals, removed from their homes and communities, may be at even higher risk for depression [123].

Risk Factors

Many of the risk factors previously described as being associated with PTSD are also associated with the development of anxiety and depression in ICU survivors. These include memories of traumatic experiences, memories of hallucinations, and memories of distress. Other associated factors include sleep disturbance, pessimism, prior history of psychiatric disorders including anxiety, and lower education level. Lower socioeconomic status is associated with the development of anxiety and depression but not PTSD. Recent work has shown that frailty, a multidimensional syndrome characterized by loss of physiologic and cognitive reserves that predispose to increased vulnerability to unfavorable outcomes, often following relatively minor stressors, is associated with decreased health-related quality of life and increased rates of anxiety and depression [2, 10, 84, 85, 101–104, 124].

There are several factors that have not been found to be associated with increased rates of anxiety and depression post-discharge. As with PTSD, these include presence or duration of delirium while in the ICU and severity of illness, admission diagnosis, and length of stay which are not associated with rates of anxiety and depression post-discharge [2, 10].

Interventions

Consultations with nurse providers post-discharge have been shown to decrease symptoms of depression in women but not in men. Telephone-based training in mindfulness and coping mechanisms has shown a reduction in a variety of psychiatric outcomes including anxiety and depression [118, 121].

ICU diaries, discussed above as a promising intervention for reducing the incidence of PTSD, also reduce symptoms of anxiety and depression. Similarly, early mobilization, early physical therapy, and non-pharmacologic interventions to promote sleep at night and wakefulness during the day can reduce anxiety and depression as well as PTSD [2, 10, 105, 107–113].

Limitations

The data for anxiety and depression suffer from the same limitations as that for PTSD with a variety of assessment methods leading to a wide heterogeneity in results [3, 10, 119, 120].

Symptoms of anxiety and depression in ICU survivors often coexist with ongoing physical and cognitive impairments that can make the psychiatric problems more difficult to identify. Therefore, patients who, with a single diagnosis of depression, might qualify for insurance coverage for outpatient treatment cannot get the comprehensive inpatient rehabilitation and counseling that they require because of the lack of a recognized diagnosis for their constellation of symptoms [121].

Post-intensive Care Syndrome-Family

It is increasingly recognized that family members of critically ill patients are at high risk for psychiatric sequelae including PTSD, anxiety, depression, and complicated grief (see Fig. 45.1). More than 90% of family members of ICU patients report feeling scared, tired, sad, anxious, having a lack of appetite, or general poor well-being. They neglect self-care, sleep less and get poorer quality of sleep, have poor nutrition, less exercise, and use more alcohol, cigarettes, and prescription medications than they did before their family member was critically ill. Mothers of critically ill infants have decreased bonding with their child when the mother suffers from PICS-F [3, 125, 126].

The prevalence of PTSD in family members of ICU survivors ranges from 13 to 56% and is higher in relatives of adult patients than in parents of critically ill children. Generalized anxiety is common as well with prevalence rates ranging from 21 to 56%. Rates of depression and complicated grief (differentiated from depression only in that the symptoms are tied to the death of a loved one for more than 2 months) range from 8 to 42% [125].

As PICS-F becomes more recognized as a distinct entity, practitioners and organizations are starting to respond. The Society of Critical Care Medicine (SCCM), the American College of Critical Care Medicine (ACCM), CHEST foundation (the philanthropic arm of the American College of Chest Physicians), and the Center to Advance Palliative Care (CAPC) have all created websites and guidelines aimed at helping families of the critically ill.

Timing

Anxiety and depression can occur at any time during the time course of having a family member in the ICU. Just as in

patients, in family members, PTSD is diagnosed at least 1 month after the traumatic experience. Prior to that, the symptoms of PTSD are referred to as acute stress disorder. Complicated grief is diagnosed if substantial depressive symptoms (marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychomotor retardation) persist for more than 2 months after the death of a loved one [125].

Risk Factors

A variety of risk factors for developing PICS-F have been identified. These include female gender, younger age, lower education level, having a critically ill spouse, being an unmarried parent of a critically ill child, having preexisting anxiety, depression or a family history of psychiatric illness, the severity of the illness of the family member, unexpected illness, the loved one dying or being at high risk for death, a feeling of lack of control, a feeling of a lack of information or incomplete information, feeling that the physician was not comforting, and feeling that the actual decision-making role was discordant with the caregiver's preferred role [125, 127–129].

Consequences

Family members suffering from PICS-F have a slower rate of return to the work force. They are less able to provide ongoing home care for their loved one after discharge. Mothers are less able to bond with their infant children which, in turn, leads to worse outcomes for neonates. These consequences are often most prevalent early on but can last for years [125, 130–132].

Affected family members postpone education, medical care, travel, and even marriage. There is increased strain on their other relationships which can lead to higher levels of stress with decreasing social support at a time when it is needed the most [133]. A study from 2002 found that 12 months after discharge the financial impact of critical care was still significant with 37 % of family members reporting that most of their savings were gone and 27 % saying that the major source of family income was lost [134].

Family-Centered Interventions

Communication and support play a large role in reducing the incidence of PICS-F. Mothers who spoke about their critically ill children during the admission had lower rates of PTSD. Family members who reported feeling high levels of social support had lower levels of anxiety [135].

Families of patients who die in the ICU who receive proactive end-of-life conferences and brochures about end-of-life care have lower rates of PTSD, depression, and anxiety. The best studied model of conference is based around the VALUE model which consists of valuing the family contribution to the discussion, acknowledging family emotions, listening, understanding the patient as a human being, and eliciting questions from the family [136].

The SCCM and ACCM guidelines on family support recommend that ICU staff receive education related to assessing and meeting family needs to reduce stress, family should receive updates frequently in a language they understand from consistent members of the team, family should be provided information in a variety of formats, and family should be encouraged to participate in care as appropriate when they are comfortable doing so [137].

Mothers of critically ill children who receive information about their child's illness via audiotape, activity book, and personalized instruction have reduced anxiety and distress and bond more with their children. Their children have improved cognitive development and a reduced length of neonatal ICU stay [138].

Other interventions that have shown promise include increasing family involvement in small tasks of care such as filing nails, applying lip balm, or helping with passive range-of-motion exercises; family debriefing visits after discharge; and family clinics after discharge that disseminate information and provide physical and psychological assessments for family members. Approximately 30 % of ICUs in the United Kingdom have associated follow-up clinics. Families report that communication with providers, being included in rounds and decision-making, enhances their sense of control and well-being and shared decision-making reduces depression and anxiety [139–145].

Future Directions

A 2012 Stakeholders' conference identified several strategies to improve long-term outcomes in ICU survivors. Perhaps most important was the need to raise awareness for PICS and PICS-F as recognized disorders in order to improve upon the existing model of care "silos" distributed among primary care, critical care, and rehabilitation providers and provide consistent coverage of rehabilitation and psychiatric services to survivors [3]. Management that promotes the paradigm shift of lighter sedation levels and early and intensive ICU mobility should be promoted, as well as the broader use of therapies such as ICU diaries and post-ICU follow-up clinics. In addition, several research gaps were identified, including screening of patients susceptible for PICS, optimizing psychiatric and cognitive rehabilitation, utilizing psychological interventions or alternative

medicine techniques, exploring the connection between sleep disorders and long-term cognitive and mental health, and understanding the long-term complications of acquired oropharyngeal dysfunction [3]. Research methods, in general, should aim to measure outcomes by more standardized measures in order to reduce heterogeneity among studies.

As awareness for the long-term impact of critical illness grows, the need to support patients and families through the challenges faced after ICU discharge becomes increasingly important. Palliative care should assume a growing role within the ICU. Contrary to misconceptions that palliative care and life-prolonging critical care are mutually exclusive, the services may be provided concurrently in order to assist patients with alleviation of physical and emotional symptoms, achieve earlier surrogate decision making, provide decision support tools to patients and families, and address goals of care, prognosis, and patient value discussions through structured approaches and family meetings [145]. There are few studies which assess interventions to integrate palliative care within surgical ICUs; however, results consistently support earlier consensus regarding goals of care, more frequent discussion of symptom management, and shorter ICU length of stay without an increase in overall mortality [146, 147]. Finally, it is important to meet the needs of ICU survivors and their families during the phase of ICU recovery. This may be accomplished by initiatives such as SCCM's THRIVE, which aim to raise awareness for and better serve patients and families through the development of support networks as well as through the promotion of new research and clinical therapies [148].

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Operative Procedures in the Intensive Care Unit

46

Greta L. Piper

Introduction

Procedures in the intensive care unit (ICU) have traditionally been limited to central lines, arterial lines, chest tubes, and other short procedures that can be performed using only local anesthesia. With the advent of the field of acute care surgery – a blend of trauma, emergency general surgery, and surgical critical care – instances have evolved in which operating in the ICU is not only possible but also necessary. Increased recognition of abdominal compartment syndrome and the use of damage control strategies have contributed to this change.

A variety of models for coverage of an acute care surgery service have emerged [1, 2]. One attending surgeon may be responsible for the incoming traumas, the emergency general surgeries, and/or the intensive care unit at a given time, even when backup schedules exist. Operating room (OR) time may be difficult to coordinate with these competing responsibilities in the setting of limited or no OR block time. As a result, surgery may need to occur in the evening or overnight when the rest of the operating room is less busy [3]. Operating in the ICU allows these cases to occur during daytime hours when multiple attendings cover different arms of the acute care surgery service.

In addition to increasing numbers of tracheostomies and percutaneous endoscopic gastrostomy tube placements in the ICU, more complicated procedures are also being performed in this setting. This aids in physician time management, limits transfers of critically ill patients, and avoids having to transition from advanced ventilator settings to less effective settings.

With the increase in damage control surgeries, abdomens are left open with temporary abdominal closures with or without packing. Return trips to the OR for emergent or non-emergent re-exploration then follow. Patients, trauma or otherwise, who develop unstable abdominal compartment syndrome physiology, may need to be decompressed with a laparotomy emergently in the ICU.

In general, two types of procedures are performed in the ICU: lifesaving procedures for which a patient is too unstable to attempt transfer to the operating room and uncomplicated procedures for which transfer to the operating room seems unwarranted. It is crucial to have an organized approach to performing both subsets of procedures in the intensive care unit. It requires coordination and support from critical care nursing, nursing leadership, physician intensivists, respiratory therapy, and central supply.

Benefits of Operating in the ICU

One major benefit of operating in the ICU is that the team who knows the patient best is the team caring for the patient throughout the procedure. It eliminates the handoff to and from the OR staff and potentially to and from a recovery room staff if the policy is for a patient to recover in a postanesthesia care unit prior to returning to the ICU. For the patient who requires multiple abdominal or wound washouts, limiting the number of handoffs becomes even more important [4].

The actual act of transferring the ICU patient to a different location (and back) is not without risk [5]. If the patient is receiving titrating infusions of inotropes or pressors, any interruption in medications or accidental dislodgment or disconnection of devices can be life threatening. Patients requiring high-pressure or advanced ventilator settings may suffer alveolar derecruitment and subsequent hypoxia when transitioned to a different ventilator or to manual bag mask ventilation for transfer.

Operating in the ICU can also save time [6, 7]. For the surgeon without block time who must wait for OR availability, the ICU provides this resource for the surgeon and patient without depending on or impacting the elective OR schedule.

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It also saves time for the nurses and other staff who must transfer the patient.

Risks of Operating in the ICU

While numerous procedures, including bedside laparotomy, have been deemed safe and feasible in the surgical ICU, operating outside of the operating room is not without risks that must be measured when determining a safe plan for each patient [8]. The operating room has optimized lighting, trained circulating nurses and technicians, dedicated anesthesia teams, and immediate access to all of the specific equipment, sutures, staplers, and instruments available in the hospital. In the ICU, laparotomy trays are general sets with fewer extra options immediately accessible for unexpected conditions. The person handling instruments and keeping counts of supplies may be an ICU nurse, a resident, or another caregiver not specifically trained for this role. Extra steps must be taken to ensure safe handling of all materials before, during, and after each procedure. Anesthesia resources may also be limited and contingency plans should be delineated in advance for airway management and medication needs.

Team Preparation

While staffing patterns in the ICU vary, it is important to have commitment from all members of the multidisciplinary team. All team members may not be required for every procedure, but if discussions and planning have occurred in advance to determine expectations, both emergent and non-urgent cases alike will be more efficient, more effective, and safer. Mayberry suggests developing a "surgery outside of the operating room" program to designate team members, identify potential logistic pitfalls, and foster a thoughtful team environment [9].

A single intensivist may be able to lead the technical aspects of a simple procedure as well as manage the sedation and ventilation for the patient. However, it is helpful, and at times necessary to have one intensivist in the surgeon role and a separate provider in the anesthesiologist role. A respiratory therapist should be present when ventilator or airway manipulation is required. One significant advantage to performing procedures in the ICU is that patients requiring advanced modes of ventilation (i.e., airway pressure release ventilation) do not have to be transitioned to different settings for transport. Also, a non-intensivist anesthesiologist may be less familiar with these ventilator strategies. With increased sedation or with use of muscle relaxant in the ICU, ventilator settings can be adjusted to maintain adequate parameters. Having an experienced respiratory therapist with this understanding is beneficial.

The operative assistant may be a resident, fellow, advanced practice provider, nurse, or other provider. A designated scrub technician may or may not be necessary depending on the procedure and the competence of the assistant.

Ideally, a bedside nurse will be solely responsible for minute-to-minute documentation while an additional bedside nurse will administer medications. If staffing does not permit this, one nurse may need to perform both roles. Support from the unit nursing leadership is necessary; scheduling nursing breaks and ensuring appropriate staffing around procedures are essential.

If a clinical pharmacist is part of the ICU rounding team, his or her participation during ICU procedures is also helpful to be certain that weight-based dosing is accurate and that additional medications and infusions are available in an expedient manner.

Training advanced practice providers (APPs) to assume roles in the ICU operating team lends both versatility and consistency to procedures. APPs can manage equipment and supplies, assist in procedures, and provide service outside of the scope of nursing expectations [10]. They also support and educate the rotating ICU residents and fellows.

A circulator/runner is essential for procedures in the ICU. As in the OR, additional supplies or resources are frequently needed that may not be in the room at the time of the procedure. A person designated to this role should have familiarity with the location of supplies in the ICU and also the ability to anticipate the needs of the team. All members of the team will become more cohesive in these situations as more procedures are performed together.

ICU-specific protocols and supply bundles for frequently performed procedures created with input from the multidisciplinary team can contribute to a safe environment and a prepared team. Following each ICU procedure, a focused team debrief can identify any issues that require corrective measures (Fig. 46.1). An example of an ICU abdominal surgery bundle is seen in Fig. 46.2.

Documentation

Documentation requirements for physicians and nurses for ICU-based operations and procedures vary among institutions. Consent should be obtained for procedures and witnessed per the institution standard. A separate consent for sedation may also be required. Documentation of the pre-procedure timeout is important. As electronic medical records have become ubiquitous, many electronic templates are available for brief or detailed procedural or sedation notes. While it is important to document the procedure performed and any notable findings, it is also critical to document the number of laparotomy pads (or other foreign bodies) removed and/or placed and any other

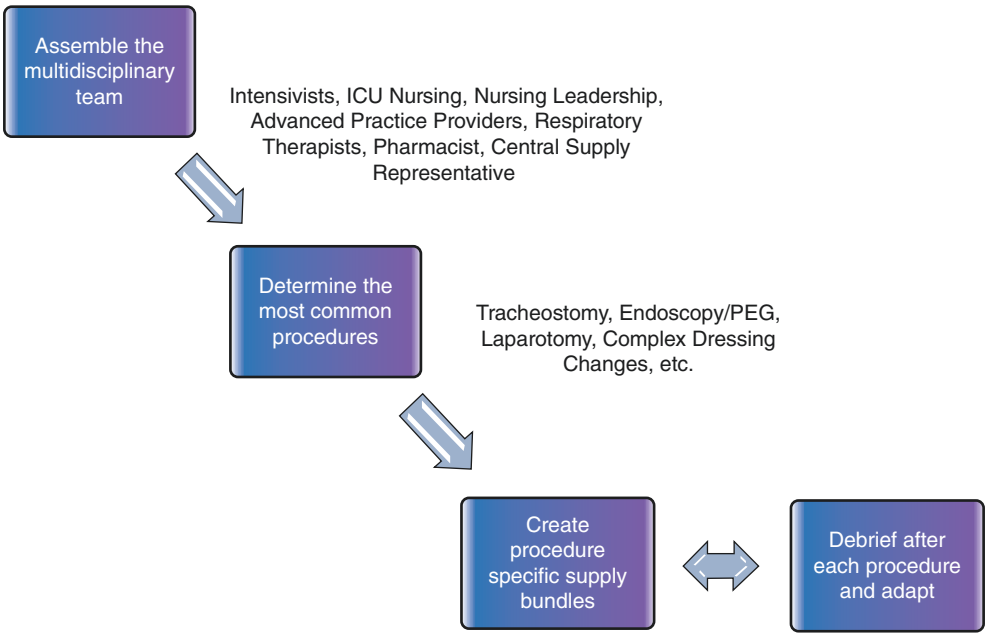

Fig. 46.1 ICU team process

Sterile skin preparant
Sterile patient drapes
Personal protective equipment (Gowns, Gloves, Caps, Masks)
Instrument tray (Same as basic OR laparotomy tray)
Laparotomy pads
Suction tubing
Sterile irrigation
Electrocautery and Grounding pad
Temporary abdominal closure supplies
Head lamp or Procedure lamp
Sutures/Staplers available to be opened when needed
Collecting container/system for used laparotomy pads

Fig. 46.2 Sample ICU laparotomy bundle

information that would be important for another provider or surgeon to know. Sponge and instrument counts also need to be recorded carefully, and any discrepancy should prompt an x-ray to confirm the absence of retained foreign bodies.

Anesthesia/Sedation Selection and Implementation

To determine the appropriate level of anesthesia and sedation for a patient, several factors must be considered. These include the procedure being performed, the expected amount of pain involved, the duration of the procedure, and whether or not the procedure requires the patient to be paralyzed. Many ICU bedside procedures are safely performed without the need for neuromuscular blockade [10]. The patient's hemodynamic status and stability help determine which sedating agents will be most appropriate. Also, certification for specific levels of sedation may be determined by the institution. If deep sedation privileges are needed, it is important to have completed these credentialing requirements to avoid working outside of the designated scope of practice. Having a second attending to manage sedation and other medications, as well as the ventilator, allows the operating surgeon to focus on the procedure being performed.

ICU Room Considerations

Converting the ICU room into a suitable forum for surgery becomes more manageable with a few simple but important alterations in the usual state of the room. To protect the privacy as well as the sterility of the procedure, the number of people in the room should be no more than is necessary. Keeping the door or curtain closed when a patient is exposed also mitigates against the risk of hypothermia. Second, ICU lighting may not be adequate for procedures. A portable procedure light or a head lamp can be invaluable in this situation. Also, the room setup may benefit from subtle rearrangements to maximize space and access to the patient, ventilator, and monitors. The clinician responsible for the patient's airway and ventilator management should be positioned appropriately to allow for adjustments and interventions. Having multiple suction setups ready is critical for both the airway and the operating field. Adjusting the bed height and position will optimize exposure for the body region the procedure involves.

Tracheostomy

Elective tracheostomy has been an accepted ICU procedure for decades. As percutaneous tracheostomy has become a frequent choice in many institutions, a range of providers are able to perform this procedure, including surgical and non-surgical intensivists and pulmonologists, in addition to non-intensivist surgeons.

It is the responsibility of the person performing the tracheostomy to determine a patient's appropriateness for open tracheostomy versus percutaneous tracheostomy as well as the appropriateness of performing the procedure in the ICU versus in the operating room. Considerations include neck anatomy, risk of bleeding, prior neck surgeries, and the comfort of the provider performing the tracheostomy. Patients who are obese or who have short necks, difficulty airways, difficult to appreciate landmarks, large thyroids, or cervical spine status that precludes extension or significant repositioning, may be better suited to the operating room, where additional options and support are available [11]. Patients with bleeding dyscrasias or who are anticoagulated or on antiplatelet therapy are also at increased risk in the ICU. Patients who have had prior tracheostomies or those who have had recent cervical spine surgery via an anterior approach are candidates for percutaneous tracheostomy, in which limited or no dissection through scarred or recently violated planes is required. As with all surgical procedures, provider experience is an important consideration. For those providers who routinely perform percutaneous tracheostomy, a wider range of patients may be appropriate for ICU tracheostomy. Those who perform a limited number will likely limit themselves to only the most ideal candidates.

The recommended staffing for both open and percutaneous tracheostomy includes two attendings [11, 12]. It is essential to have someone who is competent with the endotracheal airway, who can manipulate the endotracheal tube without losing the airway, and who can recognize the need and reestablish an endotracheal airway if needed.

There is significant variability in tracheostomy practices in critically ill patients though recent guidelines for percutaneous tracheostomy in the ICU have been published [11, 13]. A specific pre-procedure debriefing has been suggested [12] and an institution-specific protocol should be considered to standardize the procedure for the ICU team. Several tracheostomy sizes need to be immediately available. Use of bronchoscopy varies among providers, and no definitive evidence exists that sites the lack of bronchoscopy as a risk factor for complication. However, bronchoscopy is recommended as a means of tracheostomy site determination, guide-wire and dilator placement, and confirmation of the position of the tracheal cannula [11]. It also is reasonable to use the bronchoscope to suction any blood or secretions from the airways following both open and percutaneous procedures.

Endoscopy/Percutaneous Endoscopic Gastrostomy Tube Placement

Endoscopy is performed most commonly as an elective, outpatient procedure. For patients in the ICU, endoscopy may be necessary for urgent or emergent diagnostic purposes (i.e., to look for ischemia or a source of bleeding) and/or for therapeutic reasons (i.e., to stop bleeding or to place a feeding tube). In the ICU, this may be accomplished by a gastroenterologist or a surgeon (intensivist or non-intensivist).

In contrast to the typical tracheostomy patient, the patient undergoing endoscopy may or may not be intubated. Because of this, sedation and airway concerns must be carefully evaluated prior to the procedure. For the non-ventilated patient with known or suspected difficult airway anatomy, elective intubation can be considered. If the decision is made not to intubate, an airway-competent provider should be immediately available. Oxygen saturations and end-tidal CO_2 should be continuously monitored. In addition, the patient should be monitored with frequent or continuous vital signs after the procedure, until he or she has returned to the pre-procedure state.

Anatomic considerations for those potentially undergoing endoscopic gastrostomy placement include obesity and thickness of the abdominal wall, as well as prior surgeries that may alter the position of the stomach, bowel, or liver directly under the anterior abdominal wall. If the patient has had a recent abdominal or chest CT, this should be reviewed to examine the position of the stomach. A pre-procedure abdominal x-ray can give an estimation of the position of the colon in relation to the stomach. If the colon appears to be directly anterior to the stomach, a CT scan may be considered to further evaluate for a window where the stomach can be accessed percutaneously when insufflated.

Advanced planning for non-urgent procedures can help ensure availability of all necessary equipment. Familiarity with the provided equipment will also allow for additional supplies to be ready when needed and testing of the power supply, irrigation, and suctioning capabilities prior to the start of the procedure can help prevent unnecessary prolongation of sedation.

Decompressive Laparotomy/Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is generally defined as intra-abdominal pressure greater than 20 mmHg and abdominal perfusion pressure less than 60 mmHg in the setting of evidence of attributable end-organ dysfunction [14, 15]. In the later stages of ACS, the patient becomes hypotensive and unstable. Emergent decompression of the

abdomen with a laparotomy is the necessary management to restore a patient's hemodynamics and hopefully reverse end-organ dysfunction.

Primary abdominal compartment syndrome occurs when an intra-abdominal pathology directly causes the intra-abdominal hypertension, i.e., retroperitoneal bleeding, bowel obstruction, or abdominal trauma. Secondary ACS occurs when massive fluid resuscitation in the setting of generalized capillary leak leads to fluid accumulation in tissues and subsequent intra-abdominal hypertension. Chronic ACS relates to more indolent conditions such as cirrhosis with ascites or an enlarging intra-abdominal mass [16].

Signs and symptoms include abdominal distention, increased airway pressures in ventilated patients, decreased urine output, and increased bladder pressure. Hypotension related to decreased venous return is a late sign that requires urgent surgical intervention in addition to resuscitation with fluids and pressor support. If an operating room is available and the patient can be safely transferred, the patient may undergo laparotomy in the standard fashion in the OR. If the patient is too unstable for transfer, an emergent bedside decompressive laparotomy may be the preferred and safer option.

In this situation, opening the abdominal fascia may be all that is required to improve the hemodynamics of the patient. A temporary abdominal closure dressing can be placed, and supportive care continued in the same location.

Abdominal Washouts/Dressing Changes

Abdomens that remain open with temporary abdominal closure dressings often require additional exploration or washouts prior to definitive closure. Concern for bowel ischemia or bleeding and intra-abdominal abscesses or gross contamination related to hollow viscus injury may warrant further washout within a short period of time to ensure viability, hemostasis, and/or source control. Under sterile conditions in the ICU, the dressing can be removed, the abdomen irrigated and suctioned, intra-abdominal contents examined, and a new temporary closure dressing applied if needed.

Extreme caution should be employed when re-exploration involves removal of packing placed previously for hemorrhage control. For instance, removal of liver packing in the ICU is not recommended. Laparotomy pads can be used for repacking and electrocautery may be available for unexpected bleeding, but major hemorrhage is generally more suitable for management in a traditional operating room where lighting and exposure are improved and a cell saver can be used. However, bowel resection, bowel anastomosis, abscess drainage, and stoma creation have been safely performed in the ICU setting [9, 10].

Re-exploration for purposes of placing or advancing a Wittmann Patch or performing another gradual closure method can also be undertaken at the bedside [10]. Care should be taken to monitor peak airway pressures and other perfusion indicators to ensure that the patch does not cause intra-abdominal hypertension or ACS. Definitive primary closure of abdominal fascia can also be safe and feasible at the bedside, though clinician comfort determines if it is more appropriate in the traditional OR, where lighting, sterility, and instrument and sponge counts are optimized. An abdominal x-ray and/or confirmatory sponge and instrument detection technology must be utilized at the time of definitive closure, regardless of procedure location, to confirm that no foreign bodies remain.

Extremity Wound Explorations

Extensive degloving injuries, necrotizing soft tissue infections, and fasciotomies result in large, painful wounds. The frequent dressing changes that are necessary to facilitate wound healing can be difficult to perform without moderate or deep sedation or even general anesthesia at times. Daily transport to the OR and repeated interruptions in nutrition while waiting for OR availability is avoided by performing these procedures in the ICU. Partial or complete fasciotomy closure can also be achieved in this setting.

Conclusion

Operating in the ICU provides an efficient and safe alternative to the operating room in hemodynamically stable patients undergoing relatively straightforward procedures. For hemodynamically unstable patients undergoing emergent procedures, operating in the ICU can be a safer option than undertaking the risks of transferring the patient. A wide variety of procedures are feasible in the ICU, though surgeries with expected major blood loss, those with need for exceptionally good lighting or extensive exposure, and prolonged procedures are more appropriate for the traditional operating room. Careful organization and preparation are crucial to ensure patient and clinician safety in both elective and emergent procedures.

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Anesthesia-Related Issues in the ICU

47

Mark-Alan Pizzini and Benjamin L. Rubin

Airway Management in the ICU

The need to assess and manage airway issues is not an infrequent event in the ICU. Acute or progressive respiratory distress or respiratory failure in the decompensating patient often requires special equipment, medications, skills, and knowledge to successfully manage. The most common events that require intervention include cardiac or pulmonary events, bleeding, airway edema, hypoventilation, and hypercapnia. These events often require different skills and equipment in the treatment of the incident.

ICU patients frequently have underlying pulmonary concerns, including restrictive disease, obstructive disease, or combination of these. In addition, many have cardiac diseases, metabolic abnormalities, infections, or sepses, as well as structural or mechanical concerns that can lead to respiratory compromise. Many postoperative patients have issues linked to a combination of the above mentioned states in addition to the inherent complications found in the surgical population.

The first priority for a provider called to make an evaluation of a patient in respiratory distress in the ICU is to make an assessment of the patient's current condition to understand what is required to secure the airway during the critical event. A brief history, an airway exam and, if available, past intubation history, can be invaluable when selecting the method and medications to assist in intubation. Difficult airway letters and signs, including med-alert bracelets, are becoming more utilized in the hospital setting to quickly identify patients with known complex airway issues, including both ventilation and intubation challenges [1]. Postoperative patients can also be difficult to ventilate or intubate as a secondary effect due to the nature of their surgical procedures, such as ENT or head and neck surgery patients, and edema from traumatic intubations or fluid resuscitation.

Many ORs, ICUs, and ERs have created difficult airway carts (DAC) [2] to assist in emergency airway situations. Porhomayon et al. evaluated the contents of DACs through a survey of 180 ICUs and summarized the DAC contents, as a percentage of DACs containing the indicated items. Of note, only straight and curved blades and a stylet were found in 100 % of the carts surveyed. With the widespread use of alternate intubation and ventilation methods such as video laryngoscopy, fiber-optic laryngoscopy, and LMAs, the contents of the DAC can be cost prohibitive. However, the safety and increased success of securing the airway in patients with difficult airways must be taken into account [3].

In the anesthesia literature, it has been cited that impossible mask ventilation is a rare but serious event, most often associated with previous neck irradiation [4]. Difficult intubations have been cited to occur in approximately 10.3 % [5] of the population in emergent situations. Certainly the most challenging and potential catastrophic situations arise when the practitioner can neither ventilate nor intubate the patient. This has been found to occur in 0.4 % of the cases [4]. There are several variables that have been evaluated and shown to increase the likelihood that a particular patient may be both difficult to ventilate and intubate. An assessment of the variables that can lead to a difficult mask ventilation and difficult intubation should be weighed when deciding on a course of action:

1. Age >46 years old
2. BMI >30
3. Male

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4. Mallampati classification 3 or 4
5. Neck mass and radiation
6. Limited thyromental distance
7. OSA
8. Teeth
9. Beard
10. Thick neck
11. Limited cervical spine mobility
12. Limited jaw protrusion

Following the assessment, the first task in an airway emergency is to maintain the oxygenation of the patient. If there are spontaneous respirations, supplemental oxygen is provided. If there are no respiratory efforts, bag-assisted mask ventilation should be attempted. It is important to note that oxygenation and ventilation are different entities. While ventilation affects PaCO2, oxygenation (supplemental O2) affects PaO2. Providing oxygen through a small caliber orifice such as a percutaneous cricothyroidotomy or Cook catheter can provide lifesaving oxygenation in the absence of meaningful ventilation while awaiting alternative means of securing the airway or obtaining a surgical airway.

When bag and mask attempts prove unsuccessful, the ASA guidelines for difficult intubation (Fig. 47.1) indicate that the use of an LMA is appropriate. In the care of the ICU patient, several pathways in the algorithm are often unavailable, including the option of waking the patient. However, it is useful to be familiar with the algorithm for managing the difficult airway.

Laryngeal Mask Airway (LMA)

LMAs have increasingly been recognized as a useful and lifesaving tool for supraglottic airway (SGA) management, and they are part of the ASA difficult airway algorithm in SGA use. When a patient cannot be mask ventilated adequately, LMAs or other SGAs can be attempted to establish ventilation. There are several different LMAs that have proven value in difficult airway management and come in many different styles, sizes, and functions, including the Fastrach [7], ProSeal [8, 9], LMA Classic [9], and CTrach [10, 11] among others. These LMAs are conducive to allowing the passage of an endotracheal tube to secure the airway by passing a fiber-optic bronchoscope, gum-elastic bougie, guide wire exchange catheter, or intubation catheter through the LMA into the trachea [9].

Standard Intubation

Standard intubation utilizes one of several different laryngoscope blades to assist in visualization and placement of an endotracheal tube, which can be performed under general anesthesia, under sedation, or while the patient is awake. The most common styles of blades are the curved Macintosh blade and the straight Miller blades, both of which come in a variety of sizes depending on patient variables such as sex, height, and mento-hyoid distance. Used in the hospital setting, the success rate of intubations approaches 97–99 % [1] overall. The rate of first attempts is between 87.4 % [3] and 91 % [1]. There is a growing body of citations that supports utilizing a video laryngoscope for first attempts in the ICU setting [12]. When difficulty is encountered with the standard intubating blades, most practitioners opt for video laryngoscopes.

Video Laryngoscopy

Video laryngoscopes are laryngoscope blades with fiber-optic video capability, usually attached to a built-in or free-standing monitor. The most common brands are the C-Mac blade and the GlideScope. These tools have become increasingly utilized as a primary mechanism for intubation due to the increased success rate with practitioners of varying experience levels. It was found that the use of video laryngoscope improves first attempt and overall success rate in urgent and emergent intubations while lowering the esophageal intubation rate [12–15]. When neither traditional nor video laryngoscope attempts are successful in securing tracheal intubation, the practitioner should consider either a cricothyrotomy, surgical airway, or fiber-optic bronchoscopy-assisted intubation.

Fiber-Optic Bronchoscopy-Assisted Intubation

Fiber-optic bronchoscopy intubation techniques, using a pediatric or adult fiber-optic bronchoscope, can be employed in either an awake or asleep patient, orally or nasally. In the ICU, when a difficult airway is suspected that will require the use of this device, it is most common to perform this technique, while the patient is spontaneously breathing [16]. Airway topicalization with local anesthetics and sedation, if medically appropriate, will make the procedure more comfortable for the patient and easier for the practitioner. The nerves required to anesthetize to insure ease of intubation include the terminal branches of the ophthalmic and maxillary divisions of the trigeminal nerve; the glossopharyngeal nerve, which supplies the oropharynx and posterior third of the tongue; and the vagus nerve, which is responsible for the epiglottis and distal airways [16].

The most common medication used for topicalization is lidocaine, an aminoamide local anesthetic, which is metabolized in the liver. It is available in a variety of concentrations from 0.5 to 5 % and can be delivered by many different mechanisms including nebulization, direct application, and injection.

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DIFFICULT AIRWAY ALGORITHM

1. Assess the likelihood and clinical impact of basic management problems:

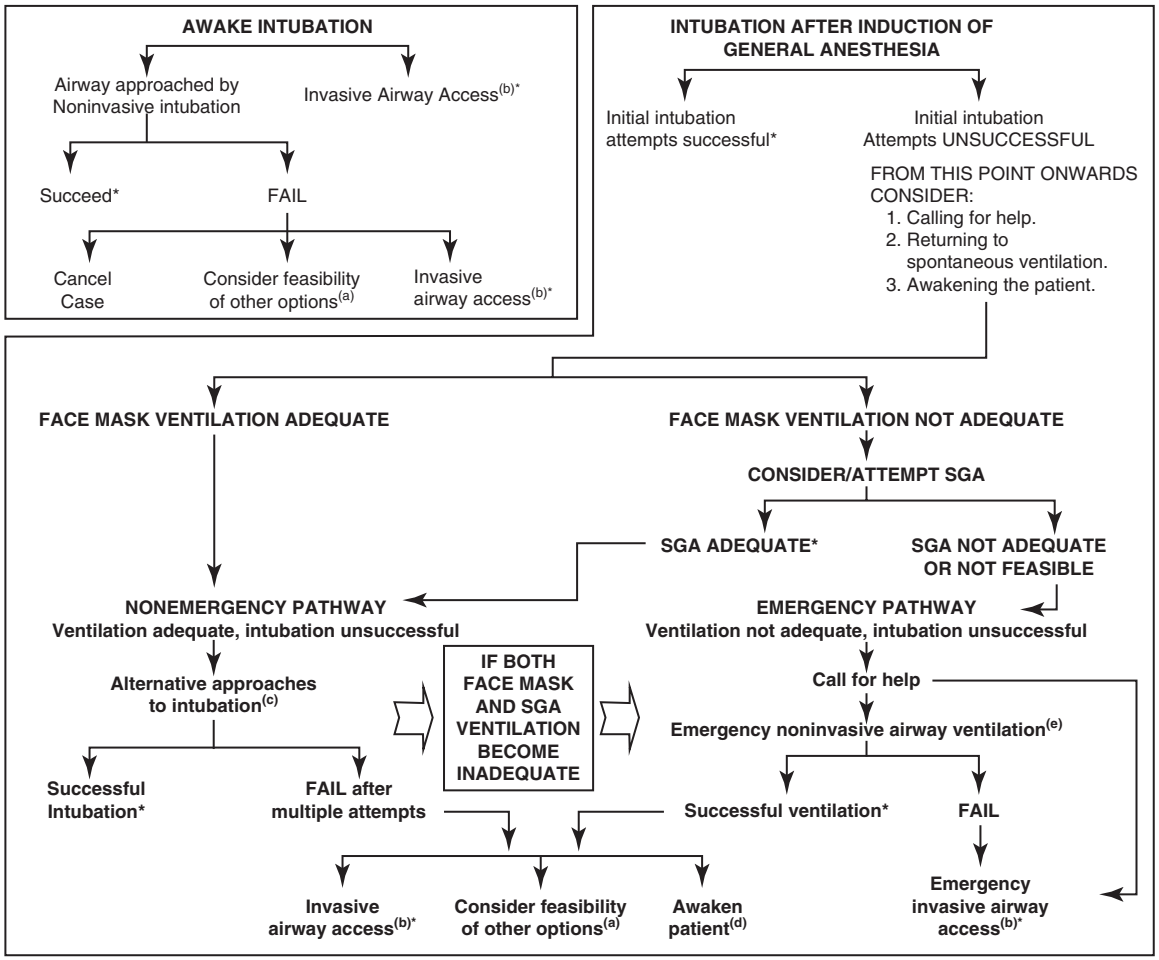
- **Difficulty with patient cooperation or consent**
- **Difficult mask ventilation**
- **Difficult supraglottic airway placement**
- **Difficult laryngoscopy**
- **Difficult intubation**
- **Difficult surgical airway access**

2. Actively pursue opportunities to deliver supplemental oxygen throughout the prcoess of difficult airway management.

3. Consider the relative merits and feasibility of basic management choices:

- **Awake intubation *vs.* intubation after induction of general anesthesia**
- **Non-invasive technique *vs* invasive techniques for the initial approach to intubation**
- **Video-assisted laryngoscopy as an initial approach to intubation**
- **Preservation *vs* ablation of spontaneous ventilation**

4. Develop primary and alternative strategies:



***Confirm ventilation, tracheal intubation, or SGA placement with exhaled CO_2.**

a. Other options include (but are not limited to): surgery utilizing face mask or supraglottic airway (SGA) anesthesia (e.g., LMA, ILMA, laryngeal tube), local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway

b. Invasive airway access includes surgical or percutaneous airway, jet ventilation, and retrograde intubation.

c. Alternative difficult intubation approaches include (but are not limited to): video-assisted laryngoscopy, alternative laryngoscope blades, SGA (e.g., LMA or ILMA) as an intubation conduit, intubating stylet or tube changer, light wand, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Emergency non-invasive airway ventilation consists of a SGA.

Fig. 47.1 Difficult airway algorithm (From Hagberg [6]. Used with permission)

Aminoester local anesthetics such as benzocaine and procaine, which are hydrolyzed by plasmacholinesterase, have fallen out of favor due to potential allergic reactions [17]. In addition, there are many citations of benzocaine topical associated with a significant incidence of methemoglobinemia [18–20].

If nonsurgical mechanisms of securing the airway fail and the patient cannot be ventilated, the practitioner can opt for a surgical airway.

Surgical Airway

The emergent surgical airway includes cricothyrotomy and tracheotomy. Selection between the two is practitioner dependent; indeed, some surgeons can perform a tracheotomy in a rapid manner. For most nonoperative practitioners in the ICU, however, a cricothyrotomy can be life saving. There are three main approaches to cricothyrotomy: needle cricothyrotomy, surgical cricothyrotomy, and percutaneous cricothyrotomy [21]. The only true contraindication to cricothyrotomy is age less than 10 years old. Since ventilation is sometimes inadequate with a cricothyrotomy and carbon dioxide can accumulate, controlled conversion to a tracheostomy should occur post-procedure.

That stated, a study looking at the emergency airway choices at level I trauma centers favored tracheotomies over cricothyrotomy nearly 2:1 [22] Since trauma centers do staff surgeons trained in tracheostomy placement, clearly skill set plays a strong role in selection.

Medications

Endotracheal intubation can be a high-risk procedure in the ICU, with up to 40% of cases associated with marked hypoxemia or hypotension [23]. Selection of induction agents, sedatives, narcotics, and muscle relaxants for use in ICU patient undergoing either intubation or an ICU-based procedure is a multifactorial decision, which can affect the outcome of the patient. Indeed, procedures in the ICU are becoming more commonplace [17]. There are many criteria that must be evaluated when choosing which medications to use, including duration of action required, comorbid medical problems, urgency of the procedure, as well as laboratory values and current patient condition. Severe cardiovascular collapse can be a life-threatening result of urgent or emergent intubations in the ICU [24].

Muscle Relaxants

Selection of a muscle relaxant, whether a non-depolarizing or depolarizing relaxant, must take into consideration the urgency of the intubation, NPO status, comorbid conditions, laboratory values, and airway assessment. The use of paralytics has been shown to be of benefit in intubations [24] with a decrease in complications [24]. In addition, there are many additional medications that can facilitate intubations in the ICU as well as make the patient more comfortable during the procedure.

Succinylcholine

Succinylcholine is a rapid onset, short duration of action depolarizing quaternary ammonium muscle relaxant. Succinylcholine binds to nicotinic receptors at the neuromuscular junction, causing depolarization and inhibition of neuromuscular transmission. It is primarily used to quickly secure intubating conditions, most often in conjunction with an induction agent such as propofol, ketamine, or etomidate. Succinylcholine increases the potassium 0.5–1.0 mEq/L in normal patients. This increase, however, can be life threatening when the baseline potassium is elevated or when secondary conditions exist such as significant burns, neurological or spinal cord injury, myopathies, and long-term immobility. It was found that the risk of acute hyperkalemia is extremely significant after a prolonged ICU stay [25, 26]. Succinylcholine, used in doses of 1–1.5 mg/kg IV, provides muscle relaxation within 30–60 s and lasts less than 10 min. The duration of action can be prolonged in patients with genetic decreases in pseudocholinesterase, pregnancy, liver disease, and renal failure [27]. In addition, succinylcholine is contraindicated in patients with a history of malignant hyperthermia. In cases where succinylcholine is contraindicated or carries a high risk of an adverse event, non-depolarizing relaxants can be utilized.

Non-depolarizing Agents

Non-depolarizing muscle relaxants competitively antagonize the action of acetylcholine in the postsynaptic nicotinic receptor [28]. Complete neuromuscular block requires at least 92% of the receptors to be occupied. The three more commonly used non-depolarizing agents are vecuronium, rocuronium, and cisatracurium.

Vecuronium

Vecuronium is an intermediate acting amino-steroid neuromuscular blocking agent commonly used in both the operating room and the ICU. The normal intubating dose of vecuronium is 0.1 mg/kg, which provides the onset of intubating conditions in approximately 3 min. It is useful in the ICU, as it has no direct effect on the cardiovascular system and it does not release histamine. In patients in which succinylcholine is contraindicated, vecuronium can be used. Despite the prolonged time to intubation with standard doses, rapid sequence inductions utilizing vecuronium can be safely performed using a 0.01–0.015 mg/kg priming dose followed by 0.1 mg/kg total dose, which can provide excellent intubating conditions in a similar time to succinylcholine 1.5 mg/kg [29, 30]. The cardiovascular stability of vecuronium is also an advantage in

unstable ICU patients. It primarily undergoes liver and biliary excretion; however, one of its metabolites, 3-desacetyl vecuronium, is active and can accumulate in patients with kidney disease [31].

Rocuronium

Rocuronium is an intermediate acting amino-steroid neuromuscular blocking agent which has a more rapid onset of action compared to vecuronium and cisatracurium. The normal intubating dose is 0.6 mg/kg and has an onset of intubating conditions of approximately 90 s. When used for rapid sequence inductions, a dose of 0.9–1.2 mg/kg provides intubating conditions similar to succinylcholine [32] and is an acceptable alternative [33].

Cisatracurium

Cisatracurium is an intermediate acting benzylisoquinolinium neuromuscular blocking agent. The standard intubating dose is 0.1–0.15 mg/kg, with an onset of approximately 3 min [34]. It is metabolized by Hoffman degradation and therefore is not dependent on kidney or liver function, which can be an important consideration in the ICU setting. It has a prolonged onset to neuromuscular block compared to rocuronium and is not ideal for rapid sequence inductions.

Induction Agents

Propofol

Propofol is an alkylphenol compound believed to produce sedative/anesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABA receptors. It has a quick onset and short duration of action, with an induction dose of 1.5–2.5 mg/kg; this dose may need to be significantly reduced in elderly or acutely ill ICU patients. It has dose dependent cardiac and pulmonary depressant effect, which can be especially significant in patients with cardiac disease or peripheral vascular compromise due to sepsis or other disease states [34]. In ventilated patients, the use of propofol has been demonstrated to decrease mortality compared to benzodiazepines alone [27] and was a safe treatment in conjunction with midazolam for sedation in critically ill, ventilated patients [35]. While physiologic complications can occur with propofol infusion including hypertriglyceridemia [36] and propofol infusion syndrome [37], single intubating doses for securing an airway or limited infusions for a procedure are unlikely to cause these complications [38].

Etomidate

Etomidate is a carboxylated imidazole that is known to depress the reticular activating system acting on gamma-butyric acid (GABA) receptors, reducing neuroexcitation [34]. Etomidate has a relatively quick onset of action at induction doses of 0.2–0.4 mg/kg, and there is minimal effect on the cardiovascular system. It is often used in severe sepsis and septic shock patients and in patients with compromised cardiovascular function. While the use of etomidate is associated with suppression of adrenal gland function, and some studies suggest there may be an increased risk [39, 40] with its use, most studies have concluded that there is no difference in mortality between etomidate and non-etomidate induction in critically ill, trauma, and septic patients [41–44]. Etomidate's ability to maintain relative hemodynamic stability in critically ill patients makes this medication a good choice for induction agents in the ICU setting.

Ketamine

Ketamine is an arylcyclohexylamine that is chemically similar to phencyclidine and produces a "dissociative anesthesia," marked by both analgesia and amnesia [34]. Ketamine acts on the central nervous system, its effects mediated by noncompetitive antagonism at the NMDA receptor Ca^{2+} channel. The cardiovascular effects of ketamine are due to a centrally mediated sympathetic response, which include tachycardia, increased blood pressure, and increased cardiac output. Ketamine has minimal effects on the respiratory drive but does cause relaxation of the bronchial smooth muscle; this is balanced by an increase in salivary secretions [45]. Induction doses of ketamine are 1–2 mg/kg in normal adults and do not cause loss of protective airway reflexes in most adults. Due to its unwanted psychomimetic effects, ketamine is often used with benzodiazepines or other agents. Ketamine alone [46] or the combination of ketamine, propofol, and midazolam co-induction has successfully been used as a substitute for etomidate in hemodynamically unstable patients [45], and first-pass success in rapid sequence inductions in the ED with ketamine has been shown to be equivalent to etomidate [47].

Sedatives and Analgesics

Sedatives and analgesics are often used in combination to obtain the desired effects for procedures or as an adjuvant for intubation in the ICU. Some of the most common medications utilized in the ICU include fentanyl, midazolam, and dexmedetomidine.

Fentanyl is a synthetic short-acting narcotic noted for its cardiovascular stability, which can be advantageous in the hemodynamically compromised ICU patient [48]. Fentanyl is highly lipophilic, with a rapid onset of action; however, the maximal analgesic and respiratory depressant effects may take several minutes and can last up to 30–60 min [49]. While opioids, such as fentanyl, provide pain control and decrease the airway reflexes, they have side effects including sedation

and respiratory depression, which can be potentiated by other medications, and do not reliably provide amnesia.

Midazolam is a short-acting benzodiazepine and is the most commonly used sedative agents in the ICU [48]. Sedation in adult patients occurs within 3–5 min after intravenous (IV) injection; this can be affected by total dose and narcotic co-medication [50]. While benzodiazepines, such as midazolam, provide sedation and amnesia, they do not provide pain control.

More recently, medications such as dexmedetomidine, an alpha2-adrenoreceptor agonist, have been utilized to provide sedation in the ICU setting. Dexmedetomidine is an α2-adrenoceptor agonist used for sedation in the ICU. It has the benefit of maintaining spontaneous respirations in patients with a lower risk of neurocognitive dysfunction in perioperative and ICU sedation [51]. When compared to propofol for sedation in the ICU, it was found that dexmedetomidine may be beneficial compared to propofol in terms not only of risk of delirium but also in length of ICU stay [52] and in cost, most likely due to decreased time to extubation [53]. Dexmedetomidine can be effectively used as a sedative in the ICU for procedures and intubations alone or with other agents. Sedatives and analgesics are often used in conjunction with hypnotic agents such as propofol to produce reliable comfort measures in intubated ICU patients.

Postsurgical Pain Management in the Intensive Care Unit

Postsurgical pain management in the intensive care unit is a broad and complex topic and involves an understanding of multimodal analgesia, opioid pharmacology, and regional analgesia as they pertain to a specific surgical procedure in the context of a given patient's disease state and medical comorbidities. Addressing this topic comprehensively is not within the scope of this chapter, as pain management is its own medical subspecialty, and the entire textbooks and journals have been published on the subject. The purpose of this section of the chapter is to provide a general overview for two commonly employed postsurgical pain management modalities: epidural analgesia and patient-controlled analgesia. A hospital's anesthesiology service is frequently consulted postoperatively regarding these two topics, so it is appropriate to discuss them in the context of surgical critical care.

Epidural Analgesia

An epidural catheter, most simply put, is a catheter through which pain medications are delivered into the epidural space in an attempt to provide dense analgesia for certain surgical procedures or for patients with certain nonsurgically related pain conditions. Epidural catheters are sometimes placed preoperatively and continued postoperatively or placed postoperatively. Epidural catheters may also be placed in patients who have not undergone a surgical procedure.

This section will address the following topics:

- General overview
- Indications and contraindications to epidural catheter placement
- Risks of epidural catheters

General Overview

The term "epidural" is frequently used by medical and nonmedical personnel, and it can refer to a number of different procedures, all of which have different indications and purposes, but they all refer, ultimately, to a medication injected into the epidural space outside the spinal cord. The epidural space is the space that lies outside the dura mater of the spinal cord and has the following boundaries: foramen magnum rostrally, sacrococcygeal ligament caudally, posterior longitudinal ligament anteriorly, ligamentum flavum and vertebral lamina posteriorly, and vertebral pedicles laterally [54]. This space is entered by placing a needle through the skin using either anatomical landmarks or radiological guidance. Once the needle enters the epidural space, medications are injected either directly through the needle and the needle is removed (this technique is commonly referred to as a "single-shot epidural") or a specially designed catheter is threaded through the needle, the needle is removed, and the catheter is left in the epidural space (this technique is commonly referred to as a "continuous epidural"). The latter technique allows for infusions or multiple doses of medications to be delivered into the epidural space.

The epidural space may be cannulated anywhere along the length of the spinal cord including the sacral region (via the sacral hiatus—this technique is referred to as a "caudal epidural anesthetic"), lumbar region, thoracic region, or cervical region. For the purposes of this chapter, only lumbar and thoracic epidural cannulation sites will be discussed, because the sacral hiatus approach to the epidural space is used primarily in children and will be seldom seen in adult ICU patients, and the cervical approach to the epidural space is used primarily by pain management physicians treating spinal pain disorders and will also likely not routinely be encountered in adult ICU patient. The principles in this chapter will focus primarily on lumbar and thoracic continuous epidural catheters, as "single-shot epidurals" are most frequently performed in the operating room, and there is no catheter or infusion to manage postoperatively.

Indications and Contraindications to Epidural Catheter Placement

No absolute indications for epidural analgesia exist, and when epidural analgesia should be employed depends on the type of surgery or injury, the patient, and the infrastructure present to manage the epidural. The benefits of epidural analgesia and which types of surgery warrant its employment are still the subject of much debate. Pain control after intra-abdominal surgery, for example, is typically addressed with intravenous opioid patient-controlled analgesia or continuous epidural analgesia. The technique that has fewer adverse effects and better pain control is unclear [55]. Liu et al. demonstrated that "epidural analgesia with bupivacaine and morphine provided the best balance of analgesia and side effects while accelerating postoperative recovery of gastrointestinal function and time to fulfillment of discharge criteria after colon surgery in relatively healthy patients within the context of a multimodal recovery program" [56].

Besides surgical, another indication for epidural analgesia in the ICU setting is for patients who present with rib fractures. Bulger et al. performed a prospective, randomized trial of epidural analgesia versus IV opioids for the management of chest wall pain after rib fractures. As rib fractures are associated with significant pulmonary morbidity, they hypothesized that epidural analgesia would provide superior pain relief to IV opioids, and the risk of pneumonia would be reduced. They concluded that "the use of epidural analgesia is limited in the trauma population due to numerous exclusion criteria. However, when feasible, epidural analgesia is associated with a decrease in the rate of nosocomial pneumonia and a shorter duration of mechanical ventilation after rib fractures" [57].

While epidural analgesia is considered the gold standard for post-thoractomy patients, for example, it is associated with potentially serious risks (discussed later), certain adverse effects, and a number of absolute and relative contraindications. Some of the adverse effects include, but are not limited to, hypotension, urinary retention, nausea, vomiting, pruritus, and motor weakness—depending on the catheter level and concentration of solution employed [58]. Certain situations contraindicate the placement of an epidural catheter. Since an epidural is an elective procedure, patient refusal is an absolute contraindication. Examples of other contraindications include infection at the injection site, sepsis, coagulopathy (discussed later), indeterminate neurologic disease, hypovolemia (relative contraindication), and elevated intracranial pressure [59]. Patients who are on anticoagulant or antiplatelet drugs may or may not be a candidate for epidural analgesia, depending on which drugs they are taking, how long the drugs have been discontinued, and how soon after surgery the drugs need to be restarted (more on this topic below). Additionally, the risks of epidural needle and catheter placement need to be considered: spinal cord hematoma, dural perforation and possible post-dural puncture headache, spinal/epidural infection, spinal/epidural abscess, and spinal cord trauma [58]. The possible adverse effects of epidural analgesia also need to be considered: hypotension, urinary retention and possible prolonged bladder catheterization, nausea, vomiting, and pruritus [58]. Treatment of these adverse effects is discussed below.

Risks of Epidural Catheters

The risks of epidural analgesia may arise from placement of catheter, the act of the having the catheter indwelling, and removal of the catheter.

The ICU practitioner who takes care of patients receiving epidural analgesia should be familiar with the following potential complications of epidural analgesia:

- Infection
- Bleeding
- Post-dural puncture headache
- Epidural drug toxicity

These four topics are discussed below.

Infection

Any time an instrument breaches the protective barrier provided by human skin, foreign pathogens can be introduced, and these pathogens can overwhelm the immune system's ability to destroy them, which can lead to infection of the skin or anatomical structures below. This can be particularly dangerous when dealing with central (i.e., spinal cord, meninges, etc.) and peripheral nervous structures (i.e., nerve roots) in a confined space with little compliance. When an epidural catheter placement procedure is performed, a needle is introduced through the skin and advanced into the epidural space adjacent to the dural mater of the spinal cord and exiting nerve roots, and a catheter is then positioned in this location. This means a needle (and later a catheter) passes through the skin, subcutaneous soft tissue, supraspinous ligament, interspinous ligament, ligamentum flavum, and epidural space, which leaves any of these structures vulnerable to infection.

Despite adherence to aseptic technique during epidural catheter placement and management postoperatively, infections do occur but, fortunately, rarely. According Grewal et. al., estimates of the rate of epidural abscess after central nerve block vary from 1:1000 to 1:100,000, and immunocompromised patients are at higher risk. Additionally, Grewal et. al. explain that the early signs and symptoms of epidural abscess may be "vague," and the "'classic' triad of back pain, fever and variable neurological deficit occurred in only 13 % of patients by the time of diagnosis, and contributed to a diagnostic delay in 75 %" [60]. The ICU practitioner must maintain a high index of suspicion, especially in

immunocompromised patients, to diagnose an epidural abscess. Delay in diagnosis and/or treatment can have devastating consequences including irreversible neurological damage or death. With an epidural abscess, fever usually appears first, followed by back pain. Neurological deficit usually occurs late [60]. Local tenderness, with or without neurological deficit, is the usual physical finding. If an epidural abscess is suspected, the imaging modality of choice is a gadolinium-enhanced MRI, and this should be performed immediately, along with obtaining a neurosurgical consultation, as the treatment is surgical decompression and antibiotics [61].

Bleeding

Another feared catastrophic complication of epidural catheter placement is the development of an epidural hematoma. Similar to an epidural abscess, accumulation of a foreign substance (in this case blood) in the epidural space can lead to irreversible neurological damage (e.g., paralysis), as the neural structures located in and adjacent to the epidural space are sensitive to damage by compressive effect. Fortunately, in a patient who is not anticoagulated, epidural hematoma is rare complication (1:150,000) of epidural cannulation. For patients who are on anticoagulation, the risk of epidural hematoma can increase dramatically with epidural analgesia. For example, in the presence of low molecular weight heparin, some sources cite the rate as high as 1:3000 [62].

The ICU practitioner taking care of patients receiving epidural analgesia needs to be familiar with not only diagnosis and treatment of epidural hematomas (discussed below) but also with safe handling of epidural catheters and safe medication administration guidelines in patients receiving epidural analgesia, specifically pertaining to administration of medications with anticoagulant or antiplatelet effects.

An epidural hematoma may develop not only as a result of epidural catheter placement but also as a result of epidural catheter removal, as the act of catheter manipulation can precipitate a hematoma as well. Since the consequences of an epidural hematoma can be so severe, the American Society of Regional Anesthesia and Pain Medicine (ASRA) continues to publish updated guidelines addressing timing of epidural catheter placement and catheter manipulation/removal with respect to anticoagulant/antiplatelet drugs as well as which medications are safe versus unsafe to administer in a patient with an indwelling epidural catheter. The guidelines also address timing of administration of anticoagulant/antiplatelet drugs once an epidural catheter is removed. As these guidelines are extensive and change regularly as new drugs come on the market, it is outside the scope of this chapter to discuss these guidelines. That being said, however, any ICU practitioner who treats patients receiving epidural analgesia should familiarize him/herself with the ASRA guidelines which are available on ASRA's website.

Finally, diagnosis of epidural hematoma relies on clinical suspicion, physical examination, and radiological imaging. Classically, epidural hematomas cause radicular pain, motor impairment, sensory loss, and urinary retention [63]. Recurrence of motor block or prolonged block in patients at risk for epidural hematoma should prompt immediate workup for epidural hematoma [64]. The diagnostic modality of choice is MRI [65], and if positive for epidural hematoma, a neurosurgery consultation should be obtained immediately for evaluation for decompressive laminectomy. The signs and symptoms of epidural abscess versus epidural hematoma can be similar, but both processes are evaluated with MRI. One distinguishing feature is the timeline: The typical timeline for development of an epidural hematoma is hours (up to 24 h) after placement, manipulation, or removal of the catheter [65], whereas the timeline for development of symptoms with an epidural abscess is typically days (median 5 days) after epidural catheter placement [66].

Post-dural Puncture Headache

Post-dural puncture headache (PDPH) is a specific type of headache that can occur after puncture of the dura mater during employment of epidural analgesia. Whereas the dura mater is punctured intentionally during a lumbar puncture for cerebrospinal fluid collection or during placement of a spinal block, the dura mater is not routinely punctured intentionally during employment of epidural analgesia (unless a combined spinal-epidural block is placed—which is outside the scope of this chapter). When the dura mater of the spinal cord is punctured unintentionally during introduction of an epidural needle into the epidural space, this is termed *unintended dural puncture* (UDP). This happens because the epidural needle travels through the epidural space and continues on through the dura mater. The incidence of UDP with epidural catheter placement is cited to be between 0.19 and 3.6 %. Once the UDP occurs, the incidence of PDPH is cited to be 88 % with a 16-gauge epidural needle and 64 % with an 18-gauge epidural needle [67].

PDPH is relatively easy to diagnose, because it typically presents within 48 h of dural puncture as a frontal, frontotemporal, or occipital headache, which is worsened by standing or sitting and improved by lying down or assuming the decubitus position. Patients may also present with nausea and vomiting, photophobia, diplopia (PDPH can cause a CN VI palsy), tinnitus, and/or hyperacusis [68].

Treatment of PDPH initially focuses on hydration, as dehydration should be avoided in a patient with PDPH. Pharmacotherapy can be tried. Oral caffeine has shown some effectiveness, and drugs like cosyntropin (caution in diabetics) and sumatriptan have been proposed, but there is a lack of conclusive evidence of their effectiveness [69]. Autologous epidural blood patch remains the most effective technique to relieve PDPH with a success rate

quoted at over 95 % [68]. This procedure was performed by the Anesthesia Service in many institutions and involves entering the epidural space with an epidural needle and injecting 10–20 mL of autologous blood drawn from a peripheral vein. Relief is usually instantaneous.

Epidural Drug Toxicity

In most circumstances, epidural analgesia in the ICU setting will be provided via infusion of local anesthetic, opioid, or a combination of both through the epidural catheter. As such, the ICU practitioner must be familiar with local anesthetic toxicity and opioid toxicity. Both are discussed below:

Local anesthetic toxicity In short, local anesthetic toxicity can present as adversely affecting the central nervous system (CNS) or cardiovascular system when the threshold of safe local anesthetic dosing is exceeded. Toxicity usually manifests in the CNS before the cardiovascular system, because the CNS is affected at lower concentrations of local anesthetics. The exception is bupivacaine, in which cardiac toxicity may precede CNS toxicity [70]. CNS excitation typically manifests at low-dose toxicity. Classically, perioral paresthesia, metallic taste on the tongue, dizziness, confusion, tinnitus, sedation, and disorientation are the signs and symptoms [71]. As doses escalate, CNS depression typically ensues, manifesting as seizures, respiratory depression/arrest, muscle convulsions, and unconsciousness. As doses escalate into the realm of cardiovascular toxicity, arrhythmias, hypotension, bradycardia, and eventually cardiovascular collapse can be seen.

Benzodiazepines are the treatment of choice for local anesthetic-induced seizures, and neuromuscular blockade may be necessary for refractory seizures. Airway management is important to help prevent hypoxemia with secondary progression to respiratory and ultimately cardiac arrest [72].

Treatment of cardiovascular toxicity initially involves administration of intravenous fluids and small boluses of epinephrine [72]. As the clinical situation becomes less stable, the clinician needs to mobilize extra help and manage the airway, ventilating with 100 % oxygen. Seizure control should be initiated if applicable and preparations made for cardiopulmonary bypass (notify CT surgery within facility or notify nearest facility with cardiopulmonary bypass capabilities). BLS and ACLS protocols should be instituted as applicable with avoidance of vasopressin, beta blockers, calcium channel blockers, and further doses of local anesthetics. Lipid emulsion therapy should be administered in accordance with institutional dosing guidelines (typically a bolus dose of 1.5 ml/kg over 1 min followed by an infusion of 0.25 ml/kg/min with continuation of infusion until circulatory stability is achieved) [73]. According to Ciechanowicz et al. "the current agreed hypothesis for ILE's efficacy in treating cardiotoxicity, although not well defined but supported by in vitro studies, is the formation of a 'lipid sink'; that is, an expanded intravascular lipid phase that acts to absorb the offending circulating lipophilic toxin, hence reducing the unbound free toxin available to bind to the myocardium" [74].

Opioid Toxicity Neuraxial opioid administration, like systemic opioids administration, is associated with undesirable side effects, the most feared being respiratory depression. Morphine, for example, which is a lipophobic opioid, is commonly used in the epidural space. When injected into the epidural space, morphine is absorbed into the systemic circulation demonstrating plasma concentration-time profiles similar to those of its intravenous administration. CSF concentration of morphine demonstrates a biphasic pattern, with an early half-life of 1.5 h and a late-phase half-life of approximately 6 h [75]. This has important ramifications pertaining to the time line of respiratory depression of morphine sulfate. Lipophilic opioids, like fentanyl, however, do not follow the same time line. As a result of the different pharmacokinetics of lipophobic (morphine and hydromorphone) versus lipophilic (fentanyl and sufentanil) opioids in the epidural space, the American Society of Anesthesiologists Task Force has published practice guidelines entitled *Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration*. According to these 2009 guidelines, their recommendations are that "all patients receiving neuroaxial opioids should be monitored for adequacy of ventilation (e.g., respiratory rate, depth of respiration, [assessed without disturbing a sleeping patient], oxygenation, (e.g., pulse oximetry when appropriate), and level of consciousness" [76]. This is a summary, but the complete guidelines can be referenced for more specific recommendations on single-shot injection versus continuous infusion of lipophilic versus lipophobic opioids, as these guidelines are very detailed and outside the scope of the overview this chapter provides. Finally, these guidelines recommend that supplemental oxygen should be available for patients receiving epidural opioids, and reversal agents (e.g., naloxone or naltrexone) should be given to patients experiencing significant respiratory depression after neuraxial opioid administration [77].

Patient-Controlled Analgesia

Patient-controlled analgesia is a system whereby the patient administers pain medication (commonly opioids intravenously) to himself/herself via a computer-controlled pump as opposed to the patient requesting each dose of pain medication from his/her nurse every time the pain reaches an intolerable level. The computer-controlled pump, referred to as a PCA (patient-controlled analgesia) pump, has a number

of parameters that require prescription by the treating physician or care provider. These parameters include initial loading dose, demand dose, lockout interval, and background infusion rate as well as, in some instances, total opioid limits over a prescribed period of time [78]. Patient-controlled analgesia is frequently employed because of its proven advantages over conventional on-demand opioid injections (intramuscular opioids were studied in comparison) [79]. These advantages include superior pain relief, higher patient satisfaction scores, fewer postoperative complications, and less sedation [78]. The success of patient-controlled analgesia depends largely on the PCA pump parameters prescribed. Morphine has been extensively studied, but many PCA regimens include other opioids like hydromorphone or fentanyl.

When selecting an opioid, the PCA prescriber needs to be aware of different opioid potencies and pharmacokinetics. For example, let us say the following regimen of PCA morphine is chosen:

- Initial loading dose: 5 mg
- Demand dose: 2 mg
- Lockout interval: 12 min
- Background infusion: 0 mg/h
- Total 1 h limit: 6 mg

If, for whatever reason, the PCA opioid were changed to hydromorphone, the morphine to hydromorphone potency conversion would have to be performed. Intravenous hydromorphone, depending on the reference, is five to seven times more potent than intravenous morphine. According to Barash et al. 1.5–2 mg hydromorphone IV is equivalent to 10 mg morphine IV [80]. For the sake of this calculation, let's say 1 mg IV hydromorphone = 5 mg IV morphine, the above morphine regimen could reasonably be converted to the following hydromorphone regimen:

- Initial loading dose: 1 mg
- Demand dose: 0.4 mg
- Lockout interval: 12 min
- Background infusion: 0 mg/h
- Total 1 h limit: 1.2 mg

It is reasonable to keep the lockout interval the same between morphine and hydromorphone since the onset of action and peak effect of the drugs are similar (onset time and peak effect IV hydromorphone = 3 min/8 min respectively; onset time and peak effect IV morphine 5 min/10 min, respectively [81]). When selecting lockout interval, consideration should be given to the onset of action and peak effect of the given opioid prescribed. For example, if the peak effect of a given opioid is 15 min, it would not be appropriate to set the lockout interval at 3 min, because the patient might choose to administer another bolus of opioid before the prior bolus has time to take effect. This could lead to inappropriately high plasma concentrations of opioid with subsequent untoward side effects (respiratory depression, nausea, pruritus, etc.).

The decision to prescribe a background infusion should be weighed against the risks. According to Miller et al. "Although routine use of continuous or background infusion as part of intravenous PCA in adult opioid-naïve patients is not recommended, there may be a role for use of a background infusion in opioid-tolerant or pediatric patients" [82]. In opioid-naïve patients, background infusions can lead to excess administration of unnecessary opioids, with undesirable side effects—respiratory depression being the most dangerous. This can occur, especially, when the patient falls asleep. In patients on chronic opioids, for example, it may be reasonable to program a background infusion to supplement their daily dose of opioid in addition to the demand opioid to treat their surgical pain.

With respect to fentanyl as a choice for a PCA opioid, consideration should be given to using this drug only in a setting where intensive care monitoring standards (e.g., continuous pulse oximetry and nursing care readily available) are employed. Some hospitals have policies reflecting fentanyl usage in different patient care locations. Fentanyl is highly lipophilic and has a rapid onset of action (onset time <1 min with a peak effect of 2–3 min), which in turn makes it more apneagenic compared to morphine and hydromorphone [81].

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Incorporating Advanced Practice Practitioners in the ICU

48

Ruth Kleinpell and W. Robert Grabenkort

Overview

The nurse practitioner (NP) and physician assistant (PA) professions began in the 1960s in response to shortages of primary care providers [1]. However, NP and PA roles have expanded over the years to meet patient care needs in specialty and subspecialty areas of practice. Nationally, a growing number of intensive care units (ICUs) are integrating the use of advanced practice providers (APPs) including NPs and PAs as a strategy for meeting ICU workforce needs [2, 3]. Currently, more than 205,000 NPs and more than 93,000 PAs are practicing in the United States [4, 5]. While these numbers are impressive, the number of NPs and PAs educated and trained to work in the ICU is much less, with more than 10,000 NPs certified as acute care NPs and approximately 4,000 working in acute and intensive care units [5–7]. According to the 2013 AAPA Annual Survey Report (15,025 respondents), 2.3 % of the PA respondents listed the ICU as their primary clinical work setting.

NPs and PAs are licensed healthcare professionals with advanced training at the master's or doctoral level in the management of patients with acute and critical illness. NPs and PAs often have similar roles in the ICU focused on patient care management, rounding, obtaining history and performing physical examinations, prescribing, and performing diagnostic, pharmacologic, and therapeutic interventions consistent with education, practice, and state regulations [8, 9]. Role components include performing procedures, among other responsibilities (Table 48.1) [8–11]. Role components also include practice guideline implementation, discharge planning, quality improvement, and research, among other responsibilities such as serving on unit- or hospital-based committees [10, 11].

Data from national surveys on the use of NPs and PAs identifies that an increased utilization in hospital settings has resulted because of increased acuity of hospitalized patients, increased restrictions placed on medical resident work hours, the need for continuity of care, and workforce shortages [10]. In academic medical center settings where the new Accreditation Council for Graduate Medical Education duty hour regulations for physicians in training have been implemented, the integration of NPs and PAs into multidisciplinary provider models has been identified as a solution to the resulting decrease in resident coverage [10].

NPs and PAs in Surgical ICU and Acute Care Settings

The use of NPs and PAs in surgical ICU and postsurgical acute care settings has been reported in a number of studies which have demonstrated the impact of NP and PA care to improved guideline implementation [12]; decreased length of stay and reduced incidence of urinary tract infection (UTI) for trauma patients [13]; decreased length of stay and costs of care for cardiac surgery patients [14]; decreased length of stay, incidence of skin breakdown and UTI, and increased early mobilization for neurosurgical ICU patients [15]; improved throughput and specialty practice roles such as burn ICU [16]; increased surgical volume and decreased surgical mortality with use of PAs in a surgical ICU [17]; decrease in complications and length of stay for trauma patients with use of NP team [18]; decreased time to start postoperative nutrition, decreased length of stay for surgical ICU and trauma patients, and higher rates of postoperative antibiotic discontinuance and controlled 6 am blood glucoses for cardiac surgery patients [19]; and decreased call time, improved communication, and increased satisfaction with use of an NP-led rapid response team [20].

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Table 48.1 Roles of nurse practitioners and physician assistants in the ICU

Patient care management
Rounding with multidisciplinary team
Obtaining history and performing physical examinations
Diagnosing and treating illnesses
Ordering and interpreting tests
Initiating orders, often under protocols
Prescribing and performing diagnostic, pharmacologic, and therapeutic interventions consistent with education, practice, and state regulations
Performing procedures (as credentialed and privileged, such as arterial line insertion, central line placement using ultrasound, suturing, and chest tube insertion)
Assessing and implementing nutrition
Collaborating and consulting with the interdisciplinary team, patient, and family
Assisting in the operating room
Education of staff, patients, and families
Practice guideline implementation
Lead, monitor, and reinforce practice guidelines for intensive care unit patients (i.e., central line insertion procedures, infection prevention measures, stress ulcer prophylaxis, etc.)
Research
Data collection
Enrollment of subjects
Research study management
Quality assurance
Lead quality assurance initiatives such as ventilator-associated pneumonia bundle, sepsis bundle, rapid response team
Communication
Promote and enhance communication with intensive care unit staff, family members, and the multidisciplinary team
Discharge planning
Transfer and referral consultations
Patient and family education regarding anticipated plan of care

Adapted with permission from: Kleinpell et al. [29] (as adapted from Crit Care Med. 2008; 36:2888–2897). Copyright 2012 the Society of Critical Care Medicine

Other studies related to use of NPs/PAs in the ICU identify that their use is a safe adjunct to the ICU team. Costa and colleagues [21] conducted a retrospective review using cohort data from the 2009 to 2010 APACHE (Acute Physiology and Chronic Health Evaluation) clinical information system and an ICU-level survey. Twenty-one ICUs (72.4 %) reported NP/PA participation in direct patient care. Patients in ICUs with NPs/PAs had lower mean Acute Physiology Scores (42.4 vs 46.7, $P < 0.001$) and mechanical ventilation rates (38.8 % vs 44.2 %, $P < 0.001$) than ICUs without NPs/PAs. Unadjusted and risk-adjusted mortality was similar between groups (adjusted relative risk, 1.10; 95 % CI, 0.92–1.31) [21]. The authors conclude that the findings support NP/PA management of critically ill patients.

Practice Considerations

Several issues related to the use of NPs and PAs in the care of surgical patients include adequate orientation and training for specialty roles, obtaining credentialing and privileging for skills and procedures that are within the scope of practice of the NP/PA, and aspects related to workload including provider to patient ratios. Reports of focused orientation models and apprenticeship training provide useful information on specific curriculum, didactic, and procedural training for NPs/PAs in the ICU (Table 48.2) [22]. Ensuring ongoing education and training can be facilitated by providing workshops, simulation experiences, and support for attendance at formal training courses and conferences (Table 48.3) [22–25].

An alternative method for providing additional training in intensive care for NPs and PAs is a postgraduate residency (or fellowship) program. These 1-year programs contain a structured curriculum with rotations through multidisciplinary ICUs [26]. The nationally certified practitioners that complete these programs will continue to need a short, organized orientation tailored to the specific, surgical critical care unit in which they will practice.

Formulating realistic work schedules and manageable workloads is an essential consideration which impacts recruitment, retention, and job satisfactions of NPs and PAs. A recent national study of 222 NPs and 211 PAs working in medical-surgical ICUs (35 %), surgical ICUs (18 %), cardiothoracic ICUs (16 %), neurosurgical ICUs

Table 48.2 Sample training course curriculum for nurse practitioners and physician assistants in the intensive care unit

Admissions and discharges
Admission process
Distinguishing medical and surgical problems and needs
Order writing by protocol
Discharge process
Critical care medicine consults
Clinical
Chest radiograph interpretation
ECG interpretation
Ventilator management
Noninvasive positive-pressure ventilation
Fluids, electrolytes, and acid-base balance; fluid resuscitation
Antimicrobial selection
Multiorgan failure management
Continuous renal replacement therapy
Shock state and vasopressor management
Prophylactic regimens
Acute coronary syndrome and arrhythmia management
Sedation regimens
Delirium management
Common ICU emergencies
Postoperative care and common surgical procedures
Overnight in the ICU
CCM billing
Devices
Venous and arterial catheters
Airways
Chest tubes and drainage systems
What to do when devices fail
CCM information systems
Data-tracking program
Hand-offs between teams and shifts
Care bundles: ventilator-associated pneumonia, central venous catheter
CCM template notes
Consultation/RRT notes
Daily progress notes
Procedure notes

Adapted from Grabenkort et al. [22]
CCM critical care medicine, *NP* nurse practitioner, *ECG* electrocardiograph, *RRT* rapid response team

(10 %), coronary care units (3 %), telemetry/step-down units (4 %), and trauma and burn ICUs (3 %) identified that the mean provider to patient ratios in the ICU was 1–5 (range, 1–3 to 1–8) for both NPs and PAs [27]. In 121 units that integrated fellows and medical residents, the mean NP or PA provider to patient ratio was 1–4 (range, 1–3 to 1–8). In pediatric ICUs, the mean provider to patient ratio was 1–4 (range, 1–3 to 1–8). Several factors were identified that affected provider to patient ratios for NPs and PAs, including patient's severity of illness, number of patients in the unit, number of providers in the unit, and other factors, such as patient's diagnosis, the number of physicians in the unit, the time of day, and the number of medical or surgical residents on service (Fig. 48.1) [27].

Summary

The integration of NPs and PAs on surgical ICU and trauma critical care teams is expanding. At the same time, opportunities exist for utilizing the roles to enhance clinical care practices and improve patient outcomes. A number of studies have demonstrated the value of the NP and PA roles in the ICU. Adequate orientation, training, role expectations, and workload are essential aspects for maximizing the skills,

Table 48.3 Sample surgical critical care educational resources for nurse practitioners and physician assistants

Workshops: chest radiograph and CT scan interpretation, electrocardiogram interpretation
Journal club discussions on common surgical procedures and postoperative management principles
Clinical conferences on specialty care topics such as liver failure, care of bariatric patient, post-transplantation care
Simulation scenarios to refine clinical decision-making skills
ICU procedure workshops: central venous catheterization; arterial catheterization; hemodialysis catheter placement; ultrasound-guided vascular access; endotracheal intubation; bronchoscopy, chest tube placement
Completion of formal coursework: Society of Critical Care Medicine's Fundamentals of Critical Care Support course
Operating room rotation for airway management skills
Communication skills workshop (palliative care discussions, discussing adverse events, prognosis, advanced directives, withdrawal of care)
Website resources: Trauma.org, SCCM.org (Virtual Critical Care Rounds), ESICM.org (Patient Acute Care Training), NEJM.org (instructional videos of procedures), Critical Care Medicine tutorials: www.ccmtutorials.com, among others
Specific examples include:
Interactive case studies http://sprojects.mmi.mcgill.ca/heart/ecghome.html; self-paced tutorials www.cardiologysite.com/html/principles2.html; three-dimensional animation www.stethographics.com/main/physiology_3d_asthma.html; instructional movies http://videos.med.wisc.edu/category.php?categoryid31. Self-assessment quizzes www.skillstat.com/Flash/ACLS_Stat531.html; interactive flashcards www.12leadecg.com/intro/flashcards.aspx; slide kits www.lipidsonline.org/slides/; www.acidbase.org; www.neuroland.org; www.criticalcarenutrition.com
The auscultation assistant: www.wilkes.med.ucla.edu/lungintro.htm
Webinars/podcasts on surgical care topics
Conference attendance at national/international meetings: Society of Critical Care Medicine, Eastern Association of Surgical and Trauma Care, European Society of Intensive Care Medicine, American Thoracic Society, American Association of Nurse Practitioners; American Academy of Physician Assistants, Society of Hospital Medicine, among others.

References: Grabenkort et al. [22], Luckianow et al. [23], Paton et al. [24], Kapu et al. [25], and Kleinpell et al. [28]

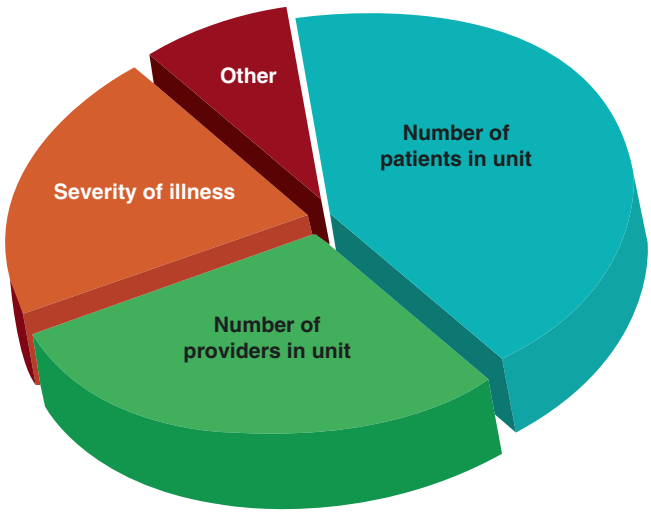

Fig. 48.1 Factors affecting nurse practitioner or physician assistant provider to patient ratios. Other: patient's diagnosis, number of physicians, time of day, residents' schedule, number of admissions and transfers (From Kleinpell et al. [27], ©2015 American Association of Critical-Care Nurses. Used with permission)

contributions, and experience of these advanced practice providers in the critical care setting.

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Contemporary ICU Design

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Diana C. Anderson and Neil A. Halpern

Introduction

The design of an intensive care unit (ICU) is a complex process and requires a multidisciplinary group of professionals. In 2010, there were approximately 6,100 ICUs with over 104,000 beds in the 3,100 acute care hospitals in the United States [1]. ICU design itself is continuously evolving as new guidelines and regulatory standards are developed, clinical models are changing, and medical technologies are advancing. It is highly probable that hospital-based intensivist leaders will be asked at some point in their careers to participate in efforts to design new ICUs or renovate existing ones. This chapter provides an overview to a wide array of design issues and is divided into three sections: an overview of ICU design, configuring the ICU space, and future trends in ICU design.

Overview of ICUs and ICU Design

The ICU provides care for the hospital's most critically ill patients and is a necessary resource for an acute care hospital. The average number of ICU beds per unit has increased between 1993 and 2012 [2]. Adult ICUs are now bigger by almost six beds, or 29 % [3]. In large hospitals, there are usually a high percentage of hospital beds dedicated to critical care through multiple-specialty ICUs (i.e., medical ICU, surgical ICU, coronary care unit, cardiothoracic ICU, neurosurgical ICU, burn ICU, pediatric ICU, and neonatal unit) [2]. In many of the smaller community hospitals, fewer beds are allocated to critical care, and there are fewer specialty ICUs; commonly one large multipurpose adult ICU handles all types of critically ill patients.

Four core principles should guide ICU-specific design. First, designing an ICU is a complex and time-consuming process. Second, an ICU is a semiautonomous mini-hospital. Third, the design requires balance between innovation and functionality, space and physical limitations, and desire and cost. Last, the design should combine technology, security, with a healing environment.

These design principles should operate in concert with the growing field of evidence-based design (EBD), a process of basing decisions about the built environment on credible research to achieve the best possible design and deliver positive clinical outcomes [4, 5]. EBD innovations optimize patient safety, quality, and satisfaction, as well as improve workforce safety, satisfaction, and productivity, with the additional benefits of operational cost savings and energy efficiencies [6, 7].

ICU Design Team

ICU design succeeds when the critical care medicine team and the hospital administration share common goals to design an "impressive" ICU, and the hospital, provides adequate space, and funding [8]. ICU design projects ideally are guided by an interdisciplinary design team which generally includes a variety of disciplines including hospital administration, the clinical team (a multidisciplinary group made up of physicians, nurses, pharmacists, infection control specialists, and other ancillary staff members), and the design team (made up of architects, engineers, and other specialists including equipment and information technology experts). Ideally, architects and engineers with a prior track record of excellent ICU design experience should be engaged.

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The Vision

Design-specific deliberations can only begin after basic ICU issues are addressed and a vision for the new ICU has been articulated [8, 9]. Issues include the location and purpose of the unit, the planned number of beds, the apportionment of space between patient and supportive areas, the logistics of unit function (centralized or decentralized), and whether a step-down unit will be associated with the ICU. The vision of the new ICU should reflect the big picture and focus on the desired atmosphere and feel, approaches to patient and family care, workflow, technology, environment, and the ICU's physical and logistical relationships with the remainder of the hospital.

Design Guidelines

The design process should be initiated by utilizing existing evidence-based guidelines, recommendations, and expert opinions to gather core knowledge of ICU design [8–14]. A primary source is the *Guidelines for Design and Construction of Hospitals and Outpatient Facilities*, published by the Facility Guidelines Institute (FGI) [15]. These guidelines (updated on average every 4 years by a multidisciplinary team of designers and clinicians) recommend minimum program, space, risk assessment, infection prevention, architectural detail, surface and furnishing needs for clinical and support areas, as well as minimum engineering design criteria for plumbing, electrical, and heating, ventilation, and air-conditioning (HVAC) systems. The FGI document is designed to meet minimum standards for design and construction and has been adopted by most states in the United States, in addition to being used in other countries.

Another fundamental resource is the Society of Critical Care Medicine (SCCM)'s *Guidelines for Intensive Care Unit Design*, which describes universal functions that should be accommodated in the modern ICU [10]. SCCM also maintains a digest of the ICU design award winners and includes architectural design drawings, pictures, and videos of outstanding ICUs from throughout the world [16]. This digest can also be used to provide benchmarks for the new ICU design.

One of the important considerations in using both the FGI and SCCM guidelines is the adoption of these tools early on in the design process by developing what is termed the "functional program" – an understanding of spaces needed to comprise the ICU. The use of design guidelines and standards enhances the built environment, and ongoing updates and revisions are necessary to keep these tools current alongside the changing nature of medical practice, technology, and evidence-based studies.

Design Timeline

The ICU design team must recognize that from design origination to occupancy may take several years [8]. Design committee meetings should occur regularly, and provision of continuously updated schematics and computerized renderings of the various design concepts to the design team speed the process along. Full-scale prototypes or "mock-ups" of the patient rooms are now standard practice in the design process, as they allow for an experiential rather than an observational experience. Mock-ups allow the staff to gain a sense of how the space and size of the room will accommodate patient care workflow in the future. Mock-ups can range from simple tape on the floor to indicate room outlines and components, to the use of cardboard walls and spaces outfitted with devices and finishings [4, 17]. Tours of existing ICUs may also be helpful in validating design ideas and identifying unanticipated problems.

Renovation Versus New Construction

Renovations of existing ICUs are usually limited in scope and may range from a cosmetic upgrade to a total overhaul. Renovations are often more complicated than new builds because of the restrictions of building in an older space (i.e., existing floor-to-ceiling heights, structural depths, and locations of elevators and staircases). Renovations also require the updating of existing space to current building codes. In new space, however, the design begins with a clean slate, and new construction is built to current code. If multiple ICUs are being built within a new facility, the hospital must carefully assess the ICU placements and core supporting spaces in order to maximize workflow and efficiencies. ICU design must also account for long-term functionality [14].

ICU Technologies

Medical devices today are actually informatics platforms [14]. For example, the purchase of infusion pumps or mechanical ventilators should include the costs of software licenses and updates. Additionally, connectivity and interactions with existing hospital systems should be considered. Optimally, the selection and deployment of new technologies should be preceded by testing in a simulation environment. A well-disciplined testing approach will reveal technologic gaps between current and new systems, thus guiding purchases and preventing avoidable errors.

ICU technologies should be standardized across the entire enterprise of critical care beds. Standardization permits efficiencies in education and assignment, device maintenance, and purchasing.

Advanced Informatics

Advanced ICU informatics systems transform patient-related data into actionable and well-displayed information using smart technologies [14]. The smart ICU coordinates the products of multiple vendors into one functional informatics platform that will meet clearly delineated ICU needs and be fully synchronized with hospital systems.

The first step to designing the "smart ICU" is the development of a connectivity envelope in each patient room which electronically integrates the patient with all aspects of care. The envelope infrastructure is composed of wired and wireless hardware that connects and communicates with data sources (i.e., medical devices, caregivers, medications), automatic identification tags on data sources for tracking purposes (real-time locating systems), and data transmission units attached to medical devices (to transmit their data to the network). The second step is the placement of middleware (the software that connects medical devices with the hospital's operating systems and provides specialized applications) on the hospital network to achieve the goals of the smart ICU.

Core properties of ICU and hospital middleware include the association of the patient with the medical devices and data, interoperability (coordination of computer languages) between the medical devices and the medical record, and time synchronization across all data and data sources. Middleware facilitates personnel and device maintenance and communication, alarm management and transmission, and data displays both locally and remotely. Middleware also provides portals for remote device diagnostics and software upgrades.

Occupancy, Post-occupancy Evaluation, and Do-Overs

Preoccupancy preparations can diminish moving day angst and can include move simulation. Non-ICU staff and the family members of current ICU patients should be made aware of the moving date in order to minimize their anxiety as well. A post-occupancy evaluation (POE) process has been developed to identify major issues and plan for short- and long-term fixes as unanticipated problems are recognized. When implemented in healthcare design, research findings demonstrate that POEs can positively impact patient and visitor experiences and satisfaction, create supportive work environments for staff and caregivers, and help achieve organizational objectives [18].

Configuring the ICU Space

The ICU consists of distinct zones, each designed to incorporate a primary function and end user, in addition to supporting interrelated functions between areas. Zones include patient care and clinical and family areas, in addition to overall unit support. Clinical zones support direct patient care, such as nursing stations and the patient room, while support areas include spaces such as administration, materials management, and staff support functions [10].

Overall ICU Layout

The layout of an ICU is arguably the most important design feature affecting all aspects of intensive care services including patient privacy, comfort and safety, staff working conditions, throughput, logistical support and family integration [19, 20]. Layout determines the location and configuration of different spaces and/or functions within an ICU, the relationship of internal and external spaces, and how their functions relate. ICU designers have applied various types and combinations of layouts (Fig. 49.1) to solve throughput challenges of patients, staff and visitors, circulation between clean and used supplies, equipment, and the end users [3]. The choices are usually dictated by the physical layout of the facility and the location of fixed hospital components such as windows, staircases, elevators, and plumbing. Layout decisions may also be guided by considerations that address safety versus efficiency, supportive versus functional environments, revenue-generating ICU patient rooms versus central supply and logistical spaces [3]. The racetrack type of layout ("racetrack" implies patient beds around the perimeter with services in the center and a loop corridor space in between) appears to be the most dominant unit type among award-winning adult ICUs [3].

Patient care, especially in specialty surgical ICUs, may require a large amount of space to allow for acute resuscitation efforts especially following trauma. Thus procedure rooms, resuscitation bays, and access to helipads may be required. The design of the specialty surgical ICU may also necessitate ready access to large transport elevators capable of accommodating the patient bed, staff and other supportive devices. Advanced care of the perioperative surgical patient may require that the elevators be equipped with utility panels that provide power, oxygen, and suction. Additionally, some emergency centers are incorporating intensive care unit type rooms into their departments.

The Patient Room

The core of the ICU experience is the patient room [9–13, 17]. Current guidelines recommend the use of single patient rooms rather than multiple occupancy rooms to enhance privacy and infection control [10, 15]. Each room should additionally provide a healing environment and have access to outdoor views through windows. Each room should be similarly

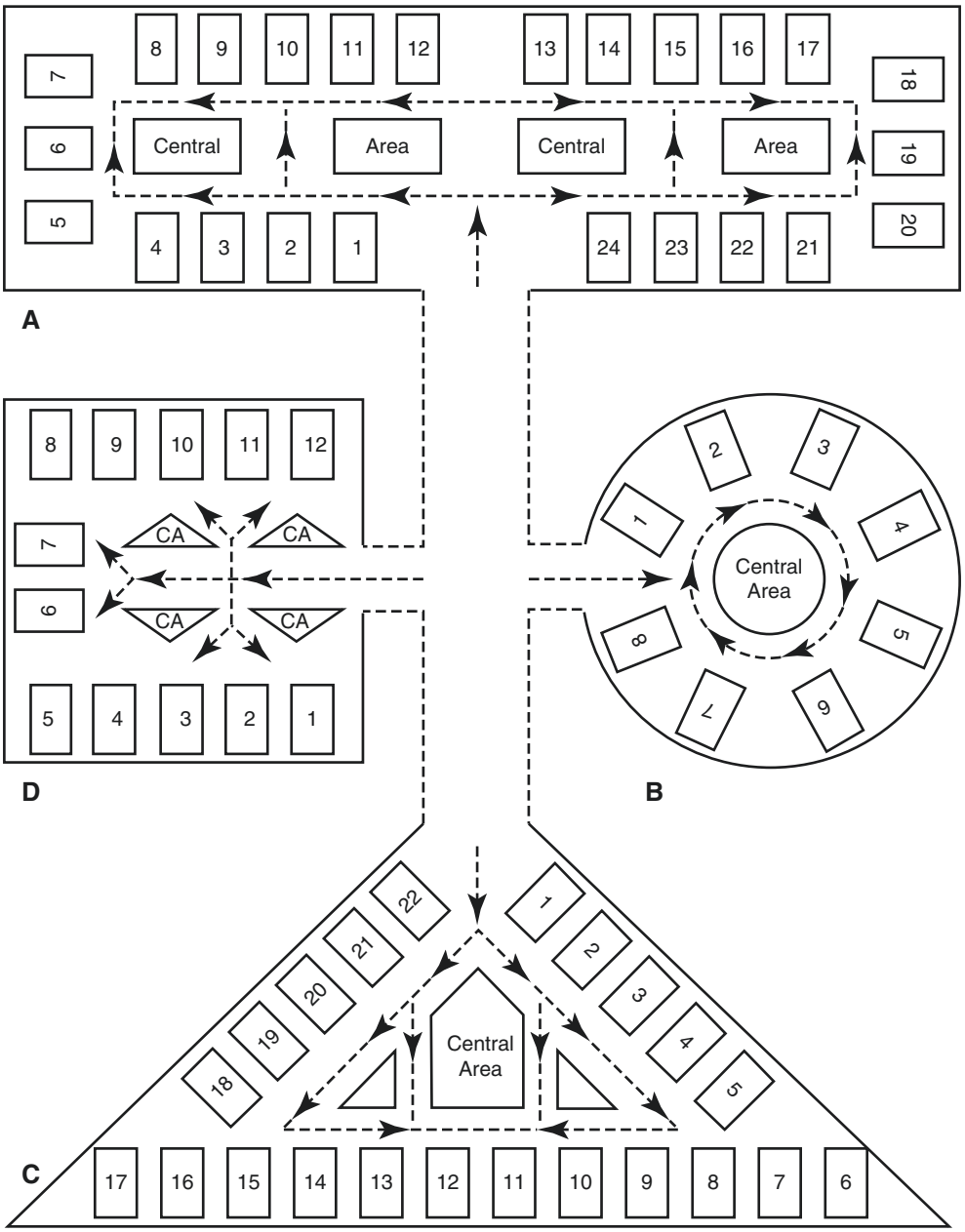

Fig. 49.1 ICUs can be planned in many configurations: rectangular (**A**), circular (**B**), triangular (**C**), and square (**D**). The "racetrack" with patient beds around the perimeter and nursing stations and supportive services in the center area (CA) is most common in current ICUs. Corridors that cut through the central areas facilitate staff movement. Modified with permission from CHEST [13].

designed and equipped to function as an autonomous area. Concomitantly, the rooms should be fully interwoven into the ICU and hospital fabric.

Patient Room Infrastructure

Much of the patient room's infrastructure involves components not usually familiar to clinicians. These include HVAC systems, electrical, plumbing, lighting, flooring, connectivity and communications, bathrooms and sinks, etc. The primary decision that guides the room's utilization involves the selection of the medical utility distribution systems. The choices are divided between fixed headwalls or floor-mounted columns versus mobile-articulating columns (booms) mounted to the ceilings or walls (Fig. 49.2, panel 1). The medical utility distribution system brings the hospital's supportive infrastructure (medical gases, vacuum, plumbing, electrical and data jacks) to the patient. Additionally, the medical utility distribution system pro-

vides the venue for installing medical devices (physiologic monitors, mechanical ventilators, infusion pumps), and communications and entertainment systems. The stationary utility systems are less expensive than the mobile ones; however, the mobile booms offer greater flexibility, patient access, and bed movement [21]. Regardless of the system selected, careful thought and even full-scale mock-ups should be considered for positioning the outlets and medical devices.

Bedside Medical Technologies

Core ICU room medical devices optimally include the ICU bed, physiologic monitor, mechanical ventilator, infusion and feeding pumps, pneumatic compression devices, patient lift, computers, chairs for patient and visitors, overbed tables, laboratory-specimen label printer, nurse-call intercom station, webcam, entertainment system, storage areas, and waste disposal bins. The design team should also address point-of-care testing (POCT) and ultrasonography and whether these devices should be placed in each room or stored centrally.

Patient Room Zones

Conceptually, each ICU room can be subdivided physically or virtually into three overall zones: patient, caregiver (work), and family (visitor) (Fig. 49.3) [10, 13]. While the room's

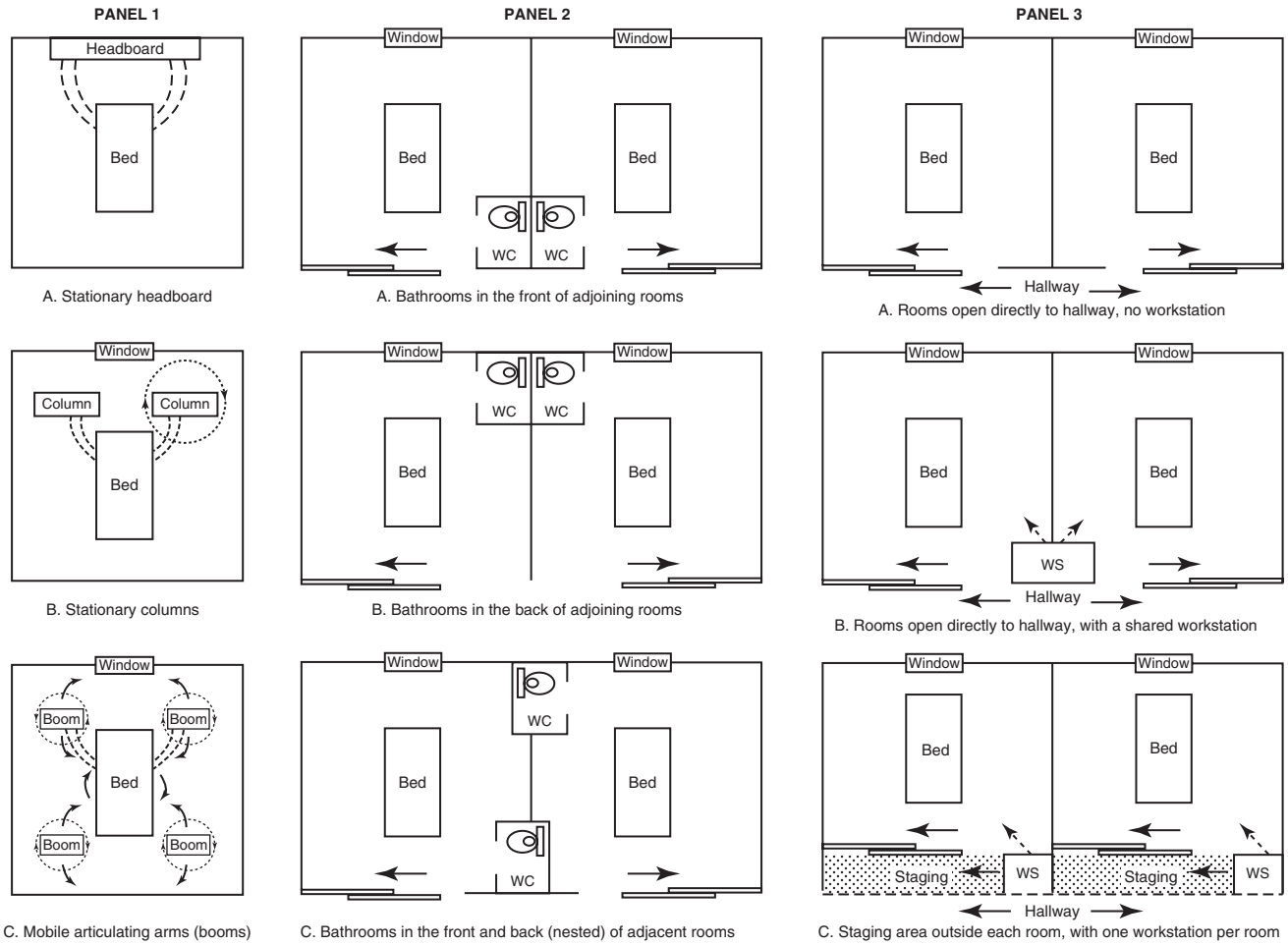

Fig. 49.2 ICU utilities and equipment (panel 1) are mounted on a stationary headboard (**A**), stationary (*left side*) or rotating (*right side*) columns (**B**), or mobile-articulating columns (booms) (**C**). The booms can be attached to the walls or ceiling, at any corner of the bed and swivel and move horizontally or vertically. In panel 2, the ICU patient room bathroom (WC) can be located in front of the room ("inboard") (**A**), back of room ("outboard") (**B**), and in the front of one room and the back of the adjacent room ("nested") (**C**) [22]. Although these decisions may be based upon the availability of plumbing, the impact on patient visualization from the hallway, window availability, and workflow should be considered by the design team. Panel 3 shows that patient rooms may open directly into the hallway without any workstations (WS) (**A**) or with a shared workstation for the two rooms (**B**). Alternatively, the rooms can be set back to provide a staging area in front of each room with one workstation per room (**C**). Modified with permission from CHEST [13]

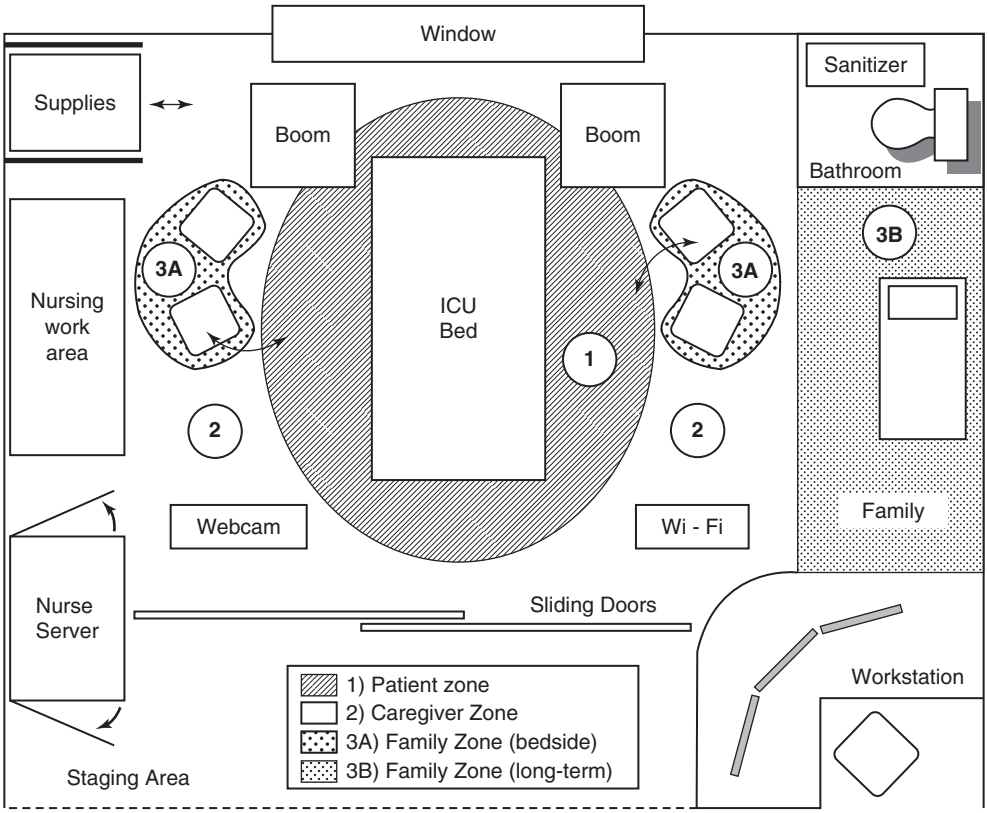

Fig. 49.3 The ICU patient room is divided into three zones: patient (1), caregiver (2), and family (bedside, 3A, or long term, 3B) zones. This figure also demonstrates a nurse server with bidirectional access, work area, supply space, booms, bathroom (outboard), webcam, Wi-Fi transmitter, and a workstation and staging area in front of the patient's room. Modified with permission from CHEST [13]

focal point is the patient bed, the patient rooms can be designed exactly the same (same-handed) or as mirror images of each other [22]. Installing all medical equipment on the medical utility distribution system clears the floor and facilitates ready access to the patient by family and staff. Elements of the caregiver zone include work areas for medication preparation, surface space, computers and displays, and storage areas. The family zone should incorporate comfortable chairs, electrical outlets, access to the hospital wireless communications systems and, if possible, long-term visiting necessities (chair-sofa-bed, table, light, sink, locker, and refrigerator).

Patient Room Logistics and Waste Management Systems

Adequate storage spaces for supplies, medications, linens, and waste management systems should be incorporated into each patient room. Storage is achieved through a mix of permanently based secured and nonsecured drawers, cabinets, and/or mobile carts. Permanent "nurse servers" (cabinets with bidirectional and secure access from both outside and inside the room) should also be considered (Fig. 49.3). The ability to access the nurse servers from outside the room improves privacy and infection control.

ICU patient rooms must now have direct access to separate enclosed bathrooms [15]. The design must determine the optimal bathroom location (i.e., front of room, back of room, or front and back of adjacent rooms) (Fig. 49.2, panel 2). Commonly these decisions may be based upon the availability of plumbing; nevertheless, the impact on patient visualization, window availability, or workflow is quite important.

Patient bathrooms should have either sanitizers to clean reusable bedpans or macerators to destroy single-use bed pans. Even with bathrooms, portable commodes are still necessary. Rolling carts or stationary containers should be available in each patient room for waste (standard, infectious, sharps) and soiled linens.

Room Environment

The physical environment affects the physiology, psychology, and social behaviors of all those who experience it [23]. Thus, the patient room environment must promote healing

and serenity and address sound, light, temperature, visuals, and entertainment.

Studies suggest that sound control positively influences patient outcomes decreasing physiological stress and lowering the incidence of rehospitalization [24]. Acoustic control within the ICU is generally done through the integration of sound minimizers (sound-absorbent finishings and ceiling tiles, acoustic baffling in the walls, soundproofed windows, and sound attenuators in the HVAC system), patient level sound mitigaters (sound-canceling headphones or sound masking), and systems that control alarms and communications broadcasts. Pilot projects are now underway to transform stark device alarms to more calming sounds.

Natural light is essential to the well-being of patients and staff. Thus, ICU patient rooms are now all required to have windows [10, 15]. Windows should have antiglare glass and sunlight reducing shades, preferably with electronic controllers. The room itself should have multiple lighting arrangements to accommodate patient and staff needs.

ICU artwork can be mounted on the ICU walls, embedded in privacy curtains and ceiling tiles, electronically projected on video displays, or integrated into televisions or television/computers. Entertainment may also be provided through visor-based video displays. A "low-tech" white board should also be available in each room for the display of positive messages, get-well cards, and family pictures.

Electronic and computer-based integration of the environmental (light, shades, temperature, artwork) and entertainment systems facilitates efficient patient and staff-centered control of the room. Environmental profiles can then be tailored to day and night, procedural lighting requirements, and individual patient needs. Multiparameter sensors that monitor temperature, humidity, light, and sound and provide alerts for uncomfortable environmental circumstances also help track and maintain the healing environment.

Front of ICU Room

The front of the ICU patient room is the interface of the room with the ICU hallway. This space controls room entry, patient privacy, sound transmission, control of infection, and impedance of smoke and allows for patient observation and monitoring. The front-of-room options include curtains or framed glass doors with integrated privacy solutions (manually or electronically controlled integral blinds, electronic glass (LCD or e-glass), or curtains behind the glass doors. Curtains are more economical to install than glass systems; however, the efficacy of curtains in controlling sound, infection, or smoke is limited. The glass systems are easy to clean. Options for the electronic glass include glass color and dimmers for opacity adjustment.

Patient rooms may open directly onto the hallway, be set back, or have a hybrid design (Fig. 49.2, panel 3). Opening directly to the hall provides the largest possible room; however, setting the room back provides a staging area that incorporates handwashing systems, storage space, coat hangers, and identification systems. A hybrid design may provide the best of both worlds.

Patient observation and monitoring is facilitated by the incorporation of a clinical workstation (decentralized) in the front of the room. These spaces are generally designed as one per room or one per two rooms, and provide direct patient visibility and local patient monitoring (Fig. 49.2, panel 3). Such workstations should have access to bedside physiologic data (mirrored on displays or web-based) and the electronic medical record.

Central Areas

The central areas of the ICU bind all the patient rooms and other supportive areas together and foster overall unit cohesiveness. The goals of the central areas are to support bedside care, provide access to central (nursing) stations and logistical support areas, and offer a welcoming and warm atmosphere. Core (central area) design is commonly governed by the hospital's and ICU's approaches to centralized or decentralized care and logistics, and space availability.

Administrative, clinical and social interactions commonly occur at the central stations. In a small ICU, one centrally located station may suffice; in contrast, multiple central stations may be needed in a large ICU with several bed pods. The layout of these areas is primarily affected by the bed configurations (Figs. 49.1 and 49.2, panel 3). Optimally, unobstructed views of the ICU beds should be available from the central stations. Differences in patient room visibility may have important effects on clinical outcomes, and severely ill patients may experience higher mortality rates when assigned to ICU rooms that are poorly visualized by the staff [25, 26].

Many ICUs are incorporating decentralized care stations outside patient rooms in addition to central work areas. This configuration allows staff to be distributed around the unit and closer to the patient rather being in a single, central location (Fig. 49.2, Panel 3). Decentralization is driven by the notion that it provides greater visibility of the caregiver to the patient [27]. Regardless of the layout, bedside webcams, centrally based physiologic monitoring stations, or other data displays are strongly suggested. The composition of the central stations includes greeting desks, quiet work and conferencing areas, offices, and restrooms. Other technologies

include nurse-call communication stations, telephones, grease boards, computers, high-definition image review stations, laboratory-specimen label printers, pneumatic tube stations, nourishment stations, emergency alerts, and cutoff switches for ICU utilities.

Corridors

ICU corridors provide pathways for transit around the ICU and promote physical and social unity (Fig. 49.1). However, physical barriers (staircases, elevators, supportive conduits, and closets) can limit optimal corridor design. If possible, separate and designated hallways for patients and supplies enhance patient privacy and minimize interactions with logistical support respectively.

The corridor finishings, artwork, sound control, and lighting set the emotional tone for the ICU. These considerations are very important as hallways are used to conduct rounds, impromptu clinical consultations, and family meetings and provide a track for patient mobilization. Some ICUs have also included large alcoves for devices and carts and respite areas for ICU visitors within the hallways.

ICU Storage Spaces, Supplies, and Medical Devices

Right-sizing the storage areas (central and bedside) requires a good understanding of the logistical approaches (centralized and/or decentralized) that the hospital and ICU will employ. Additionally, right-sizing requires correct assumptions of ICU supply utilization of consumables. Central storage spaces must also be able to handle supplementary medical devices (i.e., infusion pumps, ventilators, specialty monitoring or imaging devices).

Properly positioning the storage spaces in the ICU may prove challenging. Storage spaces should be accessible to transport or cargo elevators and be fairly close to the patient care areas. When space allocation and storage location are not handled well, ICU hallways are always cluttered.

Storage spaces may include traditional supply rooms (with stationary or track-based shelving, closed supply cabinets, or rolling exchange carts) as well as alcoves along the ICU hallways. Storage units and expensive supplies should be outfitted with electronic inventory management systems as part of real-time locating systems/solutions (RTLS).

The ICU design may also consider designation of ICU space for permanent imaging and procedural suites versus using the space for additional beds. This discussion is evolving as imaging technologies (i.e., mobile CT scanners) have currently become more economical and mobile than in prior years.

Pharmacy

Hospitals may have centralized or decentralized pharmacy and medication distribution systems and staffing models. The ICU pharmacy systems must be coordinated with the hospital's pharmacy and ICU bedsides. Options include a fully equipped satellite ICU pharmacy versus a pharmacy area with minimal resources. Both alternatives commonly utilize decentralized self-contained and secure automated medication-disposing units. Medications may also be stored in secured cabinets at the ICU bedside.

ICU Laboratory Testing and POCT

Both point-of-care testing (POCT) and centralized laboratory testing are usually required for the ICU. POCT focuses primarily on whole blood analyses using either large devices placed in defined ICU locations (ICU stat laboratories or central stations) or on carts, or smaller devices amenable for positioning at each ICU bedside. A combination of POCT modalities and locations may be used depending on the ICU workflow, necessary testing, and available space and resources. Pneumatic tube stations are still required to transport specimens to laboratories outside the ICU area as POCT is never a complete replacement for the central laboratory.

Staff Lounge and On-Call Suites

ICU clinicians regularly face extreme stress; thus, the ICU design must address the impact of space on staff efficiency, job satisfaction, and multidisciplinary teamwork. Well-designed staff lounges (break rooms) and on-call suites located within the ICU provide a place adjacent to patient care, for staff to relax and recharge. The lounges should be tastefully decorated with outside lighting, comfortable seating, televisions, as well as access to computers and ICU communications. Bathrooms, changing areas, lockers and scrub dispensers, napping alcoves, and nourishment stations complete the lounge furnishings. In ICUs that maintain 24/7 clinician availability, sleeping accommodations (on-call suites) with bathrooms and showers should also be provided.

Family Lounge (Visitor Waiting Room)

ICU visitors need a healing environment close to the ICU to recharge between visits with their loved ones. Soft lighting, warm colors, large windows, nature-themed artwork (either real or virtual), and quiet background entertainment set a serene tone. Privacy should be provided using small groups of comfortable chairs that are separated by dividers. Informatics support may include wireless Internet access, computers, and smartphone-charging stations. Nourishment areas as well as bathrooms, lockers, and coat hangers should be the norm. The inclusion of consultation rooms and social work offices helps promote family meetings and social support. Long-term sleeping accommodations, if possible, provide a space for visitors who prefer to remain nearby.

Conference Rooms

Staff meetings, educational programs, and family meetings are sustained through the construction of multipurpose conference rooms within the ICU space. The seating capacities of these rooms should be based upon predicted usage. Furnishings should include comfortable seating, conference tables with built-in informatics access, audio-visual-video systems, wireless access, smart boards, electronic attendance and scheduling systems, and food preparation and storage areas.

Infection Control and Prevention

Strategies for infection prevention rely upon infrastructure systems that provide clean air (air-cleansing systems, room-based air exchanges, and airborne infection isolation), clean water (plumbing for sinks inside and outside each patient room), waste sequestration and elimination in patient rooms, housekeeping, and environmental closets. Nonporous, well-sealed, and easy-to-clean surfaces and finishings, hand sanitizers, and fluid dispensers should be used throughout the ICU. Advanced modalities include electronic surveillance of handwashing stations, copper or silver "self-cleaning surfaces" in conjunction with surface surveillance monitors, and the use of environmental decontamination systems (i.e., ultraviolet light, hydrogen peroxide dispersion, and continuous air disinfection) [13].

Even in the setting of optimal infection control design measures, serious infections remain an ICU problem. Effective infection prevention also requires an ICU culture and workflow that promotes infection deterrence. Appropriate hand-hygiene products should be visible and accessible. Ultimately, the ICU may even include super-isolation zones that group highly infectious patients together with designated ICU traffic patterns.

Staff Communications

Telephones, smartphones, nurse-call intercom systems, pagers, and bidirectional transmitters are integral to ICU communications. These devices may all be integrated into one platform (i.e., within a nurse-call system, a primary communication platform, or an alarm system). Functionalities include point-to-point and global messaging, telephone and alarm communications, and real-time locating of staff. Even in these advanced settings, landline telephones and overhead speakers continue to be of value in providing reliable ICU communications.

Signage and Wayfinding

In addition to a well-designed ICU layout, good signage is necessary for efficient wayfinding. Directional signs should be clear in their message and easily visible, while destination signs should identify each room. Entranceway signs provide information about the ICU and can include the ICU designation (i.e., surgical ICU), management names (i.e., ICU director and nurse leader), and visiting hours.

Security, Fire, and Safety

The ICU design must address security and fire safety. Electronic identification card coded access should be used for staff at all secure doorways. The ICU "front door" optimally should be staffed by dedicated clerks. However, staffing limitations commonly preclude full-time greeters; therefore, other systems for visitor identification (i.e., closed-circuit televisions with electronic buzzers) should be installed at ICU entrances.

Beyond the basic fire safety devices (smoke detectors, automated sprinklers, fire extinguishers) and fire and smoke alerting systems (fire alarm pull stations, sound or light alerts, and overhead speakers), four design elements help ensure the safety of the ICU in the settings of fire and smoke. The first involves selection of products and furnishings with a low fire load and minimal release of heat

and toxic smoke. The second addresses the construct of compartments that are fire- and smoke-rated. The third is the use of protective technologies within the HVAC systems to prevent the spread of smoke and other products of combustion from one area to another. The last is the integration of experienced fire safety officers into the ICU design process [13].

Future Trends in ICU Design

The impact of the built environment on the healing process, infection control practices, and patient safety is being increasingly studied in the context of ICU design and architectural layout. Through the integration of this growing body of evidence into the design process and by engaging expert consultants to collaborate with the end users, ICU design has the potential to impact future organizational performance, clinical outcomes, and cost of care delivery.

Larger Units

In our opinion, future ICU design trends will likely include even larger units with more ICU beds per unit. As hospitals may look for efficiencies in managing these large units, ICUs may be standardized in design, technologies, and general functions and be located near each other. Core areas that are adjacent to or within the units may include multiuse diagnostic and treatment technologies, administrative, educational and/or research spaces, and family areas. Larger units may also become multispecialty units utilizing a variety of unit geometries (so the unit can adapt to surrounding conditions) with larger units subdivided into smaller groupings of beds supported by a balance of centralized and decentralized workstations. Concomitantly, segregation of public/visitor and patient/support circulation types will be expected.

Patient Rooms

Single-patient rooms will also likely be larger and better able to accommodate family and bathroom space. Ceiling-mounted life support systems will replace fixed models, and devices throughout the room will become wirelessly integrated, allowing for improved documentation and communication.

Environment

Both the overall unit and the patient room will become more patient and visitor friendly. Thus, amenities that enhance the patient and visitor experiences will be expected to be included throughout the ICU. The importance of nature visibility and access for patients, families, and staff will become fully recognized and incorporated into all units.

Changing Practices

The ICU is an ever-changing and rapidly advancing environment. The next generation of ICUs must be planned for the long term and incorporate design decisions that allow for flexibility in order to accommodate changing care practices and information technology (power and data).

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Telemedicine for the Intensive Care Unit

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Ann Marie Huffenberger, Niels Douglas Martin, and C. William Hanson III

Overview

The healthcare sector in the United States is undergoing a transformation. It has become apparent that hospital organizations face challenges in achieving sustainability. Challenges relate to ensuring quality and cost of care while transitioning patients safely across the continuum of care [1]. Organizations are collaborating to leverage resources and implement strategies to meet the needs of a growing, medically complex, aging population [2]. The challenges compound by a forecasted shortage of intensivist physicians [3], which is coinciding with a forecasted shortage of registered nurses [4]. State, federal, and commercial payer policies have been enacted to reward organizations to provide better health, better care, and lower costs [5, 6]. TeleICU services have been shown to reduce ICU mortality, reduce hospital length of stay, and lower rates of preventable complications [7, 8]. These remote services reinforced timely response to physiological alarms and adherence to critical care best practice protocols [7, 8]. TeleICU has emerged as a technological strategy to improve clinical outcomes in critical care populations across the nation.

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Historical Information

The teleICU concept is not new. In 1977, researchers hypothesized that remote patient monitoring would solve the problems of scarcity and misdistribution of critical care specialists. Using a two-way audiovisual platform to connect a small private hospital to a large university medical center, researchers demonstrated that telemedicine favorably influenced the quality of critical care service provided [9]. In 2001, the Society of Critical Care Medicine published guidelines focusing on the delivery of critical care, and recommended intensivist physicians lead the interprofessional teams to provide interventions necessary in urgent and emergent situations 24 h a day, 7 days a week [10, 11]. Shortly after that in 2002, the Institute of Medicine convened on health inequities in the United States and identified access to care resources as a significant contributor [12]. By 2013, approximately 11 % of adult critical care beds in the United States reported a teleICU program as an associated care paradigm [13]. The Society of Critical Care Medicine reconvened in 2015 to review models of critical care associated with improved outcomes and recommended institutional support for quality improvement programs, as well as institutional support for teleICU programs [14]. With innovative approaches to healthcare delivery, organizations are achieving scalable and sustainable teleICU programs.

Central Operations Room

TeleICU clinicians typically work together as a team in a remote centralized operations room (COR). The clinicians in the COR are considered the distant site practitioners who provide services to the originating site hospital. The COR has an arrangement of workstations, each of which has one or two central processing units (CPUs) and six or eight computer monitors. The COR workstations are often ergonomic desks that raise or lower so that clinicians can alternatively stand or sit throughout their work day. Lighting, noise, and backdrop are important considerations. Indirect lighting is superior in preventing computer eye strain. Given the prox-

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imity of workstations and the necessity for patient privacy, clinicians are cognizant of noise when interacting with patients, families, or ICU clinicians via the telemedicine platform. TeleICU programs often utilize a standardized backdrop image for patient encounters. Regarding the number of workstations necessary, clinicians may function with an intensivist to patient ratio in the range of 60 to 1 typically not exceeding 150 to 1, whereas the RN to patient ratio may be in the range of 30 to 1 typically not exceeding 70 to 1 [15, 16]. However, patient ratios are contentious and fundamentally dependent upon the role the telemedicine program.

Information Systems

A teleICU program requires three technological elements [17]. First, remote clinicians require *full access* to the clinical information systems deployed at the bedside. At a minimum, physiological, laboratory, pharmaceutical, and radiological data are necessary for real-time identification of impending or worsening conditions. Second, with an aim to enhance efficiencies in ICU population management, clinicians use *teleICU software* applications to support widespread surveillance. The applications organize a multitude of incoming information so that logical processing can occur in sequence. Complex algorithms are embedded within the data visualization features available in these applications. Third, a *connection network* is essential for the remote clinicians to communicate. Older systems provide one-way camera functionality where remote clinicians can be heard but not seen by the patients or ICU clinicians. More robust video platforms have afforded two-way camera functionality, essentially a bidirectional audiovisual link, where colleagues can see each other when they are communicating. Two-way camera functionality is superior in building the interactive, collaborative relationships that are necessary for teleICU programs to succeed.

Models of TeleICU Care

To minimize conflict among the interprofessional team, the roles and responsibilities of the remote team should be well defined and clearly evident to the clinician team at the bedside. Models of teleICU care have been developed and refined over the years and categorically will likely continue to broaden in scope. Clinicians will undoubtedly continue to collaborate and discover innovations in care paradigms as new technologies emerge.

The American Telemedicine Association [18] offers three models of care to illustrate alternatives for continuity of services. The first is a *continuous care* model where physiological (and other) monitoring of data occurs without interruption for a predetermined number of hours (i.e., 8, 12, or 24) every day. The second is a *scheduled care* model where periodic consultation occurs on predetermined schedule (i.e., morning ventilator rounds) every day. The third is a *responsive or reactive care* model where the teleICU encounter is prompted by an alert received and therefore unscheduled by context. Separate from the ATA's three models for continuity of care, Sapirstein et al. [17] offer four models of care to illustrate the operational interactions that may ensue staffing, supervision, compliance, and early warning.

Staffing Model

The staffing model builds on the premise that the teleICU intensivist can enhance the ICU staffing by providing virtual support. Remote surveillance occurs in real time through audio, visual, and electronic means. Population management software helps identify patients at risk. TeleICU nurses review patient cases with the intensivist who then acts as: (a) provider-to-provider support, (b) sole provider to the patient, or (c) a blended support model. First, *provider-to-provider* support is typical when intern physicians, resident physicians, fellow physicians, physician assistants, or advanced-practice registered nurses are available in the ICU. The intensivist offers support that may or may not document as a formal consultation. The ICU provider may retain the duty to enter the physician order into the medical record. Second, when there are no providers in the ICU, the intensivist acts as a *sole provider* and directs patient care entirely including entering all physician orders into the medical record. When this occurs, there is a consensus that the care provided by telemedicine should meet the standard of care provided in person. With that stated, at a minimum, the tele-intensivist should establish a patient-physician relationship [19]. However, the American Medical Association cites exceptions to when a patient-physician relationship is not required, in situations such as on-call, cross-coverage circumstances, emergency medical treatment, or other conditions [19]. Third, the intensivist may provide a *blended support* model where he or she may consult on one patient (or one ICU) and direct care entirely on another patient (or another ICU). While the staffing model may fill the void for an intensivist should none be available in the ICU, the staffing model was never intended to reduce the number of nurses at the bedside [15].

Supervision Model

The enhanced supervision model builds on the premise that teleICU clinicians provide an extra set of eyes for the ICU clinicians [15]. Supervision occurs when an intensivist consults with ICU providers or when a teleICU nurse collabo-

rates with ICU nurses. For example, when subtle patient changes are occurring and observed interventions lie outside the realm of best practice protocols, experienced teleICU clinicians may collaborate to educate, encourage and support, and thereby foster action that drives evidence-based practice. At other times, when ICU clinicians are engaged and actively managing an emergency or other issue, teleICU clinicians may provide supervision to proximate patients on the unit. This type of *tag team supervision* approach, that is, ensuring all eyes are on all patients, is intuitive to teleICU clinicians who have successfully integrated themselves into the culture of the ICU unit. This multilayered integrated support model fundamentally builds on mutually trusting relationships, which are at times difficult to achieve.

The supervision model may involve continuous observation of patients deemed at risk. For example, patients who are at risk for fall may be monitored continuously by audiovisual means. There are inherent limitations to this type of intervention: (a) patients must be responsive to verbal cues from the remote team, (b) ICU team must be close enough to assist the patient if necessary, and (c) remote team must have the technology and resources available to conduct continuous monitoring. Resources to conduct continuous monitoring are often not licensed personal but rather telemedicine support associates who have had specialty training to manage the population at risk. In many ways, the virtual supervision model has the potential to shape resourcefully the future of critical care services.

Compliance Model

The compliance model builds on the premise that remote teleICU clinicians are well positioned to provide clinical surveillance to a large number of ICU patients to ensure compliance with *evidence-based protocols*. TeleICU clinicians monitor clinical activities in real time to facilitate interventions and ensure compliance with critical care best practice protocols across a health system. Table 50.1 displays bundled care protocols that teleICU services have supported.

In addition to supporting compliance with bundled care protocols, teleICU clinicians collect data for process improvement (PI). Data is typically collected to illustrate (a) observed versus expected severity-adjusted ICU mortality, (b) observed versus expected ICU length of stay, (c) ICU ventilator days, (d) DVT prophylaxis, (e) glycemic control metrics, (f) stress ulcer prophylaxis, (g) incidence of ICU complication, and (h) organized and efficient utilization of ICU beds in connection with the health system admission, discharge, and transfer (ADT) center.

Process improvement is the backbone of achieving high-quality ICU outcomes [14]. In a systematic data-driven manner, teleICU services provide many elements of a successful PI program [34]. Telemedicine does not guarantee quality improvement. Because PI initiatives often fail without specific goals, a successful teleICU program will perform a detailed needs assessment, including a review of the barriers to change, and then prioritize the ICU deficiencies with outlined interventions aimed to assist in managing the problems identified [35].

Early Warning Model

The early warning model builds on the premise that teleICU clinicians continually monitor trends in data to identify impending or worsening situations that may benefit from early clinical intervention. Strategies for *real-time data management* provide the foundation for the early warning model [36, 37]. TeleICU services provide accurate sepsis identification that correlates with both improved sepsis bundle compliance and reduced patient mortality [26, 28]. When clinicians leverage the data with automated prediction tools to identify at-risk patients, organizations have reported more timely sepsis care, improved sepsis documentation, and reduced mortality [38]. As teleICU nurses conduct active data surveillance overnight, the intensivists are awake, alert, and readily available should concerns be identified or should the ICU team request support. In this improved climate, where clinicians collaborate with a focus on safety, ICU providers have reported heightened levels of confidence about patient coverage and physician accessibility [39].

Architectural IT Framework

There are options for the architectural IT framework to provide teleICU services. The telemedicine architecture can be closed or open, and the operations can be centralized, decentralized, or hybrid [40]. *Closed architecture* is a less adaptable infrastructure that has point-to-point dedicated communication from a centralized teleICU operations room. Within a closed architecture, physicians outside the hospital network are prohibited from accessing the audio, video, clinical, or trended data analysis. Medical consultants who are technologically external to the closed architecture will be unable to perform a video assessment and thereby unable to provide a full scope of telemedicine consultative services. The closed architecture system typically installs with dedicated high-speed lines within a hospital network but not utilizing the Internet [40].

Alternatively, *open architecture* is an adaptable communication infrastructure that supports connectivity by one or more clinicians, from one or more sites, typically implying connectivity to the Internet [40]. The open architecture can

Table 50.1 Bundled care protocols that teleICU services have supported

Ventilator care bundles [20]
Bundle care aimed at reducing healthcare-associated infection (HCAI) [21]
Catheter-associated urinary tract infection bundle (CAUTI) [22]
Ventilator-associated pneumonia bundle (VAP) [23]
Central venous catheter insertion bundle (CLC) [24, 25]
Central line-associated blood stream infection bundle (CLABI) [23]
The surviving sepsis campaign sepsis bundle [26–28]
Rounds to ensure adherence to lung protective ventilation (LPV) [29]
Pressure ulcer prevention bundle [30]
Palliative care bundle [31]
Organ procurement care bundle [32]
Daily sedative interruption compliance [33]

take the form of single or multiple clinicians connecting from the hospital, office, or mobile device, providing virtual care to single or multiple patients, at one or more hospital sites. The open-architecture framework is a robust telemedicine platform that more easily enables consultative services from inside or outside the constraints of a hospital network.

The *centralized* teleICU is a hub and spoke model. Within this model, distant site clinicians work in the centralized hub and provide services outward to the spoke hospital sites [41]. The connection between the hub and one or more spoke hospital sites allows the intensivist to support the ICU services provided locally. Commonly, the hub and spoke is a closed architecture where teleICU clinicians work in the centralized location and cannot conduct video assessments from sites outside the centralized location.

Alternatively, in a *decentralized* teleICU model, clinicians are not devoted to being onsite at any centralized location. In this model, one or more clinicians can utilize the telemedicine platform to provide care, concurrently or not, from any device (desktop, laptop, or mobile) equipped with camera, speaker, and microphone [41]. In the decentralized model, the teleICU clinicians can conduct video assessments from the convenience of the hospital, office, or home. In a decentralized open-architecture model, the extent of virtual support available to ICU clinicians is wide ranging, regulated predominately by organizational policies and procedures, as well as the quality of Internet connection available to the remote clinicians.

Finally, *hybrid* models combine some of the best elements of centralized and decentralized models. In a hybrid model, a large hospital organization may partner with independent physician service lines to support teleICU services across multiple hospitals or multiple patients. The hybrid difference is that intensivists are not all located at a centralized hub, but rather in multiple remote facilities, potentially decreasing the cost of the centralized hub operations and effectively leveraging the resource to a wider span of ICUs under the umbrella of teleICU services [41].

Performance Metrics

The historic drive behind teleICU has been the promise to improve outcomes by providing an efficient means to connect critical care specialists to a large number of patients in need [17]. Implementation of teleICU services has been associated with reduced severity-adjusted ICU mortality [7, 8, 42–44], reduced hospital length of stay [7, 8, 42, 43], reduced ICU length of stay [44], improved rates of best practice adherence [7], and lower rates of preventable complications [7]. Remote services confirm that high-quality care can be provided to patients managed in less costly community settings [45]. Still others have reported no significant association between the implementation of teleICU services and severity-adjusted ICU mortality, ICU length of stay, or hospital length of stay [46, 47]. In 2011, Young et al. conducted a meta-analysis of 13 published studies including 35 ICUs to affirm that teleICU services significantly reduced ICU mortality and ICU length of stay, but they found no significant improvements in hospital mortality or hospital length of stay [48]. Kahn et al. have proposed that the primary difference between teleICU programs that demonstrate improved outcomes and those that do not are differences in the models of care, specifically that full discretion for all patients may be necessary to maximize the potential of a teleICU program [35]. Lilly and Thomas have proposed that the degree of benefit directly relates to the extent in which teleICU acceptance leads to a persistent change in the processes of care delivered in the ICU [49].

While researchers have evaluated the clinical and economic impact of teleICU, and their work provides foundation for understanding operations, their studies present with a number of conceptual and methodological limitations [35]. In 2011, the Critical Care Societies Collaborative convened an interprofessional work group to develop a research agenda for teleICU to address the gaps in literature and to best inform clinical decision-making and health policy. Previously developed framework for evaluating telemedicine was considered as a starting point. Acknowledging the limitations of

the existing teleICU research, the group identified two major components of a framework: (a) standardized approach to assessing the pre-implementation ICU environment and (b) standardized lexicon for defining the telemedicine intervention. The group then organized gaps in evidence around the Donabedian framework for healthcare quality. Thereafter, they developed several high-priority topic areas to advise the framework for evaluating teleICU services: (a) structure to include teleICU, ICU, organizational climate, and readiness to change; (b) process to include optimal delivery, innovations, evidence-based care, and education; and (c) outcomes to include the effects on the patient, provider, and system [35].

Quite often stakeholders in ICU have strong opinions regarding the value of teleICU services. Opinions are often good as they are bad, especially true to those who have a monetary interest in the implementation or non-implementation of services [35]. Indeed, telemedicine services will continue to expand in coming years. The controversy surrounding teleICU is not whether it will prosper but rather how well can ICU clinicians leverage it to positively affect workflows, advance efficiencies, reduce costs associated with care, and ultimately improve patient-centered care experiences [50].

Challenges and Limitations

TeleICU programs can encounter a number of operational challenges [51]. Optimal performance is contingent upon the integration of the teleICU operations into the operations of the healthcare system. Stakeholders from all levels of the organization including executive, finance, information technology, management, and regulatory should be transparent about their support for the teleICU program and that transparency should be unambiguous to clinicians [17]. It is essential for clinicians to establish collegial relationships across the telemedicine platform. The practice of teleICU nursing is directed by guidelines established by the American Association of Critical Care Nurses (AACN) with a focus on bold, authentic leadership to optimize patient outcomes [52]. The teams on both sides of the camera must have shared knowledge, shared goals, and mutual respect. With optimized technology, expert clinical practice, skilled communication, and collaborative relationships, the patient remains the center of focus. The AACN's standards for a healthy work environment provide the clinician teams with shared principles to uphold: (a) skilled communication, (b) true collaboration, (c) effective decision-making, (d) authentic leadership, (e) appropriate staffing, and (f) meaningful recognition [52]. The CCRN-E certification validates the expertise and competency of nurses practicing in the teleICU [53]. Schleifer-Kwan et al. conveyed criterion-based competencies to assist in clarifying the role of the teleICU nurse in contrast to the role of the critical care nurse at the bedside [54]. Healthcare organizations should define and evaluate accountability for telemedicine communications and establish how a lack of collaboration will be addressed [52].

Strategies to enhance the integration of teleICU operations into the ICU operations should be established early. Integration is influenced by the degree of acceptance formulated by the leaders of the critical care teams. Resistance to integration degrades performance [42, 55, 56]. In a true collaborative care model, clinical outcomes are shared outcomes. Strategies for integration may include blended unit champions or unit liaisons, overlying membership in unit-based clinical leadership teams, integrated critical care orientation, ongoing education to ensure continued competence, shared PI or research initiatives, joint governance over nursing positions (full time, part time, or per diem), or simulated clinical emergencies to promote standardized team interactions and cohesive team processes. The value of teleICU is not in the technology but rather how well the technology is interwoven with the daily practice of the interprofessional team at the bedside [57]. Continuous evaluation of a teleICU services is essential in identifying opportunities to advance telemedicine paradigms as the technology and degree of cultural acceptance rapidly evolves in society.

There are obvious limitations associated with teleICU services. Foremost, remote clinicians cannot perform bedside procedures that are a necessary component of care prescribed. For example, central line placement may aid in the completion of elements necessary for the severe sepsis bundle [26]. While the remote clinician can direct and supervise the placement of a central line, the real advantage emerges when the central line access is established and clinicians have confirmed time zero relative to all future elements of the severe sepsis bundle [26]. By leveraging technology and promoting remote clinicians to calculate and track compliance with all elements of the bundle, clinicians work together to ensure performance. While limitations of teleICU services are apparent, a collaborative clinician effort that is supported by technology provides a most efficient model of care [26].

Complex Valuations for Return on Investment

TeleICU programs may encounter barriers to entry such as high-priced technology [58, 59], fragmented clinician support [58], regulatory and licensure obstacles [60], and reimbursement challenges [61, 62], which have inhibited widespread adoption of services [63]. Despite the lack of a direct reimbursement model, there are significant indirect financial benefits to deploying teleICU services. TeleICU programs must outline robust, sustainable business plans.

Working with the financial officers, teleICU programs can show cost avoidance and cost savings to support return on investment. Focus should be on the reductions in ICU mortality and ICU length of stay, increased compliance to best practice protocols, decreased ventilator time, decreased rate of ICU complications, and active management of ICU beds including triaging patients in and out 24/7/365, thereby enhancing throughput and tendering an increased capacity for admissions, ultimately driving revenue [63, 64].

Fifer et al. demonstrated that the capital investment and first-year operating cost of a teleICU can be recovered in approximately 1 year [65]. Franzini et al. confirmed that teleICU services were cost-effective in caring for the sickest of patients [66]. Deslich and Coustasse verified the implementation of teleICU to be more beneficial than costly, denoting the strategic advantage to providing telemedicine services [67]. Kahn and Rubenfeld advised using teleICU to sustain best practice compliance [68]. Fortis et al. described significantly reduced capital costs associated with a teleICU program that integrated the audiovisual technology within the electronic medical record; the capital cost was $1,186,220 with an annual operating cost of $23,150 per monitored bed [69].

There are other ways to measure the investment return of a teleICU program. With a mounting petition for patient-centered care, large university hospitals can enhance and support the ICU services provided by small community hospitals, thereby decreasing unnecessary tendencies for disruptions in care. In this win-win model, the large university hospital attains an increased referral source from patients who are clinically deteriorating and thus require transfer; while conversely, the small community hospital attains increased revenue from actively managing patients who are stabilizing clinically and thus benefit from staying in their community setting. Moreover, ICU physicians have reported increased satisfaction, reduced burden, and improved recruitment and retention metrics when remote intensivists are available to assist in the management of clinical issues that arise 24 h a day, 7 days a week [70]. With a focus on human capital, teleICU provides an equally challenging alternative setting for experienced critical care nurses who are physically unable to provide care at the bedside [71].

Governance

Medical Licensure

Many citizens of the world look to the United States as a leader in healthcare innovation and technology, yet the field of telemedicine has stifled in the absence of one medical license recognized throughout the nation [72]. In 2014, the Federation of State Medical Boards passed the interstate medical license compact allowing for expedited licensure by eradicating the primary source verification process if states agree. Even though a physician must still apply to each and every state he or she wishes to practice medicine, this is an advancement in the right direction. Physicians have the legal ability to practice in any of the European Union member states, and similarly, Australia has moved away from a state-based system to a single national agency that licenses all physicians [60]. While the medical license portability debate continues in the United States and stakeholders remain elusive to a collective solution that would safeguard medical care to underserved populations, if there was ever an urgency to resolve this barrier to broad adoption of telemedicine, now is the time [72].

Credentialing

Any physician, who prescribes, renders a diagnosis, offers a radiological interpretation, or provides clinical treatment via telemedicine, must be credentialed and privileged through the hospital's office of medical affairs. Credentialing is to evaluate and verify the physician's qualifications, while privileging is to verify the competency in his or her specialty [60]. The process can be complicated at times by inconsistencies that may occur within hospitals of the same healthcare system, ultimately adding time and expense to the process. Hospitals that provide care via telemedicine must revise the medical staff bylaws and the credentialing and privileging policies to include criteria for granting privileges to the remote intensivists. The bylaw revisions should address what category of the medical staff the remote intensivist will join, what level of involvement he or she will have in the medical staff committees, and what procedural rights he or she will be granted. To mitigate malpractice and negligent credentialing claims, written agreements should be established to ascertain who will be providing the care to patients and when will the care be provided to patients, including the specified representations, warranties, and indemnifications [73]. Hospitals should establish means to evaluate the quality of care delivered, while teleICU programs should establish means to evaluate the quality of service rendered by telemedicine.

Professional Fee Billing

There are challenges associated with the reimbursement of telemedicine services [61, 62]. There are several recent regulatory and legislative changes that can assist in understanding how substantial the reimbursement barrier will remain in coming years [60]. There are three major patient insurance classes: Medicare, Medicaid, and private insurers. While the federally organized program Medicare has guidelines for

telemedicine that are consistent across the nation regardless of state, the reimbursement policies for Medicaid and private insurers can vary significantly by state [60]. Most teleICU services rendered meet the eligibility requirements for *Medicare* reimbursement although policy restricts any form of payment unless the patient is within an established rural area. Forty-six states provide *Medicaid* reimbursement for telemedicine although the fiscal impact on teleICU programs varies by the definition of common services [60]. There are a series of state Medicaid programs that have legislatively mandated reimbursement for services that would otherwise be reimbursed in person, suggesting a greater likelihood of Medicaid reimbursement for teleICU services in the future. *Private insurers* are regulated at the state level and therefore reimbursement varies by the state and even insurers within a state. With the growing trend to legislatively mandate reimbursement for services that would otherwise be reimbursed in person, teleICU programs might soon submit claims for reimbursement across all insurances. Even in states where no such mandate exists, there is growing evidence to imply that private insurers have voluntarily adopted reimbursement policies for telemedicine services [61]. In summary, reimbursement for teleICU services depends on geographic location, type of service, and the clinical model. Organizations should proactively review fee schedules of the payers they bill and, when negotiating payer contracts, seek to reference the inclusion of reimbursement for teleICU services [60].

Technology Regulations

While telemedicine intensivists are limited by the acquisition of state medical licensure and hospital credentialing, Reynolds et al. confer how the technology of telemedicine devices has counterpart regulations [74]. The Federal Food and Drug Administration (FDA) issued a ruling to differentiate medical device data systems (MDDS) from those designed to perform active patient monitoring (APM). In a teleICU setting, APM devices are the bidirectional audiovisual link used to conduct active, real-time, or online patient monitoring. Devices used for APM must be FDA class II approved, subject to more stringent manufacturer controls, whereas devices used for MDDS must be FDA class I approved, subject to less stringent manufacturer controls. Although other vendors will likely acquire FDA class II certification for APM devices in the future, as of 2012, approved devices for APM in teleICU setting were limited to Philips VISICU® technology and the InTouch Health Remote Presence technology, both having significant costs associated [74]. With good reason to consider, organizations may be tempted to develop their systems and thereby unwittingly subject themselves to stringent manufacturer controls defined by the FDA. In simpler terms, an organization would be in violation of FDA ruling requiring APM certification if a decision was made to deploy uncertified cameras, speakers, or monitoring equipment to be used in the immediate clinical decision-making process. In summary, teleICU programs have a very limited selection of FDA class II-approved APM technologies. Any consideration of an innovative solution should not be without consideration to the consequences associated with operating outside the FDA requirements for manufacturing of APM equipment [74].

Future Directions

With a predicted shortage of critical care clinicians on the horizon and rapidly expanding healthcare technologies, one might presume that ICUs across the nation would swiftly achieve broad implementation of teleICU services. However, the implementation equation is not so simple. There are barriers to be reckoned, in particular, the high cost of technology, fragmented clinician support for services, and regulatory, licensure, and reimbursement challenges. An additional strife is that existing teleICU software is often a free-standing application in a period of high demand for systems integration [17]. Although the data can certainly be delivered remotely with integration interfaces, the maintenance of interfaces is onerous yet essential to the accuracy of information reported outward [75].

There is consensus on the research necessary to discover strategies to optimize teleICU services in a way that is clear and understandable to clinicians yet practical and suitable to hospital administrators who guide implementation decisions [35]. Reynolds et al. have proposed the future of teleICU services as a catalyst for innovators to shape the imminent. In this future, the centralized and decentralized systems will foster alternative staffing models for an acute care telemedicine solution, promoting sustainability through vertical and horizontal scaling, supporting patients and caregivers across the continuum of care, on an open-architecture system with mobile connectivity, and an umbrella of administrative direction over the regional critical care units [74].

Summary

Healthcare organizations are contending with intensified scrutiny. There are clear directives to provide better health, better care, and lower costs. The stakes are high for critical care medicine as some of the largest costs incurred in healthcare are associated with ICU care delivery. Organizations have turned to technology to advance the delivery of care in ICUs across the nation. The collaborative team approach enables redundancies in care, with aims to improve the quality of care by reducing variation and complication. There are

limitations to the research documenting the full advantages and potential consequences of teleICU services but what is apparent is that traditional egocentric approaches to critical care medicine are not sustainable. An ICU culture that leverages the technical and human capital available improves the quality of care. With innovative approaches to healthcare delivery, increasing market competition, strengthening relationships across telemedicine platforms, and emerging evidence for efficient resource utilization, organizations are strategically achieving scalable and sustainable teleICU programs.

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Erratum to: Coagulopathies and Anticoagulation

Jeremy W. Cannon

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We received following correction from author after publication of this book. This correction was carried out in the book.

In Figure 26.1b, the word amplification was misspelled as amplifivation. The corrected version is available below.

The updated original version for this chapter can be found at
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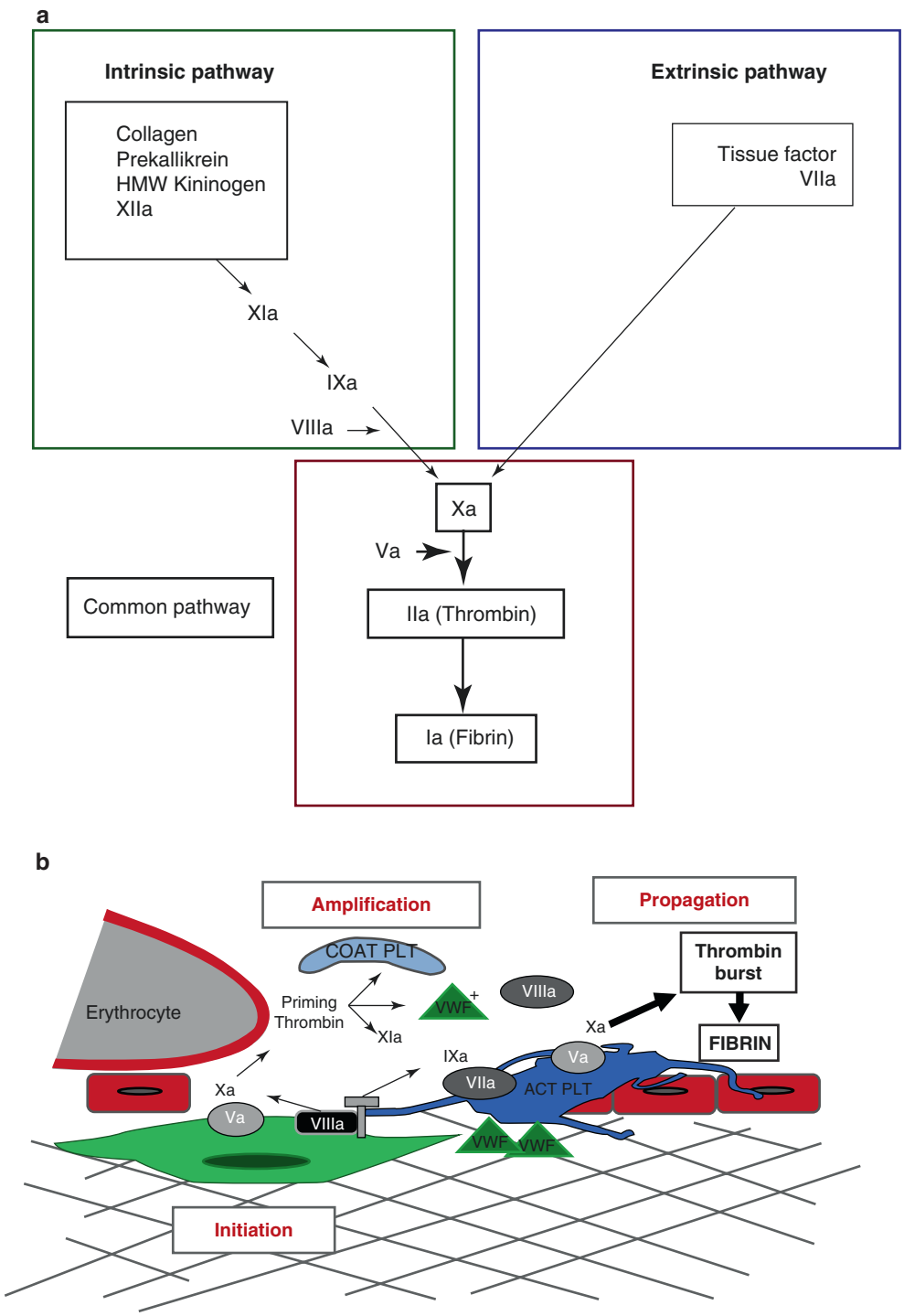

Fig. 26.1 The coagulation cascade. Traditionally, this has been conceived as an intrinsic and extrinsic pathway merging into a common pathway (**a**). However, we now understand that this is a vastly complex system of both enzymes and cells all working in concert to rapidly control hemorrhage when needed as illustrated by the so-called cell-based model of coagulation (**b**)

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