Hot Topics in Acute Care Surgery and Trauma

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Intensive Care for Emergency Surgeons

Hot Topics in Acute Care Surgery and Trauma

This series covers the most debated issues in acute care and trauma surgery, from perioperative management to organizational and health policy issues. Since 2011, the founder members of the World Society of Emergency Surgery's (WSES) Acute Care and Trauma Surgeons group, who endorse the series, realized the need to provide more educational tools for young surgeons in training and for general physicians and other specialists new to this discipline: WSES is currently developing a systematic scientific and educational program founded on evidence-based medicine and objective experience. Covering the complex management of acute trauma and non-trauma surgical patients, this series makes a significant contribution to this program and is a valuable resource for both trainees and practitioners in acute care surgery.

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Intensive Care for Emergency Surgeons

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Foreword

Research is fundamentally altering the daily practice of acute care surgery (Trauma, Surgical Critical Care, and Emergency General Surgery) for the betterment of patients around the world. Management for many diseases and conditions is radically different than it was just a few years ago. For this reason, concise up-to-date information is required to inform busy clinicians. Therefore, since 2011 the World Society of Emergency Surgery (WSES), in partnership with the American Association for the Surgery of Trauma (AAST), endorses the development and publication of the "Hot Topics in Acute Care Surgery and Trauma," realizing the need to provide more educational tools for young in-training surgeons and for general physicians and other surgical specialists. These new forthcoming titles have been selected and prepared with this philosophy in mind. The books will cover the basics of pathophysiology and clinical management, framed with the reference that recent advances in the science of resuscitation, surgery, and critical care medicine have the potential to profoundly alter the epidemiology and subsequent outcomes of severe surgical illnesses and trauma.

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Preface

The specialty of Critical Care has evidenced tremendous advancements over the past 20 years. While the field has morphed into an independent specialty, the impact of critical care therapy has been felt across multiple disciplines. In surgery, while many surgeons, particularly those practicing trauma, have pursued advanced training and certification in critical care, there remains a significant number of practitioners worldwide who lack optimal training or experience in order to apply the most modern and beneficial treatments to their patients. Other surgeons may simply lack the time required to devote full attention to the critical care needs of their patients.

Accordingly, the motivation for developing the current book was born. In essence, our goal is to provide a comprehensive overview of current critical care principles, in order to assist the acute care surgeon in the care and treatment of their patient. Such an overview seems essential as well in order to provide a format for intelligent dialogue and joint decision making between the surgeon and intensive care team.

The editors have assembled experts in various areas of intensive care, who are also surgeons, to develop dedicated chapters of the various areas of the specialty, in order to assist the surgeon in their efforts to provide the highest level of care to the patient.

It is important to emphasize that the current work is not aimed to be a textbook covering all areas of critical care, as there are many such publications already in existence, but to serve as a format to promote improved understanding, dialogue, and ultimately optimal patient care via active participation by the surgeon and intensivist.

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Mayur Narayan and Jeffry L. Kashuk

1.1 Introduction

Surgical patients requiring intensive care unit [ICU] care may originate from a variety of admitting primary services: trauma, emergency general surgery [EGS], colorectal, gastrointestinal, pancreatic, hepatobiliary, otorhinolaryngology, urology, bariatric, obstetrics/gynecology, vascular, endocrine/oncologic, oral maxillofacial, orthopedic, plastic, solid organ transplantation, and thoracic surgery [1]. The percentage of patients from these various services that will require such care will vary considerably. Furthermore, the knowledge and experience of surgeons from the various specialties and their knowledge of modern ICU principles will also vary considerably. In general, however, modern training in complex surgical procedures will tend to emphasize postoperative management and ICU principles.

Although many patients presenting to the emergency room may require urgent or emergent operation, a smaller percentage may present with labile physiology necessitating direct admission to the intensive ICU for resuscitation and monitoring prior to definitive treatment. Others may require resuscitation and monitoring in the postoperative period, including those who have undergone damage control laparotomy (surgical exploration with control of hemorrhage and contamination but leaving patients in intestinal discontinuity with an open abdomen) [2]. The cornerstone of ICU treatment of these complicated patients focuses on restoration of normal physiology and management of metabolic acidosis, hypothermia, and

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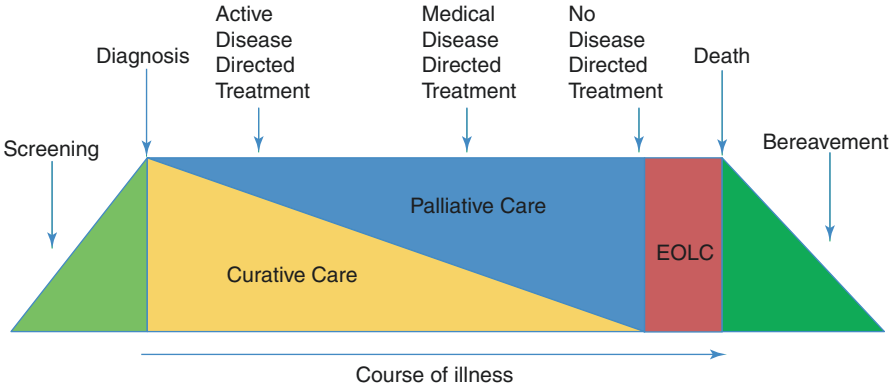


Fig. 1.1 The continuum of care from screening, diagnosis, and curative care, palliative care, and end of life care

coagulopathy [2]. Patients may require critical care services at any time during their course of illness. It is imperative that surgeons admitting their patients to the ICU understand where the patient is in this time course to best match care with resources available (Fig. 1.1).

1.2 Admission to the ICU

The most important initial step in the management of the critically ill patient is to identify, as early as possible, those who will require ICU care. Surgical patients make up a significant percentage of those admitted to the ICU. Van der Sluis et al. [3] found that nearly 60% of patients admitted to the ICU during 1 year in the Netherlands underwent urgent or elective surgery before or during an ICU admission. Many factors affect ICU admission decision-making, including bed and expertise availability, institutional protocols, and cultural norms, as well as the obvious determination as to whether the patients' disease process actually warrants ICU care. It is important to emphasize that the ICU admission process may be emotionally stressful for the surgeon, the patient, and particularly the family, who may sometimes find themselves dealing with rapid and difficult decisions that they may not have expected. The Society of Critical Care Medicine's [SCCM] ICU admission guidelines from 2016 recommend ICU admissions based on a combination of the following [4]:

- Specific patient needs that can only be addressed in an ICU, such as life-supportive therapies
- Availability of clinical expertise not readily present elsewhere in the hospital
- Prioritization according to the patient's condition
- Patient diagnosis
- Bed availability

- Objective parameters such as updated vital signs
- Potential for the patient to benefit from interventions
- Prognosis

Despite attempts to categorize these criteria, there is a lack of international consensus on how patients should optimally be triaged for ICU admission. Several studies have suggested using vital signs as a marker for functional impairment warranting higher priority. An example of this is the Swedish Adaptive Process Triage [5], which uses vital signs and chief complaints to create a triage score for ICU admission. Significant alterations of respiratory rate, oxygen saturation, systolic blood pressure, and Glasgow Coma Scale have all been associated with increased risk of mortality and therefore influence decision-making in assessing a potentially critical ill patient [5]. The surgeon managing such a scenario should remember that there is growing evidence to suggest that a distinct subset of patients may present with normal vital signs despite the presence of severely deranged physiology. Several studies have shown that the sensitivity and specificity of abnormal vital signs to predict mortality or ICU admission on initial triage were between 50 and 70% [6]. A recent study by Holena et al. [7] found that trauma center vital signs might underestimate mortality in those patients transferred from outside hospitals, leading to incorrect estimates of mortality risk. Elderly patients, immunocompromised patients, or those on steroids or with diabetes may not mount an appropriate inflammatory response and lead to underestimation of severity of illness. These patients, therefore, warrant a high index of suspicion for ICU admission.

1.3 Rapid Response Teams as an Aid to ICU Triage

The role of rapid response teams [RRTs] in determining which patients warrant ICU admission has been debated for the past decade. Some institutions use these teams as a means to minimize unnecessary resource utilization by determining a true need for an ICU bed. Although intuitively attractive, there is no clear data as to whether these teams actually improve outcomes [8]. Several studies have shown reduction in hospital-wide mortality, out of ICU mortality and out of ICU cardiac arrest with use of RRTs. Other studies found no effect on clinical outcomes but did show minimal reduction in inpatient mortality and cardiac arrest [9]. A large cluster randomized controlled trial, The Medical Emergency Response, Intervention, and Therapy (MERIT) trial from Australia, involving 23 hospitals, found no differences in the outcome from cardiac arrest, unexpected death, or unplanned admission to the ICU between the control hospitals and in those hospitals with a rapid response team [10]. Another potential concern for RRTs involves delays in activation, potentially due to poor communication, lack of team efficiency, lack of experience of the staff, and lack of resources. Surgeons should remember that a key concept of intensive care management mandates the right patient, at the right time, at the right place. SCCM's slogan is even more simple, "Right Care, Right Now," meaning the right care is delivered at exactly the right moment to achieve optimal patient outcomes.

Recently, Briggs et al. highlighted the importance of a surgeon's role on RRTs when they introduced a concept of "surgical rescue" [11, 12]. The term highlights the surgeon's central role in the assessment and operative emergency management of medical patients with surgical pathology. Potential diagnoses in these patients include bowel obstruction, intestinal ischemia, and perforation, along with biliary disease, gastrointestinal bleeding, and several other conditions. Peitzman et al. [12] expanded on the original role of acute care surgeons who tend to perform a combination of elective general surgery, surgical critical care, emergency general surgery, and trauma surgery. Surgical rescue is described as the "fifth pillar" of acute care surgery, drawing on expertise from the other four pillars of the specialty to intervene on patients who have suffered surgical complications or have developed surgical pathology during their hospitalization [12]. Further research will be required to better assess the continuing role of RRT's as a part of rescue surgery.

The Task Force of the World Federation of Societies of Intensive and Critical Care Medicine [13] has recently developed key triage decisions for ICU admission. These include:

- ICU triage aims to ensure optimal and equitable use of critical care resources. ICU triage involves weighing the benefits of ICU admission against the risks involved; many factors come into play.
- Whenever possible, intensivists should make the final decision about triage for ICU admission, considering input from nurses, emergency medicine professionals, hospitalists, surgeons, and other professionals.
- Triage scoring systems (see below), algorithms, and protocols can be useful, but they should never supplant the central role of skilled intensivists, with input from multidisciplinary teams.
- Infrastructure should be organized efficiently both within individual hospitals and at the regional level.

1.4 Frailty

Determining who needs and who gets ICU care is a complex problem [14]. Increasing age of patients who are frail and often have more comorbidities, concepts of futility, rationing, and rising costs of ICU care are important concepts that surgeons should know. Frailty is a multidimensional syndrome often described when patients have a loss of physiologic and/or cognitive reserves that confer vulnerability to adverse outcomes. There is an increased prevalence of frailty with aging and a measureable increase in utilization of critical care services by older individuals [15]. Fried et al. [16] defined frailty as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs. in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.

Numerous scales have been developed to assess the presence of frailty. These include but are not limited to the frailty phenotype, the Edmonton Frail Scale, the Rockwood Clinical Frailty Scale, and the gait speed test. The frailty index, described

by Rockwood et al. [17], is a detailed inventory of 70 clinical deficits based on the concept that frailty is a consequence of interacting physical, psychological, and social factors. As deficits accumulate, the frail patient becomes increasingly vulnerable to adverse outcomes. It has been reported that estimates of risk are strong when a minimum of 50 items are considered, but shorter versions (as low as 20 items) have also been explored. The frailty index is calculated as the number of deficits the patient has, divided by the number of deficits considered. For example, in a frailty index based on a comprehensive geriatric assessment, an individual with impairments in 4 of 10 domains and with 10 of 24 possible comorbidities would have 14 of 34 possible deficits, for a frailty index of 0.4 [18]. A potential pitfall of this index is that the 70 items of the original version are too cumbersome to administer even in the most advanced ICUs.

Bagshaw et al. [15] conducted a prospective study in adult patients aged 50 or older at six hospitals in Canada. They found the prevalence of frailty was nearly 33%. Not surprisingly, they noted that patients were older, of female gender, and had more comorbidities and greater functional dependence than those who were not frail. In-hospital mortality was higher among frail patients than among non-frail patients and remained higher at 1 year. Frail patients were also more likely to suffer major adverse events, become functionally dependent, require readmission, and have significantly lower quality of life than non-frail patients. The authors concluded that early diagnosis of frailty could improve prognostication and identify a vulnerable population that might benefit from follow-up and intervention [15].

A systematic review by Lin et al. [19] aimed to examine the impact of frailty on adverse outcomes in the "older old" and "oldest old" surgical patients, defined as ages 75–85 and over 85 years, respectively. The authors concluded that frailty in older-old and oldest-old surgical patients predicts postoperative mortality, complications, and prolonged length of stay. In sum, frailty assessment may be a valuable tool in perioperative assessment as well as in helping better identify need for ICU admission [19].

1.5 Futility vs Appropriate Care

The term "futility" is controversial in medical terminology. Brody et al. [20] stratified futility into subgroups including physiologic futility (failure to produce a physiologic response), quantitative futility (the likelihood of benefit to the patient falls below a minimal threshold), and patient-centered futility (failure to produce effects that the patient can appreciate). Schneiderman et al. [21] defined futility as "an effort to achieve a result that is possible but that reasoning or experience suggests is highly improbable and cannot be systematically produced." Huynh et al. [22] evaluated five ICUs at a quaternary care medical center and found that patients who were subject to futile care prevented the care of others.

The use of the term futility has been discouraged because decision-making should not only depend on technical medical determinations but should also involve contested value judgments about what is appropriate treatment in patients with far

advanced illness [23]. Accordingly, ethicists prefer using the term "appropriate care" with regard to the ICU [24]. A treatment that does not improve the patient's prognosis, comfort, well-being, or general state of health should be considered inappropriate and, hence, futile.

Decisions about appropriateness of care can involve moral judgments about right or good care [25]. Anstey et al. [26] conducted a study of over 150 ICUs in the state of California and reported that doctors and nurse identified 1 or more patients that were receiving inappropriate treatment on the day they completed the survey. Piers et al. [27, 28] surveyed ICU nurses and physicians from 82 European and Israeli ICUs and found that 439 of 1651 respondents (27%) perceived inappropriateness of care for at least 1 of their patients on the day of study.

Vincent et al. [29] conducted a survey of critical care physicians across Western Europe and found that 64% of physicians surveyed had admitted patients with minimal to no chance of survival. Giannini et al. [30] conducted a survey among ICU physicians in Italy. They reported inappropriate ICU admissions by 86% of respondents. The reasons given were clinical doubt (33%); limited decision time (32%); assessment error (25%); pressure from superiors (13%), referring clinician (11%), or family (5%); threat of legal action (5%); and an economically advantageous "diagnosis-related group" (1%). Studies from Japan and the United Kingdom have also determined that very elderly patients admitted to their respective ICUs were perceived to have little chance of survival [31–33].

A study by Sehatzadeh et al. [34] found CPR was offered to all patients, regardless of acquired benefits and despite a hospital policy that permitted withholding of cardiopulmonary resuscitation when appropriate. Interestingly, although ethicists studying care of critically ill patients have argued that CPR should not be performed on patients who are unlikely to benefit, physicians are often unsure about what is and is not ethically and legally permissible.

Although such documents may not be uniformly accepted clearly defined advanced directives, describing the wishes of patients may help avoid inappropriate care. Surgeons admitting their patients to an ICU should have knowledge of ethics and laws in their local environment as these are the most likely factors influencing potential liability. A recent policy statement from five large critical care societies offered a framework to manage potentially inappropriate treatments [23].

1.6 Advanced Directives

The intensive care team should review all advanced directives on admission. One method of stratifying patients based on priority was developed by the SCCM (Table 1.1). This scheme uses a five-point scale where Level 1 and 2 patients are critically ill patients requiring life support for organ failure, most often multi-organ but can be attributable to single organ. The key distinction between Level 1 and Level 2 patients in this description is that Level 2 patients admitted to the ICU *do not* wish to undergo cardiopulmonary resuscitation [CPR] should they develop cardiac arrest. Patients and families who are undecided as to their wishes in a cardiac arrest scenario should be reminded that in the absence of any documented advanced directives, the intensive care

Table 1.1 Stratification of critically ill patients

Level of care	Priority	Type of patient
ICU	1	Critically ill pts requiring life support for organ failure, intensive monitoring and therapies only provided in ICU Life support: invasive ventilation. CRRT,[a] invasive hemodynamic monitoring to direct aggressive hemodynamic interventions. ECMO,[a] IABP[a], and other situations requiring critical care (e.g., pts w/severe hypoxemia or in shock)
	2	Pts. as above, w/significantly lower probability of recovery & who would like to receive intensive care therapies but not CPR[b] in case of cardiac arrest (e.g., pts w/metastatic cancer and respiratory failure secondary to pneumonia or in septic shock requiring vasopressors)
IMU[c]	3	Pts w/organ dysfunction who require intensive monitoring and or therapies (e.g., noninvasive ventilation), or who in opinion of triaging physician, could be managed at lower level of care than ICU (e.g., postop pts who require close monitoring for risk of deterioration or require intense postop care, pts w/respiratory insufficiency tolerating intermittent noninvasive ventilation). These pts may need to be admitted to ICU if early management fails to prevent deterioration or there is no IMU capability in hospital
	4	Patients, as described above but with lower probability of recovery/survival (e.g., patients with underlying metastatic disease) who do not want to be intubated or resuscitated. As above, if the hospital does not have IMU capability, these patients could be considered for ICU in special circumstances
Palliative care	5	Terminal or moribund patients with no possibility of recovery: such patients are in general not appropriate for ICU admission (unless they are potential organ donors) In cases in which pts have unequivocally declined intensive care therapies or have irreversible processes such as metastatic cancer w/no additional chemo or radiation therapy options, palliative care should be initially offered

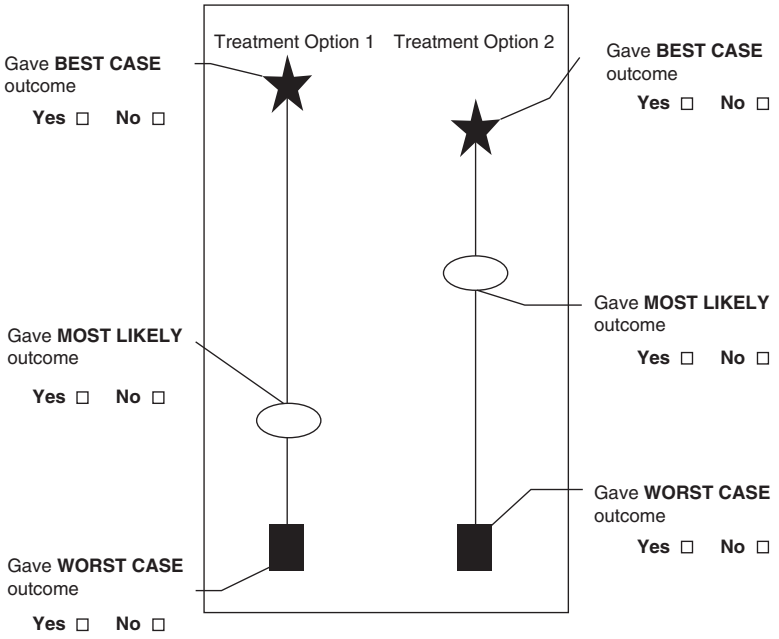
Nates et al. [4] SCCM DOI: https://doi.org/10.1097/CCM.0000000000001856
[a]CRRT, ECMO, IABP: continuous renal replacement therapy, extracorporeal membrane oxygenation, intra-aortic balloon pump
[b]Cardiopulmonary resuscitation
[c]Intermediate Care Unit

team is obligated under law to perform lifesaving procedures including compressions, shock, medications, etc. [35] It is important to emphasize that designating an ICU patient, *Do Not Resuscitate* or *Do Not Intubate* [DNR/DNI] does not translate to *do not treat*. These orders are to be employed only after treatment has failed. Wang et al. [36] recently found that 50% of patients with prior DNR on ICU admission survived to discharge, indicating that aggressive care in such situations may not be futile.

As the population ages, assessment of frailty and geriatrics care in the ICU will become more important than ever. Being mindful that care and proposed management are done "for someone" and not "to someone" can help optimize quality of life and care while minimizing the chances of prolonging suffering. Tools to aid decision-making will need to be developed to help stratify surgical risk as well as optimize outcomes. One such tool, developed by Olson et al. [37–39], is the

Best Case/Worst Case [BC/WC] framework designed to support in-the-moment decision-making. This simple yet highly effective tool may assist and improve communication by shifting the focus of decision-making from an isolated surgical problem to a discussion about treatment alternatives and outcomes (Figs. 1.2 and 1.3). As noted, the BC/WC model promotes shared decision-making and facilitates the development of informed preferences. Patients and their families should be encouraged to verbalize their choices and options at the outset of the

Best Case/Worst Case Tool Skills Checklist & Observation Form



Written diagram complete/ used patient-friendly terminology	**Yes** ☐ **No** ☐
Used narrative/ told a story when describing cases	**Yes** ☐ **No** ☐
Included patient's chronic medical conditions in discussion	**Yes** ☐ **No** ☐
Used questions or phrases to encourage deliberation	**Yes** ☐ **No** ☐
Made a recommendation	**Yes** ☐ **No** ☐

SURGEON ID: _____

TOTAL SCORED POINTS: _____ **/ 11**

ADDITIONAL COMMENTS:

Fig. 1.2 Best case/worst case scenario: a framework for difficult decision-making in surgical patients who are critically ill

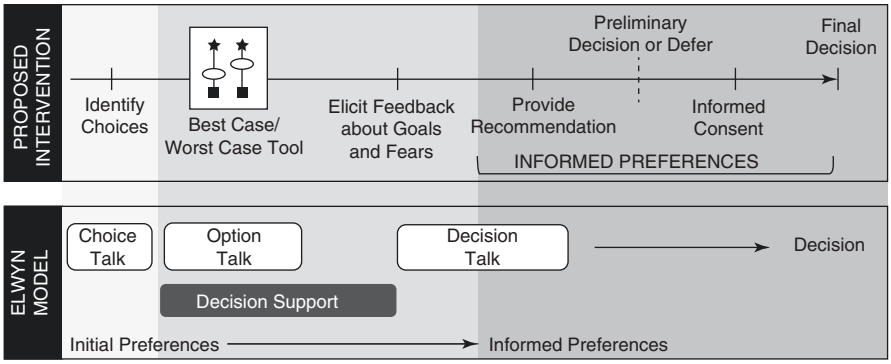


Fig. 1.3 How the "best case/worst case" tool is used within a complete clinical decision-making process. Kruser et al. JPSM April 2017 Volume 53, Issue 4, Pages 711–719.e. The proposed use of "best case/worst case" builds on a conceptual model (bottom) described by Elwyn et al. that promotes shared decision-making and facilitates the development of informed preferences

decision-making process, allowing them greater autonomy as well as improved understanding of the varying treatment options.

1.7 ICU Economics

Healthcare delivery models around the world continue to grapple with escalating costs, varying the quality of care and ethical concerns related to commercialization of healthcare [40]. It is important to recognize that care of the critically ill patient is even more costly. Those from resource-poor nations often struggle with access to basic life-sustaining resources such as clean water, food, and electricity. These areas also often lack primary medical and preventative care, creating a disproportionately high prevalence of critically ill patients. Critical care, as practiced in more developed nations, is often not feasible in such settings. More research to improve cost-effectiveness and implementation in these environments is vital. Worldwide, there is substantial variation of ICU bed availability. For every 100,000 people in the country, Germany has 24.6 ICU beds, Canada 13.5 ICU beds, the United Kingdom 3.5 ICU beds, South Africa 8.9 ICU beds, Sri Lanka 1.6 ICU beds, and Uganda 0.1 ICU bed [41]. The costs associated with care of the ICU patient in developed countries are alarming. In 2005, ICU beds in the United States accounted for nearly 15% of all hospital beds. The occupancy rates were estimated at 68%, and costs were roughly $82 billion or 0.66% of the gross domestic product [42]. It is often said that necessity is the mother invention. This holds especially true for those facing the challenge of delivering critical care with fewer resources and for those who need to manage epidemics and disasters. Alternative models have been described. A low-cost, value-based health model that focuses on maximizing value for patients by moving away from a physician-centered, supply-driven system to a patient-centered system has been developed in India. The Sri Sathya Sai Institute of Higher Medical Sciences

in Bengaluru, India, is a 333-bedded tertiary care hospital equipped with state-of-the-art diagnostic and treatment facilities; highly skilled medical, nursing, and paramedical professionals; and intensive care units, delivering *free* healthcare to all in a compassionate and holistic manner. Since its inception in 2001, the hospital has performed over 20,000 cardiac surgeries, 25,000 neurosurgeries, and 55,000 cardiology procedures and seen over 1.2 million consultations at no charge to patients and with respectable outcomes. More research is needed to assess whether replicating this model in low-, middle-, and high-income countries could have the potential for changing the face of healthcare economics [40].

1.8 Scoring Systems

Clinical scoring systems have shown potential as aids in the assessment of severity of illness and in the determination of patients most likely to benefit from ICU resources. Scoring systems are developed from data collected from multiple ICUs in an attempt to generate a numerical score that may assist in determination of subsequent morbidity and mortality. Most scores include several physiologic and laboratory data along with previous and current clinical health information. ICU scoring systems currently available are listed in Table 1.2. The Acute Physiology and Chronic Health Evaluation (APACHE) II developed from a database of North American ICU patients is a severity of disease classification system based on 12 routine physiologic measurements taken during the first 24 h after admission along with age and previous health status [43]. The score is calculated from 0 to 71 with higher scores related to higher severity and risk of mortality. Despite its common use, APACHE II score has not been shown to be sufficiently sensitive or specific to predict mortality. One major limitation of the APACHE system is that it limits the impact of multiple comorbidities by allowing only one principal diagnostic category. The Simplified Acute Physiology Score (SAPS) II is a severity score and mortality estimation tool developed from a large sample of medical and surgical patients in North America and Europe [43]. The score includes 17 variables of which are 12 physiologic variables with the others being age, admission type, and three disease-related variables. Scoring ranges from 0 to 163 total points with the probability of death being calculated using logistic regression. It should be noted

Table 1.2 ICU scoring systems

APACHE II	Acute Physiology and Chronic Health Evaluation
SAPS II	Simplified Acute Physiology Score
MODS	Multiple Organ Dysfunction Score
SOFA	Sequential Organ Failure Assessment
LODS	Logistic Organ Dysfunction
MPM II on admission 24 h, 48 h, 72 h	Mortality Prediction Model
ODIN	Organ Dysfunction and Infection System
TRIOS	Three-day recalibrating ICU outcomes
GCS	Glasgow Coma Scale

that age, sex, length of ICU stay, location of patient before ICU, clinical category, and presence of drug overdose were subsequently added as admission variables. Although the APACHE II and SAPS II have been validated in the first 24 h of admission, they have had limited effectiveness in predicting mortality following the first day of admission. The Sequential Organ Failure Assessment (SOFA) was designed to focus on organ dysfunction and morbidity with less of an emphasis on mortality prediction. SOFA scores consist of six variables representing respiratory, coagulation, liver, neurological, cardiovascular, and renal systems [44]. A recent systematic review by Haniffa et al. [45] assessed the performance of ICU scoring systems, specifically in low- and middle-income countries (LMICs). The study concluded, "applicability of prognostic models are currently hampered by poor adherence to reporting guidelines, especially when reporting missing value handling." They further suggested that mortality risk predictive models in LMIC intensive care units are at best moderate, highlighting limitations in calibration. Further study is required to determine the ideal score that prognosticates mortality and outcomes, especially in LMICs [45, 46].

1.9 Organization of the ICU

The optimal location of care of the critically ill patient will depend on local factors such as clinical capability and backup care availability [46]. Although ICU care is a practice paradigm and not merely a location, care for these critically ill patients usually takes place in a dedicated portion of a hospital that has equipment and personnel to provide the highest level of advanced life-supportive care (Table 1.3).

Critically ill patients should be rapidly transported from areas of the hospital that lack specialized staff to the ICU for improved outcomes. These units can be *general*, admitting patients from a variety of specialties, as is classically seen in the general medical ICU, or *specialized* where they are typically organized by body system or pathology, such as trauma, burn, neurosurgery, or cardiac. Smaller community hospitals are more likely to have a single general ICU, whereas quaternary-level university hospitals will have multiple specialty-focused units. ICUs can be either "open" or "closed" depending on which physician-led team will take the primary role in the management of the patient. In the open model [47], admission to the ICU can be undertaken by any of the patients' physicians. After admission, the primary physician will write orders and guide management decisions. Intensivists in this model are classified as consultants. In the closed model [3], the intensivist plays the lead role in management decisions, while the primary physician serves as the consultant. The intensivist, with input from the primary team and other consultants as required, serves as the team captain and drives clinical decisions in the ICU. Typically, the intensivist managing a critical care unit has received advanced ICU training. Intensivists can come from a variety of primary specialties and will most typically be either a surgeon, a medical intensivist (pulmonary/critical care), an anesthesiologist, or, most recently, emergency medicine physicians with additional training in critical care medicine. Transferring primary

Table 1.3 Levels of care model adopted from the Society of Critical Care Medicine (SCCM)

Level	Type of pts	Nursing-to-patient ratios	Interventions
ICU (very high) or level 3	Critically ill pts who need hourly and or invasive monitoring, such as continuous blood pressure monitoring via an arterial cannula	1:1 to ≤1:2	Invasive interventions not provided anywhere else, such as CSF[a] drainage for elevated ICP[a] management, mechanical ventilation, vasopressors, ECMO,[a] IABP,[a] LVAD,[a] or CRRT[a]
Intermediate medical unit (high-medium) or Level 2a	Unstable pts who need nursing interventions, laboratory workup, and or monitoring every 2–4 h	≤1:3	Interventions such as noninvasive ventilation, IV infusions, or titration of vasodilators or antiarrhythmic substances
Telemetry (medium-low) or level la	Stable pts who need close electrocardiographs monitoring for nonmalignaut arrhythmias or laboratory work every 2–4 h. This type of unit or ward service is mainly for monitoring purposes	≤1:4	IV infusions and titration of medications such as vasodilators or anti-arrhythmics
Ward (low) or level 0	Stable patients who need testing and monitoring not more frequently than every 4 h	≤1:5	IV antibiotics, IV chemotherapy, laboratory and radiographic work, etc.

Nates et al. [4] SCCM DOI: https://doi.org/10.1097/CCM.0000000000001856
[a]Cerebrospinal fluid, intracranial pressure, extracorporeal membrane oxygenation, intra-aortic balloon pump, left ventricular assist device continuous renal replacement therapy

critical care to the intensivist, who has no other clinical responsibilities other than the ICU, allows the primary surgical team to focus on other responsibilities rather than the time-consuming needs of critical care patients. More ICUs around the world are moving to a closed model, currently the standard in most of the United States, Europe, and Australia. There is increasing data to suggest that mortality of ICU patients is improved using the closed model [3, 48]. Additionally, many trauma centers rotate their trauma/acute care surgeons in the ICU for dedicated periods of time (typically a week at a time) providing continuity of care for their patients. In most models, the ICU physician in this scenario is relieved of other duties during this time, although staffing will ultimately depend on available work force. It cannot be emphasized enough that the care of the ICU patient mandates close attention to manage the minute-to-minute changes that can occur in these critically ill patients. All efforts should be made to avoid staffing the ICU with those who may have other duties in the hospital.

ICU teams have evolved in their construct and now consist of a multidisciplinary group of health professionals working together to provide the most comprehensive care for the critically ill patient. The team typically consists of an intensivist as described above along with ICU nurses, respiratory therapists, nutritionists, pharmacists, speech therapists, physical therapists and occupational therapists, social workers, and more frequently a representative from palliative care. Occasionally,

the team will also have dedicated infectious disease and nephrology specialists who accompany the primary team on rounds and assist with management.

1.10 Communication Best Practices

Once a patient is admitted to the ICU, it is vital that the primary surgical team coordinate hand-off with the anesthesia team and intensive care team to avoid errors in patient care. Numerous hand-off tools exist (Table 1.4). Ilan et al. [49] found that despite the existence of many hand-off tools, critical care physicians did not prefer a particular one over others. The authors emphasized the importance of a systematic approach to minimize breakdowns in communication, particularly with information that is critical. One such tool is the Situation-Background-Assessment-Recommendation (SBAR) developed by Leonard et al. [50] at Kaiser Permanente of Colorado. The technique provides a framework for communication between members of the healthcare team about a patient's condition. Panesar et al. [51] found that an electronic SBAR was associated with more complete and frequent documentation of communication between physicians and nurses. More recently, Marshall et al. [52] noted that a structured SBAR demonstrated improved handover practice when transitioning patients from the operating room to the ICU. IPASS is another commonly used tool to facilitate hand-off of critical information (Table 1.4). Parent et al. [53] noted that the University of Washington-IPASS standardized handoff curriculum was perceived to improve intensive care provider preparedness and workflow. Malekzadeh et al. [54] showed improvement on nurses mean score on safety checklists by using a standard handover protocol. Another model to improve communication, particularly from the OR into the ICU, is currently under development at one of the co-author's institutions, Weill Cornell Medicine. This hand-off mandates the presence of the operative surgical team, the anesthesiology team, and the intensive care unit team including the admitting house officer, the admitting nurse, and the appropriate house staff. Patients on mechanical ventilation undergo an initial assessment performed by a certified respiratory therapist upon arrival to the ICU, to ensure a smooth transition. Mode of ventilation, respiratory rate, tidal volume, positive end-expiratory pressure, pressure support, and fraction of inspired oxygen are documented. The bedside nurse and charge nurse participate in the intake of patients as well as on daily morning and evening rounds to ensure action plans are executed. The standard use of any of these tools

Table 1.4 Optional tools for optimizing hand-offs in the ICU

I PASS THE BATON	**I**ntroduction, **P**atient, **A**ssessment, **S**ituation, **S**afety, THE, **B**ackground, **A**ction, **T**iming, **O**wnership, **N**ext
SHARQ	**S**ituation, **H**istory, **A**ssessment, **R**ecommendations, **Q**uestions
5 Ps	**P**atients, **P**recaution, **P**lan, **P**roblems, **P**urpose
SBAR	**S**ituation, **B**ackground, **A**ssessment, **R**ecommendation

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4134157/ Malekzadeh 2013, 2 (3), 177–185 doi: https://doi.org/10.5681/jcs.2013.022, http://journals.tbzmed.ac.ir/JCS

in the ICU represents an important step forward in improving communication and may help reduce errors and omissions.

1.11 Engaging Family

It is important to remember that the ICU can be a very intimidating place for both patients and their families. The presence of multiple teams and personnel, machine alarms that ring 24 h a day, and a rounding structure that may differ from week to week all add to the potential confusing nature of the ICU [55–57]. Noise in the ICU is one of a number of factors that may disrupt the sleep of patients on the ICU. Studies have shown that staff conversations, routine patient evaluation, and blood draws in the middle of the night, as well as machine alarms, are particularly disturbing and contribute to sleep deprivation and subsequent delirium in ICUs [56, 57]. Sleep disturbances can further compound the problematic issue of development of delirium [57].

ICU teams should develop processes to orient patients and their families on arrival. This is especially of importance when the patient is admitted for a surgical emergency. The surgeon should make it a point to discuss management plans with the patient (if possible), the patient's family, and the ICU care team to avoid miscommunication. Time spent up front, supplemented by follow-up and availability of team members to answer questions, helps ease the transition to the ICU setting. In addition, discussing patterns of workflow can help improve patient and family satisfaction. Relaying whom the team members will be on a given week can help ease anxiety of patients and their families.

Communication optimization supports family presence during ICU rounds. While family presence in the ICU during the time of patient care is not routinely accepted, supporters of this concept suggest that family presence may improve their understanding of the level of detail and multidisciplinary input that goes into decision-making for their loved ones. Detractors state that there is potential for families to witness presentations from junior team members subsequently changed by the attending of the day leading to increased confusion. In addition, family presence requires additional time for rounds in an environment already stressed due to patient volume and severity of illness. Regardless of whether families are present during rounds or not, surgical teams will have to keep families up-to-date to improve communication [58, 59].

Jacobowski et al. [60] found that participation in daily interdisciplinary family rounds was associated with higher family satisfaction regarding frequency of communication with physicians ($p = 0.004$) and support during decision-making. However, this study also found that structured family rounds negatively impacted time for critical decision-making. More recently, Seaman et al. [61] employed a framework to improve ICU communication by using bedside/telephone conversations and family-centered rounds throughout the admission to address high informational needs, along with well-timed family meetings that attend to families' emotions as well as patients' values and goals.

The critically ill ICU patient often has multiple specialists providing care. In many cases, the patient is unable to participate in their own management

decisions due to illness. Family members or designated medical power of attorneys can serve as healthcare proxies to help with decision-making. It is well-known that patients' families express frustration when multiple teams are unable to coordinate a concrete treatment plan. This leads to increasing dissatisfaction and concern that care is being provided in silos instead of as a coordinated team [60, 61].

The intensivist plays a key role in making sure patients and their families are kept up-to-date by serving as the captain of the ship. One mechanism to help support patients and their families in the ICU is to conduct routine multidisciplinary family meetings. Delgado et al. [62] described a meeting format to enhance communication with families that included a pre-meeting of clinicians involved to reach consensus about goals of the meeting and designating who would lead the discussion. All meetings were initiated via an inquiry of the patient's family to assess understanding of the diagnosis, prognosis, and goals of care. Accordingly, this group noted that multidisciplinary team family meetings, especially for those who were critically ill or at high risk of death, enhanced communication between providers and the patient's family to facilitate decision-making.

More research is needed to determine ways to improve transparency and satisfaction of ICU patients and their families. Weber et al. found that dedicated afternoon rounds for families twice a week did not improve family satisfaction, stating that the ideal timing of these rounds was difficult to determine and led to dissatisfaction when families could not participate. Huntington et al. [63] found that families who felt communication regarding the care of their loved ones was deficient were more likely to seek legal assistance. They also found that patients who enjoyed a positive rapport with their physicians felt that good communication flowed from patient to physician and physician to patient. With regular communication, the patient and their family are more likely to feel that their physician is intimately involved in the ICU care being rendered.

1.12 Criterion for ICU Discharge

Patients who no longer require the resources of the ICU should be considered for de-escalation of care. The SCCM has recently provided an updated algorithm to determine if patients meet discharge criterion. These are listed below [4]:

- Every ICU should stipulate specific discharge criteria in their operational policy.
- It is appropriate to discharge a patient from the ICU to a lower acuity area when a patient's physiologic status has stabilized and there no longer is a need for ICU monitoring and treatment.
- Discharge parameters should be based on ICU admission criteria (see above), the admitting criteria for the next lower level of care, institutional availability of these resources, patient prognosis, physiologic stability, and ongoing active interventions.

- To improve resource utilization, discharge from the ICU is appropriate despite a deteriorated patient's physiological status if active interventions are no longer planned.
- Refrain from transferring patients to lower acuity care areas based solely on severity-of-illness scores.

As previously described, while severity-of-illness scoring systems may identify patient populations at higher risk of clinical deterioration after ICU discharge, their value for assessing the readiness for transfer to lower acuity care has not been evaluated. It is important to ensure communication with the patient, the patient's family, and the primary surgical team prior to patient transfer. Patients who have prolonged ICU stays will likely require more detailed hand-offs compared to those who have shorter stays. Premature discharge from the ICU can lead to increased morbidity and mortality of patients who still require increased observation and care. Multiple studies have shown that timing of ICU discharge may impact readmission. For example, patients discharged at night from the ICU fare significantly worse than those discharged during the day. Staffing resources, additional help, and fatigue seem to be potential reasons for this finding [48]. Multidisciplinary input should help determine if patients are truly ready for care de-escalation.

Cognet et al. [64] conducted a qualitative study in the general ward to determine discharge practices at an Australian hospital. Their findings emphasized the importance of communication, the use of hand-off tools, and proper messaging. Patients and their families often become accustomed to the level of care in the ICU. The word "transfer" may lead to anxiety when dealing with the relatives of ICU patients who often have difficulties adjusting to reduced staff, technology, and support.

Many institutions have implemented formal discharge planning rounds. At the R Adams Cowley Shock Trauma Center in Baltimore, MD, these discharge rounds are conducted daily at 11 am. A designated administrator, typically a surgeon who has limited clinical responsibilities for the assigned week, makes multidisciplinary rounds on every patient in the trauma hospital (~130 beds). Members of the primary trauma team, specialists, social workers, nurses, and physical and occupational therapists participate in rounds to provide a very brief statement on who the patient is, why they are in the ICU/hospital, and what needs to be done to facilitate further de-escalation of care, transfer to a rehabilitation facility, or discharge to home [65].

Studies suggest that discharge summaries are often too long while lacking important information [66]. The surgeon and the ICU team should jointly develop a system that incorporates interim summaries to remove minutiae and focus on critical events of patients' care. The summary should be able to tell a story of why the patient was admitted, what management decisions were made by organ system, what interventions were taken and by whom, and what the follow-up plan should be.

The most common causes for ICU readmission following discharge are respiratory failure, cardiovascular failure, sepsis, or neurologic issues. Several studies

have shown that readmission to the ICU significantly increases mortality beyond that predicted by patient acuity alone. Knowledge of which patients are at risk for readmission to the ICU could potentially enable the ICU team and primary service to delay discharge when appropriate. In addition to clinical determination, input from nursing, therapists, and primary specialists, scoring systems (described above) may assist in determination of patients at highest risk. These patients should be assessed to determine which transfer location best suits their needs: step-down unit, in-patient, ward, rehabilitation facility, or home.

Step-down units (SDU) can provide an intermediate level of care that are in fact a "step-down" from that of the ICU but higher than the level of care provided in a general ward [67]. Several models have been described: some incorporate step-down beds into intensive care units, while others are stand-alone units. At Weill Cornell/ New York Presbyterian Hospital, there is a closed ICU with 14 patient beds and 6 adjoining step-down beds that are staffed by the same ICU intensivist but with greater care for the patient transitioned to the primary surgical service. The University of Maryland, on the other hand, has a freestanding surgical step-down unit, with 20 beds and a designated medical director. A less common model is one that incorporates step-down beds into standard wards. These units have been suggested as one possible mechanism to improve critical care cost-effectiveness and patient flow without compromising quality. Although appealing from a design standpoint, more research is needed to provide evidence they make a difference based on patient outcomes, such as length of stay and cost.

Readmissions to the ICU after initial discharge can have implications on patient outcomes and costs. Lissauer et al. [68] found that ICU readmissions were associated with increased resource utilization. They noted that admission severity of illness was significantly higher (APACHE III score: 69.54 ± 21.11 vs 54.88 ± 23.48) in the readmitted group. Interestingly, the discharge acute physiology scores were similar between groups. Not surprisingly, readmitted ICU patients were more likely to have been admitted to emergency surgery and more likely to have a history of immunosuppression or higher APACHE scores compared to those who were not readmitted. The authors concluded that patients who require ICU readmission have a different admission profile than those who do not "bounce back." Understanding these differences could be a potential target for implementing different discharge criteria.

While early discharge could lead to readmission or poor outcomes because of a mismatch between patients requiring supportive care as compared to available resources, late discharge is similarly a well-recognized issue defined by retaining patients who no longer warrant the highest level of supportive care in the ICU. This issue is most commonly due to hospital bottlenecks and non-availability of lesser acuity beds. Unfortunately, such issues may deprive other more critically ill patients of the care they require. Accordingly, improved advanced planning of discharge from the ICU is paramount in order to circumvent this problem.

1.13 Summary

Optimal use of the intensive care unit is a process that includes complex decision-making to optimize resource utilization and may vary greatly depending upon hospital resources, staffing, and location. Many tools are available to assist the clinician in the decision-making process as to which patients require ICU admission, based upon physiological, age, anatomic, and other factors. The cornerstone of assessment and treatment includes a multidisciplinary approach, utilizing the combined input of many members of the hospital and the ICU team. Designated intensivists should coordinate the care of the critically ill patient, working closely with primary surgical teams. Similarly, ICU discharge also requires proper planning in order to effect smooth transition to graduated reduced care according to the patient's needs. In sum, the ideal utilization of ICU care is a complex process which should be patient centered, involving the surgical team, intensive care team, supportive services, and, of increasing centrality, the patient's family support system.

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2 Acute Respiratory Failure and Acute Respiratory Distress Syndrome in ACS Patient: What Are the Indications for Acute Intervention?

Jacob R. Peschman and Marc de Moya

2.1 Introduction

As surgeons are more successful in managing complex diseases, we are faced with more downstream sequelae in these recovering patients, and understanding them is more important now than ever. Respiratory failure and postoperative pulmonary complications (PPC), a term now in the literature referring to an aggregate of several potential conditions ranging from simple atelectasis to acute respiratory distress syndrome (ARDS), in the postoperative period are among the most common that will be faced. ARDS is one of the most severe forms of respiratory failure and therefore warrants special attention. The following chapter will present an overview of respiratory failure and ARDS focusing on definitions (hopefully clarifying some of the potential confusion of the different terminologies seen in the medical literature), how conditions are diagnosed, risk factor mitigation, and ultimately, basic principles of management. It is structured in a way to answer common questions and provides practical knowledge for the surgeon, not to make the reader an expert. The ARDS literature alone is extensive, with a recent PubMed search on the topic revealing 26,315 articles (April 2018). Additionally, though it is an important part of management of the most severe cases of ARDS, extracorporeal membrane oxygenation (ECMO) will not be discussed. Detailed management techniques and considerations for patients requiring or receiving ECMO are outside the scope of this chapter. Severe ARDS potentially requiring ECMO should be managed at a large volume ECMO center with trained specialists and is beyond the expected scope of most surgeons in general practice. For these patients, recognizing the syndrome, understanding its progression, and insuring appropriate initial management will be presented, and prompt referral to an ECMO specialist is the key.

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2.2 Can You Clarify Some of the Terminology I See About Respiratory Failure and ARDS?

Respiratory failure is dysfunction of the normal mechanisms of gas exchange [1–3]. It encompasses a broad range of physiologic changes and disease conditions in both medical and surgical patients. Many of the common terms which surround respiratory dysfunction are used interchangeably when they should not be or with less specificity than the definition was intended. Understanding the common terms and frameworks used to describe the underlying causes of respiratory failure is needed to help generate a differential diagnosis for your patient and to improve communication and documentation.

Respiratory distress (as opposed to ARDS) is a description of a patient showing signs of difficulty breathing (nasal flaring, increased work of breathing, tachypnea, etc.). The etiology is in many ways is not reflected with this term. Further clarity can be attempted with the labels of respiratory insufficiency or respiratory failure. These typically are used in attempts at relaying severity, but again, not etiology. Commonly, failure is reserved for those require intubation >48 h or significant (again not consistently defined) support such as noninvasive positive pressure ventilation (NIPPV). Respiratory insufficiency is often the catch all applied to the rest, usually less severe dysfunction. The only noteworthy point is that, although respiratory and pulmonary are frequently used interchangeable, the CPT code for pulmonary insufficiency is reserved for pulmonary valve insufficiency and should be avoided for documentation purposes.

Postoperative pulmonary complication similarly has no consensus definition and has become a catch all term for any pulmonary-related event occurring in the postoperative period, commonly limited to the first 7 days [4]. These frequently include pneumonia, unplanned intubation, and prolonged (>48 h) mechanical ventilation postoperatively but can also include isolated atelectasis, postoperative respiratory depression, and ARDS. Therefore, it falls on the reader to determine what is included by a specific author when this term is encountered in order to determine relevance to one's own patient population. For the remainder of this chapter, all efforts will be made to clearly define what is encompassed when the term PPC is used.

In terms of developing a framework to start separating out the broad conditions within respiratory failure, the first distinction is acute vs chronic [1]. Chronic respiratory failure encompasses a range of primary pulmonary and cardiac diseases such as chronic obstructive pulmonary disorder (COPD), asthma, interstitial lung disease, and congestive heart failure, just to name a few. The primary clinical distinction is that these conditions usually include some type of *compensation* to the patient's physiology to attempt to correct the pathology and return to a new state of homeostasis. Due to advances in medical care, surgeons are faced with surgical problems in patients now living longer with these diseases. A basic understanding of these is important, but details are outside the scope of this chapter. Whenever possible, appropriate preoperative assessment and communication between the surgeon and the patient's primary care and specialist providers should be undertaken when intervention is considered. Even in the setting of surgical diseases requiring more

urgent treatment, every attempt should be made for early involvement as a way of mitigating risk and assistance with postoperative management. Acute respiratory failure *lacks compensation* and can occur independently or due to exacerbation of a chronic condition (acute on chronic), more so than representing development over a distinct short time frame.

Acute respiratory failure can be further broken down by the "type" of respiratory dysfunction that is encountered. The nomenclature includes type I respiratory failure which denotes impaired gas exchange (hypoxemic) or type II respiratory failure which denotes impaired carbon dioxide removal (hypercapnia) [1]. These will be discussed in more detail when discussing diagnosis. There are often two additional types of respiratory failure that may be encountered in the literature. Type III respiratory failure can be used to describe perioperative respiratory failure. The reason behind some offering this separate category is to acknowledge it as having components of both hypoxemic and hypercapnic dysfunction. As opposed to the term postoperative pulmonary complications, type III respiratory failure specifically looks at the specific respiratory dysfunction due to impaired gas exchange due to atelectasis with impaired normal pulmonary mechanics. The impaired mechanics inhibit ventilation and can be due to nontraumatic diaphragm dysfunction and impaired normal respiratory muscle mechanics due to direct surgical trauma or pain. This is most commonly described after abdominal or cardiothoracic surgery. Whether this subset distinction is necessary is a point of debate for another time, but familiarity with the term should be part of the surgeon's knowledge base. Type IV respiratory failure is the respiratory failure seen in patients in shock, especially if it is due to a non-pulmonary etiology such as non-pulmonary sepsis. In this case, the state of shock, inadequate tissue perfusion, requires supraphysiologic respiratory compensation to improve oxygen delivery to meet demands. Typically, this becomes pathologic when the patient is unable to compensate to meet the tissue needs and is more common with already impaired compensatory mechanisms such as in the elderly. Treatment of this type of respiratory failure is correction of the underlying shock state and condition causing it, with respiratory intervention being primarily supportive until a return to more normal physiologic tissue needs.

In those patients that develop ARDS, there are additional terms to familiarize oneself with. Since it was first described by Ashbaugh and colleagues in adults in 1967 [5], ARDS has been appreciated as a unique clinical syndrome of hypoxemic respiratory failure. The use of the word syndrome is itself worth pointing out. ARDS is not a primary disease. It is the end result of an inflammatory response triggered by another disease process. This inflammatory response causes alveolar injury and potentially diffuse alveolar damage which cause the clinical findings of ARDS. It should also be of significant interest to the surgeon, because, what is often overlooked, is that of the 12 patients in the Ashbaugh series, 7 were either trauma or surgical patients, though most research is in the medical literature. Also, 50 years later we still are faced with inconsistencies in the definition and diagnosis of ARDS which creates challenges in research and reporting. One basic terminology challenge is that there is still interchangeable use of the terminology *acute* vs *adult* respiratory distress syndrome. Despite having an 11-year-old patient in his series,

Ashbaugh's original description used the term *acute* respiratory distress syndrome *in* adults. The earliest use of the phrase *adult* respiratory distress syndrome can be found in 1971 in a paper by Petty et al. [6] and perpetuates as recently as 2017 [7]. Though much of the literature on the topic and many of the management strategies are focused on adult populations, *acute* respiratory distress syndrome is more appropriate, identifying it as a rapidly progressive respiratory failure syndrome not limited to any specific age group.

The greater challenge has been identifying a true consensus definition of ARDS for use in clinical practice and research that accounts for the continuum of the severity while correlating with patient outcomes. Ashbaugh's original description of a syndrome of "acute onset of tachypnœa, hypoxæmia, and loss of compliance" perhaps remains the most true [5]. These clinical findings, combined with classic radiographic findings of bilateral infiltrates on chest X-ray and an absence of other pathology such as heart failure, represent the typical description of ARDS for diagnostic purposes. The two most commonly referenced definitions are the American-European Consensus Conference (AECC) definition first proposed in 1994 [8] and the more recent Berlin criteria published in 2012 [9]. The Berlin criteria were specifically designed to address some of the ambiguity created by the AECC definition and are generally used as the current standard for description and diagnosis purposes. However, given the fairly recent introduction at the time of this writing, some familiarity is needed with the AECC definition as research done using its nomenclature is still some of the highest-quality research available on the topic. The primary terminology point about the AECC definition was that it introduced the term acute lung injury (ALI). The original intent was to help acknowledge the spectrum of severity seen in patients with ARDS, primarily related to the degree of hypoxemia [8]. It was felt that the term ARDS should be reserved for "the most severe end of this spectrum," with ALI used for the entire syndrome. Like thumbs and fingers, all ARDS would be ALI, but not ALI was ARDS. ALI was defined by oxygenation criteria of a ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) of $\leq$300 mmHg. A diagnosis of ARDS would require a PaO_2/FIO_2 of $\leq$200 mmHg, though some argued for 150 mmHg [8]. As such, the cutoff between ALI and ARDS was acknowledged as an arbitrary distinction but one that allowed researchers and clinicians to use nomenclature that more accurately separated out the sickest patients with the highest expected mortality. Unfortunately, this created some confusion. The subsequent use of ALI was more often inaccurately taken to refer to milder forms of ARDS rather than the inclusive term for this entire syndrome. When the Berlin criteria were developed, due in part to this confusion, ALI was removed. However, as with *adult* respiratory distress syndrome, ALI is still commonly encountered throughout the literature and therefore requires the clinician to take note of how the term is being used when critically appraising any article. Following the Berlin criteria publication in 2012, the syndrome was referred to simply as ARDS with the severity spectrum of mild, moderate, and severe based on new PaO_2/FIO_2 cutoffs [9] (Table 2.1). Though retrospective analysis of over 4000 patients using the Berlin criteria showed improved correlation between the

Table 2.1 Diagnosing acute respiratory distress syndrome

	Berlin criteria [7]
Timing	<1 week from clinical insult or worsening respiratory symptoms
Imaging	Bilateral opacities on chest X-ray or CT[a]
Etiology	Respiratory failure not fully explained by heart failure or fluid overload[b]
Severity/oxygenation	*Mild*—$PaO_2/FIO_2 \leq 300$ mmHg with PEEP or CPAP ≥5 cmH_2O *Moderate*—$PaO_2/FIO_2 \leq 200$ mmHg with PEEP ≥5 cmH_2O *Severe*—$PaO_2/FIO_2 \leq 100$ mmHg with PEEP ≥5 cmH_2O

CT computed tomography scan, PaO_2 partial pressure of arterial oxygen, FIO_2 fraction of inspired oxygen, *PEEP* positive end expiratory pressure, *CPAP* continuous positive airway pressure
[a]Not otherwise fully explained by effusions, lung/lobar collapse or nodules
[b]Objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present

new severity classifications than the AECC definition [9], subsequent studies have still revealed areas where it is lacking, especially as related to response to ventilator adjustments within the first 24 h of recognition [10].

2.3 How Do I Recognize Respiratory Failure and What Qualifies It as ARDS?

Respiratory failure can be manifested clinically in several ways depending on the underlying etiology. Common findings of symptomatic hypoxemia, often described as respiratory distress, will include oxygen saturation (SpO_2) <90%, tachypnea >24 breaths per minute, decreased tidal volume, or increased work of breathing [3]. Primary hypercapnia can manifest similarly in attempts to increase minute ventilation and blow off CO_2, or hypercapnia can be the result of respiratory depression with decreased respiratory rate, depressed mental status, and poor inspiratory effort often related to medications (typically narcotics). True hypoxemia is defined as a PaO_2 <60 mmHg on room air and hypercapnia as a $PaCO_2$ >50 mmHg on room air [2]. Initial work up should include a chest X-ray to look for common causes and an ABG to qualify and quantify the degree of hypoxemia or hypercapnia. Common causes of respiratory failure can be seen in Table 2.2. Continuous respiratory monitoring is available. It can be especially useful to detect signs of postoperative respiratory depression and should be considered in high-risk and early postoperative patients. Available modalities include continuous pulse oximetry and continuous capnography. Recent meta-analyses of these techniques suggest that continuous pulse oximetry with nursing notification is superior in identifying patients with postoperative respiratory depression to standard intermittent checks, with possible reductions in number activations of rapid response teams and ICU admissions [11]. Continuous capnography is even more effective at identifying patients with respiratory depression than continuous pulse oximetry, though without adequate evidence to comment on the effect on clinical outcomes such as ICU admissions [11].

Table 2.2 Common causes of acute respiratory failure in surgical patients

Hypoxemic (type I)	Hypercapnic (type II)
Atelectasis	Obtundation or coma
Pneumonia	Medication overdose
Pulmonary contusion	E.g., narcotics and benzodiazepines
Pneumothorax	Respiratory muscle
Fluid overload	Fatigue/dysfunction/trauma[a]
Aspiration	Neuromuscular disorders
Abdominal compartment syndrome[a]	COPD exacerbation
ARDS	

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disorder
[a]May have components of both hypoxemia ad hypercapnia

The diagnosis of ARDS remains a combination of clinical information, laboratory, and imaging findings as defined by the Berlin criteria and summarized in Table 2.1. Onset must be acute as defined as less than 1 week. Radiographic imaging must be obtained and demonstrate bilateral infiltrates/pulmonary edema. This radiographic finding must be present in at least two quadrants of the lung. Chest CT or X-ray are both acceptable modalities. It is also worth noting that radiographic evidence alone does not support or exclude the diagnosis of ARDS. Interobserver reliability of chest X-ray interpretation to exclude of causes of bilateral infiltrates has been marginal in prior studies of intensivists and radiologists, though interpretation skills can increase with training [12]. Additionally, bilateral infiltrates due to ARDS can be found on CT despite being absent on chest X-ray [13].

The cause of the pulmonary infiltrates/edema and clinical status must also be determined to be non-cardiogenic in origin and not due to pure volume overload. Per the Berlin criteria working group, this can be assessed clinically by the treating provider if ARDS risk factors are present (see disease conditions in Table 2.3 [9, 14–16]). The overlap between ARDS due to blood transfusion must also be distinguished from true transfusion-related acute lung injury (TRALI) which is a similar inflammatory response process but uniquely attributable to a reaction to donor white blood cells [17]. If ARDS risk factors are absent, an objective assessment is required which may include invasive monitoring or echocardiography. There is no specification on who must perform the echocardiogram, with recent Society of Critical Care Medicine (SCCM) guidelines establishing that point of care performance by trained intensivists is adequate [18]. Along those lines, the role for bedside ultrasound assessment has continued to expand with evidence supporting its use in volume status assessment independent of echocardiography and as a potential guide for fluid management in ARDS [19, 20]. The group of ARDS patients without a risk factor are also of particular interest as they tend to have a higher mortality, upward of 60%, and likely warrant additional diagnostic testing including bronchoalveolar lavage and CT (if not performed) to better identify the inciting pathology [21].

The last component needed for ARDS diagnosis is the PaO_2/FIO_2 ratio at a period of time when (1) the patient's FIO_2 is known (no requirement for stability of oxygen needs as this represents a single point in time) and (2) the patient is receiving

Table 2.3 Summary of risk factors for development of ARDS

	Non-pulmonary	Pulmonary
Disease conditions	Non-cardiogenic shock[a] Non-pulmonary Sepsis[a] Pancreatitis[a] Severe burns[a] Drug overdose[a] Multiple transfusions[a] Major trauma[a] Traumatic brain injury Multiple fractures	Pneumonia[a] Aspiration[a] Inhalational injury[a] Near drowning[a] Pulmonary Vasculitis[a] Trauma Pulmonary contusion[a]
Patient comorbidities	Alcohol abuse Obesity (BMI >30) Hypoalbuminemia	Asthma Smoker
Medical therapies	Active chemotherapy Liberal fluid administration Delay in sepsis treatment Blood product transfusion	>10 mL/kg PIBW TV mechanical ventilation
Perioperative management	Surgery[b] Spine Major abdominal Cardiac Aortic ASA class ≥3 Multiple anesthetics during admission Perioperative factors Larger crystalloid volume Blood transfusion	Intraoperative factors Increased mean driving pressures Increased FIO_2

BMI body mass index, *PIBW* predicted ideal body weight, *TV* tidal volume, *FIO_2*, fraction of inspired oxygen
[a]Berlin criteria
[b]Risk increased if emergency

a minimum of 5 cmH_2O of PEEP (ventilated) or continuous positive airway pressure (CPAP) (noninvasive ventilation). This ratio must meet the cutoff value of ≤300 mmHg to qualify as ARDS. Severity is further defined based on lower PaO_2/FIO_2 ratios in mechanically ventilated patients as having moderate (≤200 mmHg) or severe (≤100 mmHg) ARDS. Use of SpO_2 rather than PaO_2 has been studied and showed correlation but has not supplanted the ABG [22].

2.4 How Frequently Will I See Respiratory Failure, and How Bad Can It Be for My Patient?

As can probably be assumed from the significant time spent on just defining respiratory failure and ARDS, determining the actual incidence and prevalence of them is quite difficult. Without consensus definitions that are clear and consistently applied over time, variation will continue to be seen in incidence and prevalence rates based

purely on how a condition is defined by a specific study. Recent studies have quoted rates of PPCs ranging from 6–80% though most frequently around 30%, with severe PPCs (requiring intubation or ICU care) in less than 5% [4, 23–26]. This again changes based not only on how PPC is defined but the operation that was performed (higher in emergency, abdominal, and cardiothoracic populations). Atelectasis, when included in the definition, is the most common complication, followed by pneumonia. PPCs are typically quoted as either the most common or second most common complications (after wound complications) following a surgical procedure and represent a significant source of increased hospital length of say, morbidity, cost, and mortality.

ARDS incidence is similarly difficult to determine due to inconsistently applied definitions [27]. Several trends have borne out however. First, ARDS appears to be diagnosed more frequently in the United States than in European countries, with the incidence of ALI (term used due to studies being published prior to Berlin criteria) between 30 and 78.9 per 100,000 person-years [28] with variation by region [29]. This is compared to typically five to seven cases per 100,000 person-years in multiple European countries [30, 31]. The reason behind this tenfold difference is unclear although cultural, economic, and healthcare-related issues have been proposed [32]. Conversely, trauma and surgical patients have been found to have lower incidences of ARDS compared to most medical populations with rates closer to 7–10% in trauma patients in the United States and Europe [7] and 6% in nontrauma surgical patients [33]. Across all groups, however, modern in-hospital mortality rates in severe ARDS are still upward of 20–40% [9, 34, 35]. Within this range, higher mortality is associated with pulmonary sources of infection (pneumonia) and lowest in when associated with trauma at 24% [28]. Most die within the first 3 weeks of diagnosis [30]; however, even after discharge, 2-year mortality rates among ARDS survivors have been found to be as high as 64% [36]. These patients also have higher rates of healthcare utilization and more report significant persistent disability [37–39].

2.5 What is Different About the Pathophysiology of ARDS that Makes Management Different?

While a wide range of different pathologic conditions can cause respiratory failure, and each has unique physiologic consideration, ARDS is somewhat different. As ARDS is not a disease in and of itself, the pathophysiology is really a description of the development of diffuse alveolar damage. This process has classically been described as occurring in sequential phases: an exudative phase, proliferative phase, and finally (in some) fibrosis [40, 41]. The exudative phase begins with the insult. Then, the resulting response by neutrophils, macrophages, platelets, and components of the adaptive immune system leads to inflammation and breakdown of the normal cell interfaces between the pulmonary capillary endothelium, the interstitium, and the alveolar epithelium. This breakdown allows accumulation of exudative fluid in both the interstitium and the lung airspaces. This subsequently inhibits oxygen exchange through multiple interconnected mechanisms. First, the buildup

of fluid within the airways decreases functional surface area for gas exchange. Next, the exudate itself decreases the function of pulmonary surfactant, further decreasing permeability for gas exchange. The resulting cell damage to type 1 pneumocytes further reduces surface area for gas exchange as well as loss of the ion channels capable of generating osmotic gradients that are needed for the lung to remove alveolar fluid. The damage to type II pneumocytes further reduces surfactant production. Early response to these cell injuries also includes development of hyaline membranes and alveolar collagen. This acutely further reduces gas exchange and longer term is part of the development of fibrosis.

The damage to the vascular endothelium is equally deleterious. It results in increased permeability causing fluid buildup, microthrombi causing pulmonary hypertension with right heart strain, and loss of normal hypoxic vasoconstriction autoregulation preventing the response of shunting blood flow away from nonfunctional lung, thereby worsening the overall ventilation-perfusion mismatch. These findings, when seen morphologically with the hyaline membranes, represent diffuse alveolar damage which is considered the pathognomonic finding for ARDS on either autopsy or open lung biopsy [27]. Diffuse alveolar damage can occur in the absence of ARDS due to other diseases. The clinical syndrome of ARDS can also be seen without diffuse alveolar damage especially in mild and moderate cases on autopsy [42].

The proliferative phase is the recovery phase. As alveolar epithelium and vascular endothelium are restored, the previous damage can be reversed with cells capable of generating surfactant and regulating fluid helping the lung return to more normal function. The fibrotic phase is perhaps the most poorly understood. Often referred to as the fibroproliferative response (to acknowledge the pathologic collagen production/fibroproliferation occurring during the exudative phase) or fibroproliferative ARDS (to acknowledge the resulting long-term pulmonary dysfunction), it occurs as a result of excess type I and type III collagen in the recovering lung leading to cystic changes and decreased compliance [43]. It is hypothesized that this occurs due to breakdown in the normal balance of profibrotic and antifibrotic regulatory mechanisms early in recovery. Follow-up studies have found impaired pulmonary function tests in 25–50% of survivors at 6–12 months after the initial ARDS diagnosis [39]. This can be a significant issue contributing to ongoing disability, though it is often difficult to determine if this is truly due to the lung fibrosis or overall neuromuscular weakness as a result of critical illness. Unfortunately, few risk factors have been identified to allow early recognition of the patients who will go on to develop fibrosis. This leaves us without a good way of predicting who will warrant closer follow-up monitoring or to identify high-risk groups for investigation into targeted therapies [43].

2.6 Is My Patient at Risk for Respiratory Failure and What Can I Do to Mitigate It as Much as Possible?

The ability to identify patients at risk for developing PPCs and ARDS has been widely investigated in both medical and surgical populations [14–16, 23, 24, 26, 44–54]. Multiple clinical predictive models are available such as the Assess

Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score for any surgical patient [55] and the Lung Injury Prediction Score (LIPS) [14] specifically for ARDS. The ARISCAT score can be calculated preoperatively with a score ≥ 26 indicating increased risk [55]. The LIPS can be calculated for an individual patient based on comorbidities, disease conditions, and physiologic data, with a score of ≥4 considered higher risk equating to an ALI prevalence of 7% [14]. Additionally, for ARDS, risk varies based on the inciting disease process, with a summary of the pulmonary and non-pulmonary risk factors in Table 2.3.

While the use of predictive models like these does provide some information to the clinician for risk prognosis, the primary value is for ongoing research efforts targeting risk reduction strategies. The most widely studied is the use of lung protective ventilation—the concept of using low tidal volumes (and potentially PEEP) in patients without ARDS as a prevention strategy [24, 25, 55–61]. Since the seminal ARDSnet group publication in the *New England Journal* in 2000 showed that use of low tidal volume (6 mL/kg PIBW target) compared to traditional tidal volumes (10–15 mL/kg, mean of 11.2 mL/kg in study) significantly reduced mortality to 31% from 40% in ARDS, the approach to mechanical ventilation in all patients has changed. Ventilator-induced lung injury (VILI) due to barotrauma (increased pressure in small airways and alveoli), volutrauma (excess stretch of alveoli), and atelectrauma (shear injury due to complete opening and collapse of the alveolus) not only propagates but can potentially lead to the inflammation that causes diffuse alveolar damage [62, 63]. The principle of lung protective ventilation in patients without ARDS with lower tidal volume in many ways made its way into practice organically. The 2016 PRoVENT trial prospectively tried to validate the concept but could not confirm a difference between tidal volume groups [59]. However, a major limitation was that their "high" tidal volume cohort still had typical volumes ranging from 7–9 mL/kg PIBW. This was the lowest ever documented control group mean tidal volume in a large study, supporting the idea that protective low tidal volume ventilation had already been widely accepted and implemented [59]. This leads to challenges with further investigations. Interestingly, though most large meta-analysis that include early trials and retrospective reviews from 12–20 years ago (before wide adoption of the 2000 ARDSnet trial results) favor lung protective ventilation in uninjured lungs, recent prospective validation studies have not been as favorable. In response, further research into even lower tidal volumes (target of 4 mL/kg) is ongoing. Similar difficulty has occurred in attempts to evaluate PEEP. A minimum setting of 5 cmH_2O of PEEP in any ventilated patient is now seen in most practice [60, 64, 65]. Similar lung protective ventilation strategies have been performed to look at ventilation techniques in uninjured lungs intraoperatively. Findings including airway pressures >20 cmH_2O [52], tidal volumes >10 ml/kg PIBW [52], increased mean driving pressures [15], and FIO_2 >70% [15] are among the perioperative factors associated with postoperative development of ARDS.

For the surgeon, additional preoperative and intraoperative ARDS risk reduction strategies exist, primarily focused on the inciting disease, especially sepsis. Delay in initiation of treatment of septic patients including fluid resuscitation and antibiotics, by >3 h from presentation, has shown to increase risk of ARDS in small single-center studies [16, 66]. No studies have been published looking for correlation between

timing to definitive surgical source control and ARDS. However, retrospective reviews have found delays to source control associated with increased overall mortality [67]. Another is fluid management. ARDS must be distinguished from hypoxemia due to simple volume overload or heart failure as these are treated differently, commonly with diuresis. However, fluid in the lung airspaces and interstitium is also a significant part of ARDS pathology. While fluid management in patients with ARDS will be discussed in more detail, excess fluid is also a risk factor for ARDS development. Association between the development of ARDS and larger volumes of crystalloid fluid volumes has been shown intraoperatively (as little as 3 L vs 2 L) [15], in non-septic patients [68], and in prehospital hemorrhaging trauma patients (9% increased ARDS risk per additional 500 mL) [51]. Thoughtful fluid administration must be a balance between avoidance of over resuscitation and risks of inadequate resuscitation, especially in treatment of sepsis [66, 68].

Multiple transfusions (or TRALI itself) are a defined risk factor by the Berlin criteria and another area under direct oversight of the surgeon. For blood products, studies have shown ARDS development associated with red blood cells, fresh frozen plasma, and with platelets [15, 25, 52]. ARDS can occur with any transfusion but may have dose-dependent increased risk as well [46]. Therefore, transfusion indications should be strongly weighed against the risks. This is in keeping with overall movement toward more directed and restrictive transfusion practices in all critical care anemia [69]. Like fluid administration, however, if a bleeding patient requires blood, ARDS risk consideration is in no way prohibitive. In fact on retrospective review on trauma patients in the pragmatic randomized optimal platelet and plasma ratios (PROPPR) data, crystalloid volume and not blood products was more predictive of development of ARDS [51]. Also noteworthy in the trauma and surgical population, the ratio of FFP:PRBCs has not been shown to correlate with risk of ARDS [70], though the overall mortality benefit is repeatedly shown in the trauma literature when ratios approach 1:1.

When the surgeon can provide preoperative counseling, several lifestyle modifications can reduce the risk of respiratory failure and ARDS development in the postoperative period. Active smoking, alcohol abuse [45, 54], and body mass index (BMI) all represent potentially modifiable risk factors. Smoking >20 cigarettes correlates with an odds ratio (OR) of ARDS development of up to 5 [45, 53, 54], and BMI >40 increases the OR to nearly 1.8 [49]. Both BMI and smoking also appear to increase the odds of developing PPCs and ARDS in dose-dependent fashions. These risk factors are not new to surgical counseling as they all are also associated with multiple other adverse surgical outcomes. An additional preoperative consideration is inspiratory muscle training with incentive spirometry. Recent Cochrane review supports its use in reducing rates of atelectasis, pneumonia, and length of stay in abdominal and cardiac surgery patients, though significant heterogeneity exists in the duration and type of training [71]. Unfortunately, the data does not support the same degree of benefit when instituted postoperatively, which is most often when it is started, especially for the emergency surgeon [72]. A multimodal approach including early mobilization, education, and several different pulmonary interventions including respiratory therapist involvement, cough and deep breathing, and incentive spirometry has been shown to be more beneficial [73].

For patients that do develop ARDS, additional modifiable and non-modifiable risk factors have been identified that portend worse outcome. The modifiable factors are the ones targeted by available interventions and will be discussed in the following management sections. The non-modifiable patient and disease factors include conditions such as increased age, neoplasm, immunosuppression, active chemotherapy, APACHE II, and SOFA scores [35]. Persistent PaO_2/FIO_2 ratio $\leq$200 mmHg after 24 h from diagnosis of ARDS is also associated with increased mortality [74]. Interestingly, while increased BMI is a risk factor for the development of ARDS, in the surgical population, it has actually been associated with a lower mortality for those that develop ARDS postoperatively [75]. As these factors in general cannot be altered, knowledge of their influence is most useful to aid in discussions of prognosis with patients and families, especially as it relates to decisions about potential withdrawal of life-sustaining therapies in the critically ill. Clinical prediction scoring systems using many of these factors can aid with this and are widely available [76].

2.7 My Patient Has Developed Respiratory Failure, Now What Can I Do?

Patients with respiratory failure are critically ill, and until their trajectory has been determined, even mild cases warrant close monitoring, potentially in an ICU setting. At that point, care will be provided by an interdisciplinary care team including the surgical team, intensivists, low ratio nursing care, respiratory therapists, physical and occupational therapists, nutritionists, and any other ancillary consulting services as warranted by the underlying disease process and sequelae. Initial management will depend on the underlying etiology. Remaining true to that form, the remainder of this chapter will be dedicated to the management aspects of respiratory failure with specific highlights on ARDS in a format similar to a systems-based approach used in many ICU rounds to provide a head to toe practical framework. A basic algorithm proposed by the authors for management is also available in Fig. 2.1. Several organizations have published more comprehensive ARDS management protocols, such as the University of Michigan which is available in its original form on their website and through links from the American Association for the Surgery of Trauma (AAST) [2]. The development of a protocol based on the experience and capabilities of a hospital's own ICU should strongly be considered. A summary of key management principles for ARDS can also be seen in Table 2.4.

2.7.1 Neurologic

Patients with respiratory failure due to obtundation or altered mental status require immediate evaluation and airway protection. Narcotic use for postoperative pain control represents a significant potential risk. Monitoring for this condition is key, as discussed previously, with continuous pulse oximetry or more favorably capnography. Due to the low side effect profile, administration of reversal agents such as naloxone for narcotics and flumazenil for benzodiazepines should be considered early

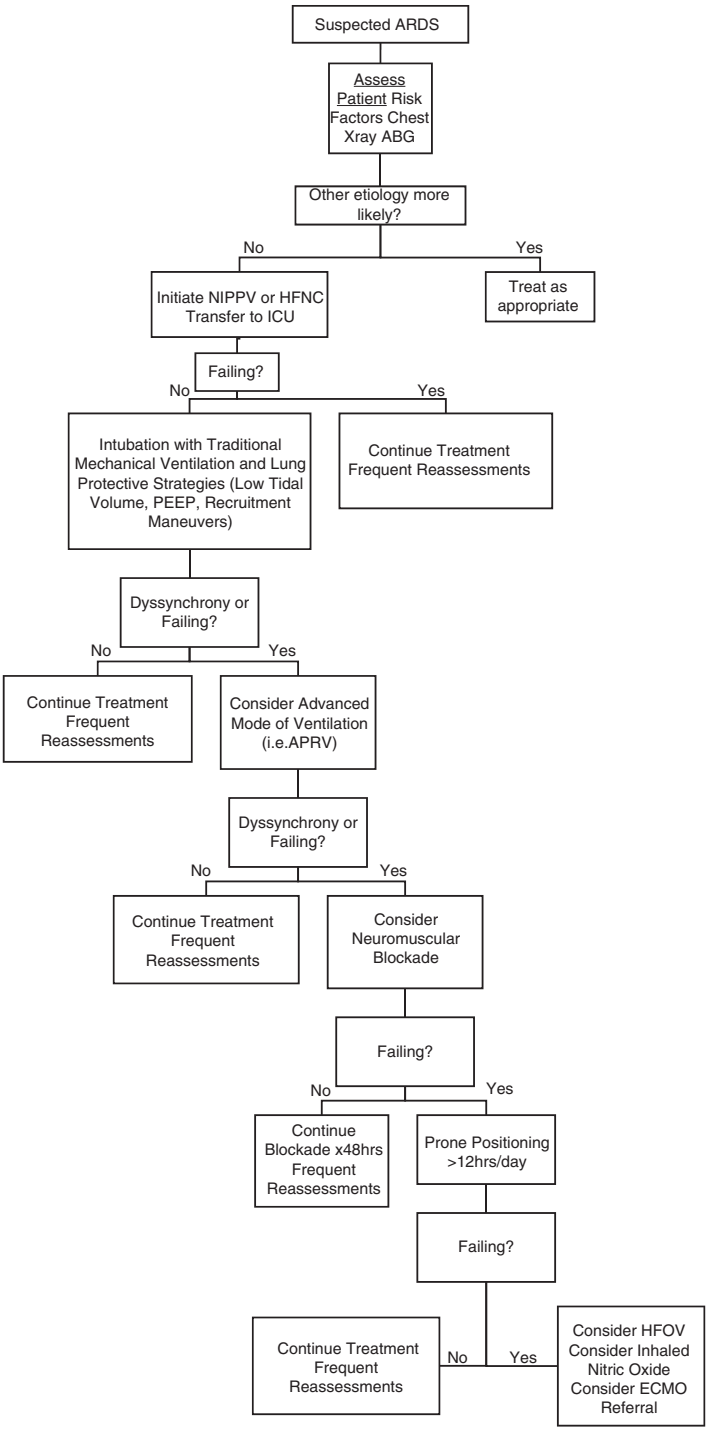

Fig. 2.1 Basic management of respiratory failure

Table 2.4 Summary of ARDS management

System	Intervention
Neurologic	Maintain light sedation for mechanically ventilated patients, ideally with non-benzodiazepine sedatives Perform daily sedation holidays Objective monitoring (e.g., BIS) should be utilized for patients receiving neuromuscular blockade 48 h of neuromuscular blockade can improve mortality
Cardiovascular	The routine use of pulmonary artery catheters is discouraged
Respiratory	Trial of noninvasive positive pressure ventilation or high-flow nasal cannula is appropriate in mild ARDS Utilize low tidal volume ventilation of 4–8 mL/kg PIBW with plateau pressure <30 cmH_2O Utilize higher compared to lower levels of PEEP in moderate to severe ARDS There is no role for *routine* use of high-frequency ventilatory oscillation Utilize >12 h/day of prone positioning in severe ARDS There is no role for the *routine* use of inhaled surfactant, statins, beta-2 agonists, or inhaled nitric oxide
FENGI	Utilize conservative over liberal fluid management strategiesInitiate early enteral nutrition with an anti-inflammatory lipid profile and antioxidants without excess caloric loadConsider stress ulcer prophylaxis
Renal	There is no role for the *routine* use of veno-venous hemofiltration outside of management of renal failure
Hematologic	There is no role for the *routine* use of intravenous unfractionated heparin or inhaled activated protein C Utilize standard venous thromboembolism prophylaxis with unfractionated or low molecular weight heparin
Endocrine	There is no consensus for the *routine* use of corticosteroids in ARDS Corticosteroids should not be initiated after 14 days from diagnosis
Infectious disease	There is no role for prophylactic antibiotics or antifungals
Musculoskeletal	Utilize early mobilization practices

ARDS acute respiratory distress syndrome, *PIBW* predicted ideal body weight, *PEEP* positive end expiratory pressure

and with a low threshold. Naloxone has been found to reverse respiratory depression in over 80% of patients when administered for respiratory depression in hospitalized patients [77]. When administered, continuous patient monitoring is needed though as reversal agent half-lives are typically shorter than the inciting agent. Repeat dosing or continuous infusion may be needed to prevent recurrence of the condition [78].

Sedation principles put forth in the SCCM Clinical Practice Guidelines should be followed for intubated and non-intubated patients admitted to the ICU [79]. These include assessment and treatment of pain, maintaining light levels of sedation with non-benzodiazepine sedatives, utilization of objective monitors for sedation level for patients receiving neuromuscular blockade (e.g., bispectral index), and daily sedation holidays when clinically appropriate [79]. No specific guidelines or large trials have evaluated sedation strategies in ARDS [80]. Subgroup analysis of the ARDSnet tidal volume trial data did not show differences in sedation needs between conventional and low tidal volume groups [81].

Neuromuscular blockade has been shown to improve oxygenation, reduce ventilator days, and decrease 90-day mortality for severe ARDS in multiple randomized trials [82, 83]. Benefits exist with 48 h of neuromuscular blockade early in the course. The primary benefit is felt to be improvement of respiratory mechanics for those patients who remain hypoxemic due to dyssynchrony with the ventilator. With newer modes of ventilation considered more comfortable to the patient, and appropriate pain and sedation management strategies, the use of neuromuscular blockade is frequently reserved for the most refractory patients. Routine paralysis is not recommended by the few societies with published guidelines [84].

2.7.2 Cardiovascular

Cardiovascular considerations specific to ARDS are related to two primary topics, use of invasive monitors and hypotension. As with the general trend in critical care, pulmonary artery catheters (PAC) have not been shown to improve outcomes and have increased cost and risk of complications [85, 86]. Therefore, their routine use is discouraged. Hypotension is predictive of development of ARDS and of worsened outcomes in those who develop ARDS. Hypotension is usually due to the underlying disease process and other medical interventions, not due to ARDS itself. Therefore, management is directed at the underlying disease, with no specific ARDS considerations. The only specific consideration in those mechanically ventilated, however, is hypotension induced by high levels of PEEP [87]. This occurs due to increasing intrathoracic pressure which decreases venous return and ultimately left ventricular filling volume and output. Though typically transient, with application of PEEP to levels at or above 20 cm H_2O, it can become a consideration. Additional fluid volume can overcome this but must be weighed against volume overload considerations.

2.7.3 Respiratory

This is clearly the topic of most importance in management of respiratory failure and ARDS. The threshold to act for surgical patients showing signs of respiratory failure is low. Specific physiologic cutoffs and indications for intubation and mechanical ventilation can be institution specific and also at the clinical discretion of the provider. In general common indications include apnea, significantly low or high respiratory rates (>30 breaths per minute), hypoxia, hypercapnia, increased minute ventilation >10 L/min, or markedly impaired vital capacity (<30% predicted) [2]. Initial management will involve provision of conventional supplemental oxygen, high-flow nasal cannula (HFNC), and noninvasive positive pressure ventilation (NIPPV), either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). There may be a role for NIPPV specifically following extubation in patients undergoing abdominal operations. Small studies suggest benefit for preventing all cause reintubation (relative risk 0.25), though again based on

low-quality data [88]. It is also a first-line support therapy for patient with COPD exacerbations, having been widely shown to reduce both morbidity and mortality. The role of noninvasive support as definitive therapy remains limited to management of some mild ARDS or as a bridge to intubation in a more controlled setting. Small studies have showed possible decreases in intubation rates with NIPPV, but meta-analyses have not supported significant benefit with rates of eventual intubation typically of 50% [89, 90]. Additionally, no clear time frame has been delineated for how long a trial of NIPPV should before declaring failure and proceeding with intubation. Therefore, any NIPPV trial should occur in a monitored setting in case symptoms of increased work of breathing, tachypnea, or persistent hypoxemia are noted warranting intubation. The role for HFNC in postoperative management and ARDS is also gaining traction. Recent meta-analyses have shown at the very least non-inferiority to traditional NIPPV and improvement over standard oxygen therapy in ARDS [91] while providing better patient comfort and perhaps suggesting reduced rates of postoperative reintubation [92].

Patients with progressive respiratory failure and more severe ARDS require intubation. The nuts and bolts of ventilator management is the subject of a future chapter. The American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and the SCCM recently published consensus guidelines for mechanical ventilation management in ARDS [93]. The highlights of these include *strong support* for the use of low tidal volume ventilation defined as 4–8 mL/kg PIBW with plateau pressures <30 cmH_2O, *moderate support* for the use of higher levels of PEEP compared to lower PEEP (15 cmH_2O vs 9 cmH_2O) and recruitment maneuvers in moderate to severe ARDS, and *strongly against* the routine use of high-frequency oscillatory ventilation, though use in selected refractory patients with specific disease processes remains in many clinical protocols at experienced centers. The guidelines specifically did not make recommendations on therapies other than mechanical ventilation, ECMO, or to the use of advanced modes of ventilation such as airway pressure release ventilation (APRV) though may address these in future publications. APRV of note has gained significant interest in critical care as a mode of open lung ventilation that utilizes long periods of high pressure to maintain lung recruitment while allowing spontaneous patient breathing throughout the cycle, decreasing dyssynchrony [94]. There is particular interest in this mode of ventilation in the trauma literature [95], with the primary hindrance of adoption being the unique ventilator settings and adjustment that require familiarity by the entire ICU care team. Optimizing PEEP with esophageal pressure monitoring is also a strategy currently being explored; however, no specific recommendations for or against its use currently exist. Hypercapnia may develop as a result of these respiratory strategies and is tolerated, known as permissive hypercapnia, when balanced against the need to improve oxygenation (goal >88%) and maintain plateau pressure <30 cmH_2O. Medical management of resultant respiratory acidosis may be needed to counteract this strategy, and special attention of the risks needs to be considered in patients with traumatic brain injury in whom acidosis is known to be detrimental.

The ATS/ESICM/SCCM guidelines also gave *strong support* for the use of prone positioning for >12 h/day for those with severe ARDS. Prone positioning has

been studied significantly in ARDS with earliest studies going back to 1988 [96]. The idea behind prone positioning is based on improving the ventilation/perfusion match within the injured lung as originally described by West et al. in 1964 [97]. By placing the patient in a prone position, the typically better aerated anterior portions of the lung become better perfused, improving overall arterial oxygenation. Additional benefits may exist related to shifting to the interstitial and airspace fluid buildup, prompting removal in areas of intact type 1 pneumocytes. The data supporting prone positioning had always been somewhat limited by technique (designed rotational bed vs nursing care turning), concern for increased need for sedation or paralysis, safety concerns about access to the patient, and limitations in movement due to injuries or recent surgery, though most of these have been dispelled [98–101]. The duration of prone positioning had also been part of the inconsistency in its use, though some clarity came with the results of the PROSEVA showing duration of 16 h resulting in lower 28- and 90-day mortality in a well-controlled randomized trial [102]. Guidelines recommending longer durations are coming forth, and individual ICU centers are (and should be) developing protocols to increase its application in a safe manner.

The final respiratory consideration worth briefly discussing is some of the pharmacologic therapies that have been attempted. Though basic science concepts would indicate roles for surfactant replacement, statins (anti-inflammatory properties) [103], and the use of beta-agonists (improve aeration and remove fluid) [104] and inhaled nitric oxide (improve ventilation-perfusion matching) [105], the routine use of all of these therapies has been more or less disproven with several large-scale trials being stopped due to futility. Additional promising research is occurring in several immune-modulating therapies in animal models, such as valproic acid [106], though no significant human trials have been performed to recommend for or against their addition to practice at this time.

2.7.4 Fluids, Electrolytes, Nutrition, Gastrointestinal (FENGI)

Fluid management is a broad ranging topic. As discussed previously in several points in this chapter, liberal administration of fluids has been shown to increase risk of ARDS development in multiple populations [12, 47, 65]. In patients with ARDS, fluid management strategies have been studied multiple times, with the large-scale randomized controlled trial by the ARDSnet group in 2006 comparing a liberal vs conservative fluid strategy (defined based on MAP and CVP and protocolized fluid management responses) considered the gold standard by many [107]. Over the 7-day study period, the conservative group was found to be essentially net fluid even compared to 7 L positive in the liberal group. Though no mortality difference was found, decreased ventilator days and better oxygenation were seen in the conservative group, essentially adding further evidence of the shift toward conservative fluid therapies. Several limitations with the study exist, however, including the use of central venous pressure monitoring to guide fluid administration (and PAC in some patients) which since that trial has been largely discarded in ICU practice.

Additionally, cognitive outcomes were actually found to potentially be worse in the conservative groups at 1 year [108]. These limitations have continued further investigations regarding fluid status monitoring including the use of ultrasound [109]. Use of colloids +/− diuretics as a means of decreasing total fluid volume has also been investigated in ARDS patients, as well as sepsis and trauma, with general consensus in the trauma community and current ESICM guidelines recommending against their routine use [110, 111].

Nutritional support is paramount to any critically ill surgical patient. Early enteral nutrition has a myriad of benefits. ARDS specific considerations have prompted research into immune-modulating formulations and feeding protocols designed to limit potentiating hypercapnia [112]. Excess caloric intake, more so than fat-carbohydrate ratio, is associated with acidosis and worsening hypercapnia and should be avoided [113]. Early initiation of enteral nutrition is recommended for all ICU and surgical patients, defined as within 24 h with increase to goal within 48–72 h [113, 114]. For ARDS specifically, though no large-scale randomized trial has overwhelmingly shown benefit in the use of specific formulations or addition of macronutrients, moderate-quality evidence is favorable and enough to support SCCM recommendations for ARDS formulas "characterized by an anti-inflammatory lipid profile (i.e., omega-3 fish oils, borage oil) and antioxidants" [113]. Additionally, phosphorus should be supplemented as renal function tolerates [113]. The need for stress ulcer prophylaxis in ARDS patients is also not clearly defined and remains a controversial topic. Risks and benefits will need to be weighed based on underlying disease condition, duration of mechanical ventilation, and provision of enteral nutrition as with any other critically ill patient [115].

2.7.5 Renal

As fluid management has been discussed, the remaining renal discussion is the role of hemodialysis therapies. For patients with renal failure, appropriate management should be determined by the care team and nephrologists. The application of veno-venous hemofiltration for inflammatory states and sepsis, either early in the course of renal failure or independent of it, is an area of current interest in critical care research. The principle is based on observations during other trials and the basic science concept of removing inflammatory mediators from the blood stream as a mode of reducing the overall inflammatory burden and shortening its course. Smaller-scale trials have shown potential survival benefit in ARDS on meta-analysis [116] with hemofiltration specifically for removal of inflammatory mediators; however, it is not widely adopted in practice. Cochrane reviews have not shown risk nor benefit, and further research is needed [117].

2.7.6 Hematologic

Transfusion practices have previously been discussed. There is no specific role for leukocyte-reduced PRBCs for ARDS. As part of the pathophysiology of diffuse alveolar damage which involves microthrombi leading to destruction of the pulmonary

vasculature, interest in the role of anticoagulation has persisted in ARDS research. The Unfractionated Heparin for Treatment of Sepsis (HETRASE) trial looking at anticoagulation in sepsis raised questions about benefits to the subgroup of ARDS patients primarily in faster lung recovery [118] but was not supported by later retrospective review [119]. Additionally, aerosolized activated protein C had been shown in small trials to potentially speed lung recovery due to coagulopathic changes in ARDS, though no subsequent studies have supported routine use [120–122]. Venous thromboembolism prophylaxis with standard low molecular weight heparin or unfractionated heparin is recommended in ARDS patients, with choice and dosage based on the underlying disease in accordance with CHEST guidelines [123–125].

2.7.7 Endocrine

The use of corticosteroids is yet another controversial topic in ARDS care. The early research, including Ashbaugh's 1967 series, suggested improvements in outcomes due to anti-inflammatory effect [5]. Since that time, significant investigation has been performed into the role of steroids for the early amelioration of the inflammatory cycle as well as the long-term fibrosis seen in fibroproliferative ARDS [126–129]. The primary issue at present both clinically and in research is patient selection. It remains unclear how to risk stratify those patients that may benefit from steroids, and avoid administration in patients who would not, to avoid potential harm. Additionally, a mortality benefit has been inconsistently demonstrated in single-center studies and meta-analyses and even shown risk of increased mortality in those who received steroids after 14 days in the largest ARDSnet trial on the subject [126, 130]. Currently, the international groups that have published ARDS management guidelines have been split for [84] or against [131] routine use, though general consensus is consistently against of late initiation after 14 days [27].

2.7.8 Infectious Disease

Respiratory failure due to pneumonia is common and can incite ARDS. Broad-spectrum antibiotic treatment for healthcare-associated pneumonia (HCAP) or ventilator-associated pneumonia (VAP) should be initiated earl, ideally after obtaining respiratory cultures, and tailored accordingly based on results [132]. When the diagnosis is unclear, clinical predictive models such as the clinical pulmonary infection score can help determine if treatment is needed, though its reliability in surgical and trauma patients is questioned [133, 134]. For patients with suspected aspiration, routine antibiotics are not routinely recommended though early bronchoscopy (within 24 h) may be considered based on low-quality evidence in reduction of subsequent pneumonia development [135]. There is no current role for prophylactic antibiotic or antifungal treatment in patients with ARDS. Early research into the role of the lung microbiome has shown links to development, and the clinical course, of ARDS in trauma patients who smoke, though the clinical application of this is unclear at present [136].

2.7.9 Musculoskeletal

Early mobilization is broadly supported in the care of ICU, trauma, and surgical patients. Ventilated patients are a group that can significantly benefit as mobility while on the ventilator can be performed safely and has been shown to reduce sedation needs, decrease delirium, and decrease ICU and hospital length of stay [137, 138].

2.8 Conclusion

Respiratory failure and acute respiratory distress syndrome are important for the emergency surgeon to understand. Further research into specific aspects of ARDS care is needed and ongoing. Prevention strategies exist and should be applied preoperatively, intraoperatively, and postoperatively whenever possible. For those that develop ARDS, early recognition and initiation of appropriate respiratory support including low tidal volume lung protective ventilation and general supportive care are paramount to reducing patient mortality.

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3 Nuts and Bolts of Ventilator Management: When Is Invasive or Noninvasive Mechanical Ventilation Appropriate for Your Patient?

Michael C. Smith and Addison K. May

3.1 Introduction

Respiratory failure is among the most common reasons for ICU admission for the patient who undergoes emergency surgery. Over the past several decades, noninvasive ventilation has emerged as a useful tool in the management of the patient with respiratory failure [1–4]. There are a variety of options available to the intensivist to ameliorate this problem, and there is no "one-size-fits-all approach." A thorough understanding of the pathophysiology of the patient's respiratory failure, as well as the mechanisms of the different modalities of respiratory support, is essential to selecting the appropriate mode of support for a particular patient. Particularly important to understand is that all of these strategies are simply a means of support, rather than a cure for the underlying condition. To facilitate understanding of the optimal ventilation support strategy for an emergency surgical patient, in this chapter we outline the different modes of ventilation, the mechanics of the function of each, and the pitfalls of these various strategies. We then describe the approach to the patient with respiratory failure, to help guide the approach to either invasive or noninvasive ventilation.

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3.2 Modes of Ventilatory Support

3.2.1 Invasive Mechanical Ventilation

The classic treatment for respiratory failure is invasive mechanical ventilation. Since the introduction of mechanical ventilation in 1952 [5], positive pressure ventilation has been utilized in the intensive care unit for a variety of conditions. To accomplish this, the airway must be secured, either via intubation (orotracheal or nasotracheal), or undergo a surgical airway procedure (tracheostomy or cricothyroidotomy). The patient is then connected to the ventilator circuit. From here, the intensivist and respiratory therapist may utilize a variety of modes to exert different amounts of control over various aspects of oxygenation and ventilation.

One advantage of invasive ventilation is that it offers maximal control of respiratory function. Clinicians can tailor the ventilator settings to the particular support that their patient needs, so as to allow for correction of the underlying pathophysiologic problem [6–9]. As patient recovery happens, this support can be modulated to facilitate liberation from the ventilator. The patient does not have to put forth any respiratory effort, though such effort can be utilized and accommodated by the ventilator. Additionally, the patient's airway is protected, so procedures such as bronchoscopy can be performed, and enteral nutrition can be delivered safely.

Invasive mechanical ventilation also has its disadvantages. Endotracheal intubation via an orotracheal or nasotracheal tube is quite uncomfortable for patients who are awake, and most require sedation. Patients have no ability to cough against a closed glottis while intubated, so management of secretions must be done via suction. These patients are at risk for ventilator-associated pneumonia, which itself carries a mortality of 13% [10]. Patients may also be at risk of acute dislodgement of the endotracheal tube if agitated or during turning or movements. This risk frequently limits the mobility of patients, despite an emphasis on mobility in all ICU patients, resulting in deconditioning and risk for decubitus ulcers [11].

3.2.2 Noninvasive Mechanical Ventilation

Various forms of noninvasive ventilation exist to support the patient in respiratory failure. In general, all these modalities require a patient who can protect his or her own airway and provide some respiratory effort. The commonly utilized modes of noninvasive ventilation are high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and bi-level positive airway pressure (BiPAP). Below, we describe each mode, its mechanics, and its advantages and disadvantages. These various modes of noninvasive ventilation can be successful in supporting the patient through the episode of respiratory failure until the underlying condition is corrected, and thus the respiratory failure resolves, which can in turn eliminate the risks related to endotracheal intubation and invasive mechanical ventilation [12, 13].

3.2.3 High-Flow Nasal Cannula

Supplemental oxygen is the most commonly utilized mode of respiratory support. A high-flow nasal cannula (HFNC) is an aptly named device, which delivers oxygen to patients at up to 60 l/min. Supplemental oxygen delivered to patients through standard nasal cannulas and masks is typically limited to 15 l/min. The device has an air/oxygen blender and a humidifier, which passes through heated tubing and is delivered to the patient via nasal prongs, much like a standard nasal cannula. The fraction of inspired oxygen (FIO_2) can be manipulated from 21% to 100%. At high flows, this system can generate a positive end expiratory pressure (PEEP) of 3–5 cm H_2O [14–18].

HFNC delivers a reliable FIO_2 via the most comfortable system of any of the modes of noninvasive ventilation, with low rates of intolerance [19]. It is particularly useful for patients who cannot tolerate a mask, either due to anatomic concerns or injuries or claustrophobia. It is an easier device to apply than mask-based modes of noninvasive ventilation. The patient may eat, drink, and speak using his or her mouth if there is no contraindication. Finally, HFNC, in not having an enclosed mask, does not add dead space ventilation due to the rebreathing of carbon dioxide [20].

The main disadvantage of HFNC is that it does not apply positive pressure. Though at high flow it may generate a low level of PEEP, this is likely negated when the mouth is opened. Additionally, it does not contribute to augmentation of tidal volume or minute ventilation. Thus, if the patient's minute ventilation is low, it is unlikely that HFNC will be an effective modality in treating respiratory failure.

3.2.4 Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is a mode of noninvasive ventilation which provides a constant positive pressure throughout the respiratory cycle, without any increase during inspiration. It is commonly administered via a mask, which can be nasal or oral. CPAP may be used to increase functional residual capacity and may counteract intrinsic PEEP. However, the most common use of CPAP in emergency surgical patients is in those who have a diagnosis of obstructive sleep apnea (OSA) already on CPAP at home [1, 12, 21].

3.2.5 Bi-level Positive Airway Pressure

Bi-level positive airway pressure (BiPAP) is similar to CPAP, in that positive pressure is transmitted from a ventilator to the patient. The difference between the two is that in BiPAP, there is an inspiratory and an expiratory pressure, rather than a continuous, unchanged positive pressure. Like CPAP, BiPAP is delivered via a mask which can fit over the nose or over the nose and mouth [12, 22]. There is also a

helmet which may be utilized for BiPAP [12, 23]. Most machines are equipped with a flow sensor to detect the patient's respiratory cycle and synchronize the delivery of positive pressure with the patient's inspiratory effort. The goal of BiPAP is to combat atelectasis, improve gas exchange, and reduce dyspnea and work of breathing.

The advantages of BiPAP are related to its provision of positive pressure ventilation. The patient's work of breathing is somewhat offset by the pressure delivery of the machine, his or her gas exchange improved, and thus dyspnea decreased. Additionally, patients on BiPAP do not require any sedation. The success of BiPAP in the setting of chronic obstructive pulmonary disease (COPD) exacerbation is well-documented, and it is standard therapy for this condition [24–27].

The disadvantages of BiPAP are related to its delivery through a mask. Regardless of the interface used (nasal, oronasal, or helmet), patients can experience discomfort or claustrophobia, with difficulties managing secretions [28]. The masks also must be fitted optimally to the patient, as leaks can interfere with effective achievement of positive pressure [29]. Conversely, if the mask is too tight, or the therapy is continued for too long, then pressure ulcers may develop [30]. Given that inspiration and expiration happen through the mask, rebreathing of carbon dioxide can contribute to hypercapnia [23, 29, 31]. Provision of nutrition can prove difficult during BiPAP, as either the patient would need to remove the mask to eat or would need placement of a naso-enteric tube, which itself could cause difficulty obtaining a seal. Finally, patients must have the ability to remove the masks themselves in the event of emesis.

3.3 Choice of Approach

When caring for the patient in respiratory failure, the intensivist has multiple tools with which to treat the patient. Though some may make it seem like an instantaneous decision, there are several things to consider when deciding to utilize invasive or noninvasive ventilation. First, there are several contraindications for noninvasive ventilation. Furthermore, to best make a decision, one must have a firm understanding of the underlying pathophysiology of the patient's respiratory failure. While it may seem advantageous to "avoid intubation" for a patient, so doing may be harmful or fatal. It cannot be understated that decision to intubate a patient is not a failure on the part of the treatment team; rather it is a prudent decision that may be lifesaving, and no guilt or regret should be felt when making that decision.

As noninvasive ventilation is delivered via a mask through an unsecured airway, there are important contraindications to consider when deciding between noninvasive and invasive ventilation:

- Poor neurologic status (i.e., delirium, coma)
- Inability to protect the airway
- Upper airway obstruction
- Upper gastrointestinal bleeding

- Recent facial surgery or anatomic abnormalities which preclude proper mask fitting
- Vomiting

For these patients, the prudent decision is to proceed with intubation sooner rather than later, as noninvasive ventilation will not only be unsuccessful but also dangerous [12, 13, 32, 33].

Additional factors to consider, though not contraindications to a trial of noninvasive ventilation, include [12, 13, 29, 34–36]:

- Greater severity of illness (i.e., higher APACHE II or SAPS II score)
- Time required for the underlying pathophysiology to resolve
- Inability to seal the face mask
- Older age
- Acute respiratory distress syndrome
- Need for vasopressors
- Need for renal replacement therapy

Under these conditions clinical judgment plays a greater role. If one decides to pursue noninvasive ventilation, he or she must pay close attention to the patient, with a low threshold to proceed with endotracheal intubation and invasive mechanical ventilation.

With this in mind, we outline several considerations when approaching the emergency surgical patient with respiratory failure. First, one must consider the urgency of the situation. In the immediate, life-threatening condition, the patient should be intubated without any further thought of noninvasive ventilation. The intensivist should ensure control of the airway and mechanical ventilation and then pursue treatment of the other life-threatening conditions.

Next, one must consider the anticipated time course of the illness. If the condition is imminently reversible and a short time course is anticipated, then it is prudent to proceed with noninvasive ventilation. We are far more eager to give a trial of noninvasive ventilation in a patient who is fluid overloaded (and thus correctable in a short time), as opposed to the patient with abdominal sepsis who will require at least one procedure aimed at source control plus several days of antibiotics to ameliorate his or her condition. Though this requires some degree of prognostication, such should be considered in the acute period.

As with any treatment strategy, one must consider the risks of the particular mode of respiratory support. Endotracheal intubation carries with it the risks of subglottic stenosis and ventilator-associated pneumonia [37, 38]. Noninvasive ventilation can mitigate those, but itself has risks of pressure ulcers from the mask [30]. Additionally, the nutritional risk of utilizing noninvasive ventilation for a prolonged time is significant, especially in the patient who undergoes emergency surgery. As well, the risk of aspiration by the patient on noninvasive ventilation should be considered.

Logistically, if one chooses to pursue noninvasive ventilation for the treatment of respiratory failure, this should be done in a monitored setting. Moreover, this must be a unit where urgent intubation can be undertaken. It should have fully stocked airway carts or bags, laryngoscopes, video laryngoscopes, and equipment to perform emergent surgical airways. Along with this, the unit should have standard procedures for intubations (i.e., checklists) and round-the-clock personnel to perform these should the need arise. As such patients may decompensate quickly, this consideration is of utmost importance.

Finally, with all these in mind, certain patients will still pose uncertainty for the intensivist. The judgment of an experienced clinician, while hard to measure, cannot be understated. The patient who you "just don't have a good feeling about" or the one who "just seems to keep heading in a poor direction" should be intubated. As stated previously, this is a sign of strength, and not a decision to feel bad about.

3.4 Conclusion

The patient in respiratory failure presents an interesting clinical dilemma, as there are several treatment modalities in the armamentarium of the intensivist. An attention to the underlying pathophysiology, which yields information about urgency, time course, and overall trajectory of illness, can shed light on proper decision-making. As with any decision, this must be continually reevaluated and the course changed when it seems ineffective. It cannot be understated that endotracheal intubation and mechanical ventilation do not represent a treatment failure and weakness on the part of the team; rather they are a sign of clinical strength, prudent decision-making, and often the most important decision one must make for a patient.

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4 Principles of Weaning from Ventilatory Support: When and Why to Wean and When to Consider a Tracheostomy

G. Pizzilli, E. Brogi, V. Agnoletti, L. Ansaloni, and F. Coccolini

4.1 Introduction

A third of patients admitted in intensive care units (ICUs) worldwide are mechanically ventilated [1], and up to 34% of patients ventilated for more than 48 h receive a tracheostomy [2]. Weaning and tracheostomy are two high-priority topics in intensive care. Risks linked with prolonged ventilation and extubation failure motivated physicians to try to define the best method for discontinuing mechanical ventilation. Expected need for prolonged mechanical ventilation and failure to wean from mechanical ventilation are two main indications for tracheostomy. We found articles about weaning from the 1970s with first randomized controlled trials (RCTs) performed in the 1990s [3], and tracheostomy is used extensively in ICUs by the polio epidemic [4], but for both weaning and tracheostomy, still there are no clinical guidelines or gold standards to suggest the best practice, and many controversies are still evinced by literature. One of the reasons behind the lack of evidence relates to heterogeneity in individual characteristics and severity of disease of patient populations subjected to mechanical ventilation and reported in RCTs. This makes more complicated to take the right decision for the right patient and often experience besides knowledge guides decision-making. In this chapter we address general issues regarding weaning process and its stages and main controversies about indications, technique, and timing of tracheostomy.

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4.2 Weaning: Definition and Relevance

The term *weaning* is used to describe the process of gradual reduction in the level of ventilatory support from a patient to enable spontaneous ventilation. Some authors use other terms, withdrawal, discontinuation, or liberation, since it implies rapid removal of a burden that is no longer necessary [5]. As soon as the imbalance between ventilatory capability and demand begins to resolve, weaning should start because both, prolonged mechanical ventilation and premature extubation, expose patients to risks. Mechanical ventilation increases the likelihood of complications such as pneumonia, ventilator-induced lung injury, and oversedation [6]. On the other hand, failed extubation is linked with mortality in several studies. In a recent review, failure of planned extubation is reported to be between 2% and 25% and is associated with increased ICU mortality with a merged odds ratio of 6.79 (95% CI = 3.88–11.87) [7]. Furthermore it may directly cause clinical deterioration with augmented SOFA score [8]. Thus it is crucial to screen systematically each day patient's readiness to allow prompt weaning [9]; this is also an independent predictor of successful extubation and survival [10].

4.3 Classification of the Difficult-to-Wean Patients

Categorization of weaning situations provides a better comprehension of the problem and its association with prognosis. In 2007 during the Sixth International Consensus Conference on Intensive Care Medicine, a task force proposed to classify patients according to the difficulty and the length of weaning process [11]. They identified three groups: simple weaning group for patients who proceed from initiation of weaning to successful extubation on the first attempt; difficult weaning group for patients who require up to three spontaneous breathing trials (SBTs) or as long as 7 days from the first SBT to achieve successful weaning; and prolonged weaning group for patients who fail at least three weaning attempts or require >7 days of weaning after the first SBT. In 2017 Bédenau et al. in a multinational prospective multicenter observational study propose a new classification [12]. Unlike the previous one, they included patients not weaned with SBTs and those not weaned successfully. They considered a 7-day delay without mechanical ventilation as successful extubation whether noninvasive ventilation was used or not. Three groups were identified excluding patients transferred or died before any separation attempt. They identified:

- Short weaning group: success within 24 h by first separation attempt (75% of patients).
- Difficult weaning group: weaning terminated after more than 1 day but in less than 1 week after the first separation attempt (13.3% of patients).
- Prolonged weaning group: weaning was still not terminated 7 days after the first separation attempt (11.4% of patients).

Mortality differs in the three groups and was, respectively, 5.8% in the short weaning, 16.5% in the difficult weaning, and 29.8% in the prolonged weaning. Categorizing patients is fundamental to understand the prognosis. This stresses the concept that risk of dying increases every day after the first separation attempt.

4.4 The Weaning Process

Deciding the time to discontinue mechanical ventilation is often an arbitrary clinical decision influenced by judgment and experience rather than data [3], but clinicians' ability to predict short-term weaning has low sensitivity and specificity [13]. Even if the use of local protocols for discontinuation may reduce the duration of mechanical ventilation [14], still we don't have unique formula for weaning process because its outcome is influenced by a wide spectrum of reason related to the underlying illness which determined the need of intubation and by patients' individual characteristics.

Tobin and Jubran described weaning in seven stages [15]: (1) preweaning, till the causes determining the need of mechanical ventilation are resolved; (2) suspicion, when a physician begins to think that the patient might be ready to come off the ventilator; (3) measuring and interpreting weaning predictors, when the clinician screens the possibility to perform a weaning trial obtaining physiological measures; (4) perform weaning trial as a confirmatory test, decreasing ventilator support by a spontaneous breathing trial (SBT); (5) extubation or reinstitution of mechanical ventilation depending on SBT success/failure; (6) use of noninvasive ventilation after extubation; and (7) reintubation. Even if this description is not widely used, many authors agree that most important stages are the suspicion (stage 2) and assessing readiness to wean (stage 3) because these are common cause of delayed weaning [5, 11]. An exemplification of weaning process' key points is described in Fig. 4.1.

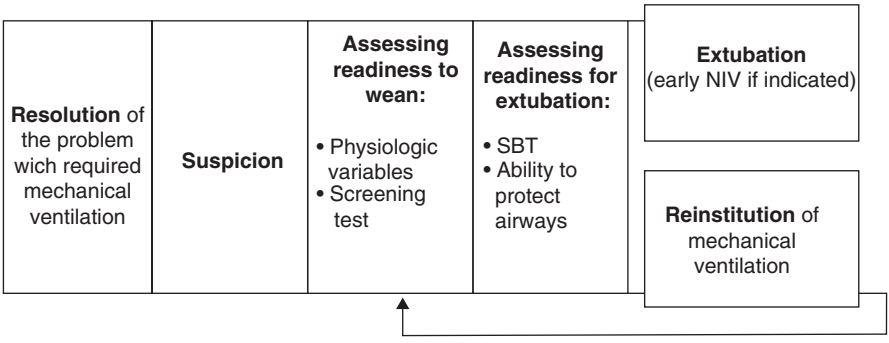

Fig. 4.1 Key points of a weaning process

4.5 Assessing the Readiness to Wean

Assessing readiness to weaning by daily screening of the respiratory function followed by trials of spontaneous breathing should be initiated as soon as the problem that caused the patient to require ventilation is resolved. Ely et al. showed that screening patients daily to identify those who can breathe spontaneously and perform a trial of spontaneous breathing successfully promotes the earlier discontinuation of mechanical ventilation [9] which, his turn, is an independent predictor of successful extubation and survival [10]. Physiologic variables and screening tests, termed weaning predictors, are the tools used for screening readiness for weaning trial. Many weaning predictors have been proposed [16, 17]. An international consensus conference emphasized that the first weaning trial must be performed as soon as the patient meets the following criteria [12]: cardiovascular stability with no need or minimal vasopressors, no continuous sedation, and adequate oxygenation defined as paO_2/FiO_2 of at least 150 mmHg with positive end-expiratory pressure (PEEP) up to 8 cm H2O. These criteria should be viewed as considerations for probable weaning rather than as strict criteria that must all be met simultaneously. One of the most used screening tests is the rapid shallow breathing index (RSBI) (respiratory frequency/VT) [16, 18] obtained with the patient connected to a Wright spirometer or to the ventilator in the "flow by" mode with no pressure support (PS) zero PEEP over a minute or till the respiratory pattern achieves equilibrium [15]. RSBI was used in many different studies with values <100–105 breaths min^{-1} L^{-1} showing an average high sensitivity of 0.87. RSBI, as all predictor test, should be performed when the prior (pretest) probability is very low (ideally <20%) [19] so it should not be performed for patients in whom the clinical probability of successful weaning is high. If the variables predict a reasonable likelihood of weaning success, clinicians progress to the next step.

4.6 Assessing Readiness for Extubation Attempt

"At the point of extubation, a clinician needs to ask him or her- self two questions: (1) will the patient be able to sustain spontaneous ventilation following tube removal? and (2) will the patient be able to protect his or her airway after extubation?" [20]. The ability to sustain spontaneous ventilation is assessed by performing a spontaneous breathing trial (SBT); the ability to protect airways is related to cough, amount of secretions, and mentation. SBT is a safe test to assess the ability of the patient to sustain spontaneous breathing and should consider a confirmatory test of screening tests performed in the previous phase [19]. It consists in patient spontaneously breathing through the endotracheal tube (ETT) either without any ventilator support or with minimal ventilator support. Only 13% of patients who successfully passed the SBT and were extubated required reintubation [21, 22]. The duration of a SBT should be between 30 min and 2 h [23]. During SBT

physiological parameters should be strictly monitored, and trial should be stopped in the presence of a respiratory frequency of more than 35 breaths/min, SaO_2 below 90%, HR above 140 beats/min or a sustained increase or decrease in the HR of more than 20%, systolic blood pressure above 200 mmHg or below 80 mmHg, and agitation, diaphoresis, or anxiety [12]. Several different techniques to perform SBT have been evaluated, T-piece, low level of PSV, ATC, or CPAP, and still no single method showed to be superior to other [21, 22, 24–26] even if SBT with low levels of PSV (inspiratory pressure augmentation) is recommended in recent clinical practice guidelines with moderate quality of evidence [27]. Some physicians prefer to apply pressure support of 5–8 cm/H_2O with the rational of overcoming resistance by endotracheal tube. Nevertheless if it's been demonstrated that the tube resistance is similar to the glottic and supraglottic resistance [28] and the addition of PS produces large reductions in inspiratory work of breathing and respiratory effort [29–31], hence some authors argued that applying any level of pressure support causes physicians to underestimate the patient's respiratory resistance after extubation [20]. One of the most common causes of SBT failure is weaning-induced cardiac dysfunction triggered by increased left ventricular afterload, the increase in the work of breathing, and the increase in sympathetic tone created by the emotional stress and potentially by hypercapnia and hypoxia [32]. Sudden increase in pulmonary artery occlusion pressure (Ppao) measured by a pulmonary artery catheter (PAC) during unsuccessful weaning attempts has been documented till 1988 by Lemaire et al. [33, 34]. Echocardiographic indices (E/A, E/Ea ratio) allow accurate detection of pulmonary occlusion artery pressure elevation during SBT [35]. Increase in arterial pressure and heart rate during unsuccessful weaning is also a weak but suggestive index of weaning failure of cardiac origin [36]. B-type natriuretic has been used as a predictor tool for weaning failure as well as diagnostic of unsuccessful SBT due to heart failure [37]. In a recent remarkable review, those parameters have been proposed as diagnostic tools (together with hemoconcentration and volumetric hemodynamic monitoring of extravascular lung water) for weaning-induced cardiac failure, and a treatment based on fluid removal and antihypertensive drugs administration has been proposed [32]. Diaphragm weakness due to prolonged mechanical ventilation is another key and underestimated factor in SBT outcome; it's associated with long duration of weaning and increased mortality [x]. Evaluation of diaphragm function by ultrasound is a reliable technique in prediction of SBT failure; Grosu et al. assessing diaphragmatic thickness revealed that diaphragm thinning occurs within 48 h after the initiation of mechanical ventilation [38].

Airway protection affects as well extubation outcome: cough strength, amount of secretions, and sedation should be carefully evaluated before extubation [39, 40]. Girard et al. performed a RCT comparing a daily interruption of sedatives with daily SBT with usual care with SBT; patients in the intervention group were discharged earlier from intensive care and from hospital and were 32% less likely to die [41].

4.7 Does Post-Extubation Noninvasive Positive-Pressure Ventilation Prevent Reintubation?

Noninvasive positive-pressure ventilation (NIPPV) for patients who develop respiratory distress within 48 h after extubation does not prevent reintubation [42, 43]. In RCT Esteban et al. observed an increase mortality in NIPPV group possibly due to treatments aimed at reducing the need for reintubation. On the contrary other studies showed that NIPPV reduced rate of reintubation when applied immediately after extubation on patients with risk of failure or without [44]. Preemptive use of NIPPV in patients is found to be effective rather than applying it when post-extubation respiratory distress develops specially in hypercapnic patients [45].

4.8 The Role of Tracheostomy in Difficult-to-Wean Patients

Anticipated need for prolonged mechanical ventilation (MV) and failure to wean from mechanical ventilation are two main indications for tracheostomy [46, 47]. However, the capability to accurately predict the need for protracted mechanical ventilation is still challenging. Tracheostomy facilitates weaning by decreasing the work of breathing in patients with limited reserve. Several studies showed that tracheotomy could substantially reduce the mechanical workload by reducing the resistive and elastic pulmonary work (transpulmonary pressure measurements) and by improving synchrony with the ventilator [48, 49]. Furthermore, the use of tracheotomy cannula allows a reduction in the resistive work in comparison to endotracheal tube (ETT) due to the inner diameter and the major length of ETT. However, the effect on dead space ventilation is irrelevant [48]. Even more, tracheostomy reduces the need for sedation, improves patient comfort, and ameliorates the management of airway secretions, all factors that can play a vital role during the weaning process. Still more, tracheostomy patients presented a reduction in the risk of ventilator-acquired pneumonia (VAP) and fewer accidental extubation episodes in comparison with patients with orotracheal tubes [50–52]. Consequently tracheostomy may offer a more secure airway than a ETT [53]. However, the effects and role of tracheostomy on weaning, hospital stay, and mortality are still controversial [47, 54]. Regardless of the abovementioned advantages of tracheostomy, there is no evidence that this results in reducing the weaning time or in improving the weaning process [55].

4.9 Tracheostomy: Definition and Relevance

Tracheostomy refers to an operative procedure that creates a surgical airway in the cervical trachea. This procedure creates an opening into the trachea through the neck to allow the passage of air. A tracheostomy tube is a curved tube that is inserted into a tracheostomy stoma. There are different types of tracheostomy tubes that vary in certain features for different purposes.

As abovementioned, the main indication is prolonged mechanical ventilation followed by difficult weaning and neurocritical diseases. Tracheostomy has become a progressively common intervention in critically ill patients [56] especially after the introduction of percutaneous techniques. In fact, the number of tracheostomy procedure almost doubles in the last year with more than half of tracheostomies (57%) being percutaneous, performed by the intensivists or by a dedicated team at the bedside [57–60]. The majority of the tracheostomies were performed during the second week of ventilation (7–15 days) [58, 61–63], and, essentially, the percutaneous procedures were performed under bronchoscopic control (98%) [61, 63]. Data on hospital stay, duration of mechanical ventilation, and length of stay in tracheostomy patients diverges widely in different studies [47, 54, 58, 64, 65].

Basically, tracheostomy in the ICU provides a stable and safer access to patient airway for prolonged mechanical ventilation. In fact, protracted endotracheal intubation increases the risk of VAP by deactivating the laryngeal mechanisms, reducing the effectiveness of cough, decreasing the mucociliary function, and promoting oropharyngeal contamination [46, 66]. As a consequence, the risk of nosocomial pneumonia increases with the length of endotracheal intubation [66]. In addition, prolonged endotracheal intubation is associated with the development of sinusitis and may cause severe airway damage. In the absence of contraindications to tracheostomy, in a difficult-to-wean patient, tracheostomy has been encouraged because it decreases the work of breathing [46, 47], improves respiratory mechanics and airway management [67], improves patient comfort [59], reduces sedative drug consumption [68], decreases oropharyngeal trauma [66], improves earlier patient mobilization and earlier transition to oral feeding, and allows prevention of ventilator-acquired pneumonia [53, 65].

The ideal timing (early vs. late) and techniques (percutaneous techniques vs. open surgical) for tracheostomy have been issues of significant debate. Significant international discrepancy in regard to present practice for tracheostomy exists, advocating a necessity for greater standardization for tracheostomy in ICU [61, 62].

4.10 Indications, Contraindications, Complications, and Mortality After Discharge

As aforementioned stated, the most common indications for tracheostomy are acute respiratory failure requiring prolonged mechanical ventilation and traumatic or neurologic impairment with the expected need for airway management through mechanical ventilation [69]. Above all, tracheostomy is performed primarily in critically ill patients in whom multiple attempts to wean from mechanical ventilation have been unsuccessful and in whom prolonged mechanical ventilation are highly probable. Consequently, the timing of tracheostomy in patients likely to benefit this procedure is strictly connected to accurately predict the need for protracted mechanical ventilation [46].

The decision to perform percutaneous tracheostomy in this group of patients should be individualized [70] and should take into account, above all, the expertise

of the performing physician. Morbid obesity, the inability to extend the neck, enlarged thyroid gland, repeated tracheostomy, severe coagulopathy, and unusual neck anatomy are considered as relative contraindications to percutaneous tracheostomy [71, 72]. In such case, if complications occurred during the percutaneous tracheostomy, the practitioner must be ready to convert to the open surgical technique.

Tracheostomy complications can be considered in three time frames: immediate, early, and late [67, 72]. Immediate complications may occur during the tracheostomy procedure and include pneumothorax, bleeding, pneumomediastinum, subcutaneous emphysema, vocal cord dysfunction (recurrent laryngeal nerve injury), posterior tracheal perforation, and tube obstruction. Early complications may arise while the tracheostomy tube is in place and include accidental decannulation, infection around the tracheostomy stoma and stoma scar, and tracheoinnominate artery fistulas. Late complications may result after longer-term presence of a tracheostomy and include tracheomalacia, tracheoesophageal fistula, stomal granulation, stenosis, and delayed closure of tracheostomy.

Tracheal stenosis can occur at the stoma site, subglottic, at the level of the cuff [69, 72]. Most stenoses tend to be asymptomatic unless they reduce the tracheal lumen by more than 50%. Stomal stenosis develops secondary to infection and local inflammation, whereas stenosis at the cuff site is related to ischemia due to high-pressure cuffs. The introduction of high-volume, low-pressure cuffs has decreased the incidence by stenosis [73]. Substantial stenosis can be treated either surgically or endoscopically. Tracheoinnominate fistula is a life-threatening condition that occurs in less than 1–2% of tracheostomies; treatment consists of immediate surgery [69, 72]. Fistulas between other major arteries (e.g., the inferior thyroid artery, an anomalous carotid artery) have also been observed [72].

Complications specific to percutaneous tracheostomy include tracheal cartilage fracture (cartilage protruding into the tracheal lumen), paratracheal placement of the cannula, and postoperative decannulation with an inability to recannulate the trachea due to the absence of a well-formed tract [67].

High-risk groups of patients present a greater probability of tracheostomy complications: children (especially newborns and infants), smokers, alcohol abusers, diabetics, immunocompromised patients, therapy with steroids, and patients with chronic diseases or respiratory infections.

Long-term survival is incompletely understood [74]. In a recent review article, Damuth et al. [75] showed that almost 50% of patients tracheostomized are not liberated from ventilation in the hospital and only less than 15% of patients are discharged home from the hospital mostly because only half were liberated from mechanical ventilation. Finally the overall mortality for mechanically ventilated tracheostomized patients at 1 year was 59%; furthermore tracheostomized patients with percutaneous technique because of respiratory disease showed to have, in a recent paper [76], a higher ICU mortality (50%) compared to those with neurological disease (13.6%) but better quality of life when compared with all other subgroups.

4.11 Early vs. Late Tracheostomy

The optimal timing of tracheostomy in critically ill patients with acute respiratory failure is controversial [77]. The real challenge in deciding when to perform tracheostomy is the competency to correctly foresee the need for prolonged mechanical ventilation. If prediction of protracted ventilation is not correct, then some patients underwent tracheostomy unnecessarily, whereas late tracheostomy strategy will result in prolonged and pointless exposure to translaryngeal endotracheal tube. However, no objective data exist that give an adequate direction on the best timing to switch from an ENT to a tracheostomy [46]. The standard of care has varied substantially over the last years, and the current trend seems to be that the most frequent timing of PDT was between 7 and 15 days [60–62]. In particular situation, such in the case of permanent airway management loss, the decision is straightforward. However, such situations represent the minority of the case, and, therefore, when to perform tracheostomy on a patient with an ENT is a matter of discussion, and the decision on "when" to perform tracheostomy is left in the hand of the practitioner and local protocol.

Evaluating the literature, there is little evidence to guide optimal timing due to a paucity and the methodological diversity of RCTs comparing the effectiveness of early (defined as <10 days) versus late (>10 days) tracheostomies [78–80]. Regardless of the potential benefits to early tracheostomy (e.g., improved respiratory physiology, reduction in sedative consumption), recent RCTs have failed to show short- or long-term mortality benefits. Rumbak et al. [78], in a 2004 prospective randomized study, evaluated the effect of early versus late percutaneous tracheostomy in critically ill patients. Time in the intensive care unit and on mechanical ventilation and the cumulative frequency of pneumonia, mortality, and accidental extubation were evaluated. Early group showed significantly less mortality (31.7% vs. 61.7%), pneumonia (5% vs. 25%), accidental extubation episodes, and inferior intensive care unit stay and mechanical ventilation time when compared with the late group. The author concluded that the advantages of early tracheotomy balance the risks of protracted ENT. A 2012 Cochrane systematic review and meta-analysis evaluated the effects of early (<10 days) versus late (>10 days) tracheostomy in terms of mortality in critically ill patients [77]. Even if the patients receiving early tracheostomy had lower risk of mortality in comparison with patients to late tracheostomy, the authors concluded that the available evidence should be regarded with caution and should be considered as inconclusive. A 2015 systematic review and meta-analysis of RCTs was conducted on the comparison of early versus late tracheostomy as regards mortality, duration of mechanical ventilation, sedation, and intensive care stay [81]. Early tracheostomy was not associated with any difference in mortality [risk ratio (RR): 0.93 (0.83–1.05)], in duration of mechanical ventilation [−0.19 days (−1.13–0.75)], in intensive care stay [−0.83 days (−2.05–0.40)], or in incidence of VAP. The authors stated that they did not find evidence of reduced mortality, duration of mechanical ventilation, intensive care stay, or VAP in early tracheostomy group; consequently,

an early tracheostomy strategy leads to more procedures and a shorter duration of sedation. In selected patients, such as with severe maxillofacial and neck trauma, burns, and neurological injuries, early tracheostomy is mandatory. In this group of patients, tracheostomy could be effective to reduce the duration of mechanical ventilation, in intensive care stay and cost [82, 83]. On the other hand, late tracheostomy is indicated in case of prolonged respiratory support. Consequently, the decision on the timing should be personalized on the base of patients' characteristics [82]. In conclusion, there is no advantage to early tracheostomy in the majority of ICU patients with acute respiratory failure. In this case, waiting until 10 days of intubation and mechanical ventilation is recommended in order to better evaluate the necessity of prolonged respiratory support and consequently of tracheostomy; on the other hand, special patient populations may benefit from early tracheostomy (trauma and burns of neck and facial). Therefore, the current strategy is to apply an individualized approach taking into consideration the patient underlying comorbidities, reason for mechanical ventilation (MV), potential complications of the procedure, and life expectancy.

4.12 Percutaneous Versus Surgical

Percutaneous tracheostomy is increasingly utilized as an alternative to conventional surgical tracheostomy. National and international survey showed that the majority of tracheostomy procedures in critically ill patients were performed by a dedicated team using the percutaneous approach at the bedside [57, 60] and that the percutaneous procedures were performed under bronchoscopic control (98%) [61, 63]. A 2000 meta-analysis demonstrated a lower incidence of peristomal bleeding and postoperative infection when percutaneous are compared with surgical procedure [84]. A 2006 meta-analysis including 17 RCTs with a total of 1212 patients demonstrated that percutaneous reduces the overall incidence of wound infection, relevant bleeding, and mortality when compared with surgical tracheostomy (2.3% compared from 10.7%). The authors concluded that percutaneous tracheostomy, performed in the ICU, should be considered the procedure of choice in critically ill adult patients [82]. Similar findings were also reported in a meta-analysis conducted by Higgins and Punthakee [83]. Furthermore, percutaneous tracheostomy is cost-effective due to the fact that the procedure is performed in the ICU rather than consuming operating room facilities and personnel [55, 85]. Currently, percutaneous procedure is considered the procedure of choice in critically ill patients.

Multiple- or single-step dilatation, guidewire dilating forceps, rotational dilatation, and retrograde tracheostomy were all performed at bedside in the ICU. A detailed description of the aforementioned technique is illustrated elsewhere [46]. The single-step dilatation technique was associated with fewer failures and complications in comparison to rotational dilation and guidewire dilating forceps. The single-step dilatation technique represents the most reliable in terms of safety and success rate and represents the most common percutaneous technique performed in ICU [79]. The translaryngeal technique is technically more demanding, because

require two intubation, however, it is indicated in patient with active at high risk of bleeding. This technique is associated with more severe complications and more frequent need of conversion to other techniques compared with guidewire dilating forceps and single-step dilatation techniques and is contraindicated in patients with difficult intubation [46, 82]. It is however worth keeping in mind that in specific situation and when complications occur, the practitioner must be ready to convert to the open surgical technique [59].

4.13 Ultrasound

The use of ultrasound (US) during or prior to the tracheostomy procedure allows the direct visualization of entry site into the trachea and the determination of the tracheal ring. The US scan has been increasingly used in recent times to estimate the distance from skin to the trachea to ensure the accurate placement of the introducer needle into the trachea and midline punctures [67]. This feature is particularly useful in patients with difficult surface anatomy, severe obesity, and previous tracheostomy. Even more, US scan of the trachea permits the identification and the avoidance of vascular structures in the anterior neck (e.g., the midline thyroid veins) or of an enlarged thyroid isthmus [46, 67]. US represents a new safety adjunct tool to increase the efficacy of PDT [86]. Above all, real-time ultrasound should be considered especially in obese patients with difficult surface landmarks and in patients with altered cervical anatomy and with repeated tracheostomy.

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5 Circulatory Failure and Support in the ACS Patient: What Are the Optimal Methods of Providing Circulatory Monitoring and Support?

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5.1 Introduction

Acute care surgery encompasses the care of some of the sickest patients in the hospital. Expedient diagnosis and management literally determines life and death in many of these patients. Circulatory collapse is often associated with shock but the reverse is not necessarily true. Shock is defined as a dysfunction in cellular respiration manifested in nearly every organ system. Circulatory collapse can be described as the manifestation of hypotension and the compensatory physiologic mechanisms to address hypoperfusion. It can be classified into one of four types: distributive, cardiogenic, hypovolemic, or obstructive.

The physical exam can vary widely depending upon patient factors and shock classification but will consistently reflect poor organ perfusion. Often, the history helps refine the approach to managing patients with confusing or unreliable exam findings. Treatment of the specific cause of shock is the most effective management option. Patients benefit from early identification and appropriate preoperative resuscitation and optimization. Significant comorbidities especially cardiovascular and pulmonary diseases can complicate resuscitation and require careful consideration in order to avoid exacerbating a fragile physiologic state. In this chapter, we will discuss (a) the pathophysiology of shock and how this should affect treatment, (b) current methods of assessing circulatory failure, (c) development of an organized management plan to the patient in need of circulatory support, (d) assessment of the efficacy of resuscitation, and (e) management options for the patient in refractory shock and persistent circulatory failure.

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5.2 Pathophysiology of Circulatory Collapse

Regardless of the cause of circulatory failure, shock is the most common clinical result. Shock is defined as cellular hypoxia and a cessation of cellular aerobic respiration. The sequelae of cellular hypoxia involve a disequilibrium of membrane potentials, intracellular edema, and leakage of intracellular contents [1, 2]. These events lead to some degree of an inflammatory response. The severity of inflammation is related to many patient and pathologic factors including duration of hypoperfusion, the extent of tissue damage, host-pathogen interactions, and ischemia-reperfusion injury. Rapid control of shock may result in minimal perturbation of the inflammatory cascade. In contrast, significant tissue injury or prolonged hypoperfusion can produce an overwhelming systemic inflammatory response that may require an active, ongoing, and dynamic resuscitative approach. Pro-inflammatory mediators activate the endothelium and leukocytes. There is accumulating evidence that shock severity corresponds to structural and genomic changes contributing to individual susceptibility to shock and major injury [3–5].

The clinical manifestation of shock is the result of an overwhelming derangement of biochemical processes. The production of nitric oxide by inducible nitric oxide synthase or metabolites from the arachidonic acid pathway contributes to inappropriate vasodilation as seen in distributive shock. Activated leukocytes upregulate cellular adhesion molecules that cause an accumulation of additional activated leukocytes to pulmonary and systemic capillaries. Chemotactic cytokines further contribute to the recruitment of cells into multiple organ sites. Many of these activated cells produce oxygen-free radical species that lead to further tissue damage [6]. Severe shock can also result in massive parenchymal apoptosis in addition to necrosis, leading to further organ dysfunction and release of damage-associated molecular patterns (DAMPs) which further activate leukocytes [5]. As these imbalances proceed unchecked, the process will evolve into a multi-organ dysfunction syndrome. From here, patient outcomes can range from recovery to a chronic inflammatory response or death [3]. The inflammatory response typically can last days to weeks, underscoring the paramount importance of supportive care. Currently, we have no therapeutic intervention to attenuate the inflammatory response, but there is evidence to suggest that the adaptive immune system contributes to the downregulation of inflammation and a return to homeostasis [7].

Shock represents a continuum. It can be explained in terms of early, middle, and late physiology [8]. The early stage includes the physiologic compensation for cellular injury or decreased tissue perfusion. An example of this includes the patient in Class 1 hemorrhagic shock. Often, this patient has no significant derangement in vital signs except for possibly an increased pulse pressure or slight anxiety. The young and healthy may have hyperdynamic compensatory mechanisms and lack any substantial vital sign abnormality until they have progressed into severe shock.

Middle shock represents what can be thought of as circulatory failure as it is commonly understood clinically [8, 9]. The compensatory mechanisms are overwhelmed, and the patient acquires the physical exam and physiologic derangements

associated with hypoperfusion including hypotension, tachycardia, tachypnea, agitation, etc. In hypovolemic shock this usually corresponds with a loss of >20% of blood volume and in cardiogenic shock a decrease in cardiac index of <2.2 L/min/m^2 [10].

Finally, the late shock continuum corresponds with multi-organ failure (MOF). This is the result of progressive hypoperfusion and irreversible organ injury. In this setting, shock can be refractory to management and death becomes highly probable. Clinically, these patients will require maximum intensive care interventions and are at risk of developing refractory shock.

5.3 Circulatory Assessment

The physical examination is vital in the initial assessment of circulation. Altered mental status can range from anxiety, agitation, and lethargy to obtundation. Tachypnea, tachycardia, diaphoresis, and decreased urinary output can signal hypoperfusion. Hypotension is the hallmark of circulatory collapse and shock and is the most common manifestation of hypoperfusion. However, even this vital sign can be misleading in special populations especially the young, the athlete, and those with excessive sympathetic tone. Patients with heightened sympathetic tone are especially perilous as sedation can precipitate a dramatic decrease blood pressure. Measuring blood pressure reliably with a cuff can be challenging in patients with severe hypotension and in the obese. The physical exam can quickly provide some rough estimates, while a more reliable mechanism is established. The conventional teaching states that a palpable peripheral pulse (radial or pedal) correlates with a systolic blood pressure of >80 mm Hg, a palpable femoral pulse correlates with a systolic blood pressure 70–80 mm Hg, and, if only the carotid pulse is palpable, the systolic blood pressure is between 60 and 70 mm Hg. However, there is evidence that this may grossly overestimate the degree of hypotension and should not be considered sufficient or accurate for comprehensive clinical decision-making [11].

The cause of shock associated with circulatory collapse should be expeditiously determined to mitigate the systemic inflammatory response and reduce organ injury.

In the clinical environment, the physiologic parameters used to characterize shock severity are cardiac output (CO) and systemic vascular resistance (SVR). CO is determined by heart rate and stroke volume. Stroke volume is influenced by preload, myocardial contractility, and afterload. SVR is regulated by vessel length, blood viscosity, and vessel tone. Initial interventions for shock usually begin with dealing with one of these factors depending on the underlying cause of shock. To address these factors, clinicians most often will attempt to give volume intravenously and/or manipulate vessel tone with vasoactive agents. The classification of shock has characteristically been described by their hemodynamic profiles in terms of their effects on CO and SVR with the aid of pulmonary artery catheterization (Table 5.1). There is plenty of overlap among groups. In extreme cases or in mixed or combined shock, the rules may not always apply [12].

Table 5.1 Shock classification

Shock classification	Preload (PCWP)	CO[a]	SVR	Mixed venous oxyhemoglobin saturation[b]
Cardiogenic	↑	↓	↑	<65%
Distributive	↔ (early) or ↓ (late)	↑or ↓ (sometimes)	↓	>65%
Hypovolemic	↔ (early) or ↓ (late)	↔ (early) or ↓ (late)	↑	>65% (early) or <65% (late)
Obstructive				
PE, PH, tension PTX	↔ (early) or ↓ (late)	↔ (early) or ↓ (late)	↑	>65%
Tamponade	↑	↓	↑	>65%

PCWP pulmonary capillary wedge pressure, *CO* cardiac output, *SVR* systemic vascular resistance, *PE* pulmonary embolus, *PH* pulmonary hypertension, *PTX* pneumothorax

[a]Cardiac output can be measured by using cardiac index or by assessment by echo or cardiac ultrasound

[b]Mixed venous oxyhemoglobin saturation cutoff is 65% by pulmonary artery catheter and 70% by central venous catheter

5.3.1 Ultrasound in Shock Assessment

Ultrasound has several advantages. It is portable, quick, and repeatable. It exposes the patient to little or no risks of ionizing radiation. In the late 1990s, ultrasound was integrated into the Advanced Trauma Life Support (ATLS) protocol in place of the diagnostic peritoneal lavage. Known as FAST or focused assessment with sonography in trauma, it has become the preferred method of exonerating hemodynamically significant hemorrhage in blunt trauma. The practice consists of assessing four abdominal views which make up the perihepatic, perisplenic, pelvic, and pericardial views [13]. The typical FAST exam has now evolved into extended FAST or eFAST [14, 15]. This includes assessment of the lung and pleura and is extremely sensitive at identifying pneumothorax but can quickly recognize significant pleural effusions or hemothorax [15].

Ultrasound has since been incorporated more than ever into the initial assessment of patients with circulatory failure and is repeatedly used during resuscitation. In addition to ruling out intracavitary hemorrhage, it provides information on preload, detects ventricular dysfunction and valvular abnormalities, and indicates hemodynamically significant pulmonary embolism and tamponade. Ultrasound is also proving essential in guiding the resuscitation process by detecting preload independence and intrinsic cardiac dysfunction [16].

Limitations do exist as ultrasound is very operator-dependent, and there is a learning curve. Challenges to optimum views involve body habitus, bandages, and conditions that cause air to track through tissues such as subcutaneous emphysema, pneumomediastinum, large wounds, or other tissue defects.

5.3.2 Lactate and Base Deficit

Lactate has long been considered an important marker of hypoperfusion. It now appears that this substrate has more of a nuanced connotation. While it is produced

during times of stress, lactate itself does not necessarily reflect anoxia or the severity of hypoperfusion. Canine studies have shown that with moderate-intensity exercise and readily available oxygen supply, lactate is still produced [17]. Many stimuli that cause the release of catecholamines appear to increase lactate production regardless of the oxygen tension. Lactate clearance is heavily dependent on hepatic clearance. In acute or chronic liver dysfunction, the accumulation of lactate can and should be expected. Lactate in the background of shock appears to signal physiologic stress, but not necessarily the severity of hypoperfusion [18].

Base deficit often correlates with serum lactate and is frequently used in guiding resuscitation. Base deficit usually refers to the amount of bicarbonate expressed in mEq/L within whole blood titrating toward the standardized normal human blood pH of 7.40. By the early 1990s, a base deficit of −8 was found to correlate with a 25% mortality when excluding adults over 55 years and no significant head trauma [19]. Several studies continue to support base deficit as critical in prognostication especially at admission [20].

One of the disadvantages of using base deficit is the effect of saline resuscitation fluids. Large volume saline resuscitation and especially hypertonic saline can contribute to a nongap acidosis.

Once the diagnosis of shock has been ascertained, the cause of shock should be identified. Each type shock has unique features and requires distinct treatment plans. Often the phase of care should be quickly transitioned into a setting that provides close monitoring and treatment of the underlying cause. Most likely these patients will be optimally managed in the intensive care setting or the operating theater.

5.4 Types of Shock

5.4.1 Hypovolemic

Hypovolemic shock is further characterized as hemorrhagic and nonhemorrhagic. Both are the result of reduced intravascular volume, i.e., preload. The heart rate attempts to compensate for reduced stroke volume which leaves the cardiac output relatively unchanged in the early phase. There is a critical threshold after ongoing and uncontrolled volume loss that results in reduce cardiac output.

Hemorrhagic shock can be differentiated into four classes which correspond to physical exam findings. The class of shock correlates to the percent of blood loss (Table 5.2). The validity of this table is questionable in several clinical scenarios and special populations. This includes young children, the elderly, patients with traumatic brain injury, and those who are intoxicated. Special populations such as children can compensate for very large amount of losses until they decompensate precipitously. The elderly has little capacity to compensate for losses, and the clinician should have a lower threshold to resuscitate [21]. Permissive hypotension or hypotensive resuscitation in the setting of traumatic hemorrhagic shock has been shown to decrease transfusion requirements, coagulopathy, and death [22, 23]. For hemorrhagic shock due to trauma, the goal is to provide damage control resuscitation

Table 5.2 Classes of hemorrhagic shock

	I	II	III	IV
Blood loss (mL)	≤750	750–1500	1500–2000	> 2000
Blood loss (%)	≤15	15–30	30–40	>40
Pulse rate (bpm)	<100	100–120	120–140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Urine output (mL/h)	>30	20–30	5–15	Anuria
Mental status	Slight anxiety	Mild anxiety	Anxious, confused	Lethargy, obtundation

(DCR). The primary objective is rapid control of hemorrhage. Crystalloids should be minimized, and blood products should be provided to maintain a MAP of 55–60 until hemorrhage is controlled. Additional adjuncts such as the early use of tranexamic acid continue to gather support and should be strongly considered early in any patient suspected of hemorrhagic shock [24–26].

Common causes of nonhemorrhagic hypovolemic shock that confront the ACS surgeon include severe gastrointestinal, skin, and third-space fluid losses. Gastrointestinal losses include diarrhea, vomiting, and high ileostomy outputs. Typical skin losses occur in major burns, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Third-space fluid losses can be seen after the postoperative period, intestinal obstructions, or pancreatitis. Management involves appropriate crystalloid resuscitation and electrolyte replacement.

5.4.2 Distributive

Inappropriate peripheral vasodilation is synonymous with distributive shock. There are several forms each with a unique pathophysiology. The most commonly encountered for surgeons include septic shock, systemic inflammatory response syndrome, and neurogenic shock. Less frequent causes include anaphylaxis, drug and/or toxin induced, and Addisonian crisis.

5.4.2.1 Septic Shock

Septic shock is the most common form of distributive shock and is associated with mortality of upwards of 40% [27]. Since Rivers and colleagues landmark paper, the principles of early goal-directed therapy were introduced as standard of care for management of septic shock [28]. Since that time, three multicenter, randomized controlled trials have questioned the centrality of protocolization for sepsis [29]. However, the core tenets seem intact. Early patient identification, fluid resuscitation, timely antibiotic administration, and source control remain consistent themes. Serum lactate appears very important in prognostication regardless of the severity of hypotension. If the patient remains refractory to fluid resuscitation, vasopressors are indicated. Norepinephrine remains the first-line choice. Epinephrine can be used as an additional agent if the patient remains refractory. Vasopressin can be added to reduce the norepinephrine requirement but should never be the first-line agent.

It is typically not titrated but started as an infusion at 0.03–0.04 unit/min. Cardiac abnormalities can be dynamic and can comprise systolic and diastolic dysfunction. Normal or low cardiac output can result in septic shock, and these patients have worse outcomes. When septic shock is associated with low cardiac output, dobutamine is associated with a survival advantage although studies comparing epinephrine are lacking [30].

5.4.2.2 SIRS-Related Shock

A variety of other conditions can result in a systemic inflammatory response syndrome (SIRS) in conjunction with shock physiology. SIRS-related shock results in a clinical picture that can range between hypovolemia and a septic-like appearance. Common causes of SIRS-related shock include severe pancreatitis, burns, global hypoperfusion states as seen after trauma, significant blunt or crush injuries, amniotic fluid syndrome, air embolism, fat embolism, idiopathic systemic capillary leak syndrome, and return of spontaneous circulation (ROSC) after effective cardiopulmonary resuscitation (CPR) [12].

5.4.2.3 Neurogenic Shock

Neurogenic shock is a form of distributive shock. It can often be difficult to discern in the multiply injured patient. The patient exhibits hypotension with bradycardia due to disruption of the autonomic nervous system with subsequent sympathetic denervation [31]. Neurogenic shock may present at admission or several weeks later. Lesions that give rise to neurogenic shock are at or above the sixth thoracic vertebrae [31]. Hypotension exacerbates spinal cord ischemia and leads to secondary injury. Fluid resuscitation is first-line therapy. If hypotension remains refractory, then vasopressors should be used to maintain a MAP goal of 85–90 mm Hg. The first-line choice of vasopressor depends upon the clinical situation. If bradycardia and hypotension are concurrent, then dopamine or norepinephrine should be considered. If the patient is refractory to these medications, then epinephrine may prove beneficial. Phenylephrine is not a useful agent in these situations since it is associated with reflexive bradycardia. Before phenylephrine is added as an agent, β-agonism should be established. Vasopressin has no established role and may even worsen spinal cord injury [32].

5.4.3 Cardiogenic

Cardiogenic shock is the outcome of pump failure and reduced cardiac output. This is defined by low cardiac output in spite of normal or high preload or right atrial pressure. Hypovolemia and cardiogenic shock may both have decreased cardiac output. Exam findings to aid in discrimination may include peripheral edema and elevated jugular venous distension (JVD). Chest exam may reveal crackles or new murmur with chest radiography demonstrating evidence of pulmonary edema or an enlarged heart. Cardiac ultrasound can also be especially helpful in differentiating between these forms of shock. Sonography can evaluate chamber sizes, wall motion

abnormalities, presence of intracardiac masses, inferior vena cava (IVC) characteristics, and evidence of effusion or tamponade [33]. Pulmonary artery catheterization can prove valuable in these cases. A cardiac index less than 2.2 L/m^2 is associated with cardiogenic shock especially when the pulmonary artery wedge pressure is >18 mm Hg. A mixed venous oxygen saturation less than 70% is also indicative of a cardiogenic origin of shock. Management of cardiogenic shock requires addressing the cause.

Cardiogenic shock encompasses a range of cardiac or extracardiac causes. This can include left ventricular failure, right ventricular failure, valvular dysfunction, and cardiac arrhythmias. Right ventricular failure is frequently associated with obstructive shock, and this will be discussed later in further detail.

Left ventricular failure is the most common form of cardiogenic shock and is frequently associated with acute myocardial infarction or ischemia. Patients will either demonstrate systolic or diastolic dysfunction. Decreased contractility characterizes systolic dysfunction, whereas chamber stiffness is a hallmark of diastolic dysfunction. Myocardial ischemia, ventricular hypertrophy, and cardiac tamponade all are important causes of diastolic failure. Evaluation with echocardiography is critical to distinguish between them [34].

Valvular disease more often will complicate shock of other causes, but in the acute setting, new valvular abnormalities can yield a profoundly unstable patient. Papillary muscle or chordae tendinae rupture is usually the result of complicated myocardial infarction. Retrograde dissection of the ascending aorta can result in an acute aortic valve rupture with ensuing tamponade [35]. Echocardiography is essential in establishing the diagnosis, and usually the patient will require revascularization, operative repair/replacement, or both.

Arrhythmias can complicate other forms of shock. Ventricular arrhythmias frequently accompany cardiogenic shock. The underlying cause should be sought and can comprise of myocardial ischemia, pain, withdrawal or intoxication, and several others. Symptomatic arrhythmias should follow advanced cardiac life support (ACLS) recommendations. Rhythms associated with cardiogenic shock commonly involve sustained ventricular tachycardia or complete heart block. Unstable ventricular arrhythmias may require cardioversion followed by commencement of antiarrhythmics. Bradyarrhythmias associated with circulatory collapse even without formal heart block regularly benefit from pacing [12].

5.4.4 Obstructive

Obstructive shock is most often a manifestation of an extracardiac cause of pump failure. Like cardiogenic shock, patients present with low cardiac output and elevated venous return or preload. Early identification is imperative because resuscitation strategies should reflect judicious fluid administration and vasopressor choice. Maintaining preload is important, but volume overload can prove antagonistic. Common extracardiac etiologies include pulmonary embolism, cardiac tamponade, tension pneumothorax, constrictive pericarditis, and restrictive

cardiomyopathy. Patients with a history of pulmonary hypertension and right ventricular dysfunction are exceptionally challenging to manage especially in the setting of another form of shock. If no extracardiac cause can be confirmed, then it can be assumed that the patient has an isolated right ventricular failure that deserves further work-up. The differential should include left heart failure, acute right ventricular infarction, or worsening pulmonary hypertension. Echocardiography is required to establish the diagnosis, so a high index of suspicion is valuable [34].

5.5 Management of Shock

The initial management of circulatory collapse should begin with an organized resuscitation approach beginning with the assessment of the airway, breathing, and circulation (ABCs). Hypoxemia should be addressed aggressively with a low threshold to obtain a secure airway. Once the airway has been secured, the mechanics of breathing with positive-pressure ventilation should be mitigated to optimize venous return. In general, low tidal volumes diminish the effects of intrathoracic pressures and are considered lung protective.

Once a plan of action has been established for airway and breathing, the next consideration is access. In addressing circulatory shock, access should allow large volumes. For peripheral access, the largest gauge with the shortest catheter length should be used. Two large bore IV catheters, especially 18 gauge or higher, can provide flow rates equivalent or greater than a large gauge central venous catheter such a sheath introducer or multi-lumen access catheter (Table 5.3) [36, 37].

5.5.1 Invasive Monitoring

After the diagnosis of shock has been determined, that patient's care should be transitioned to close monitoring within the operating room or intensive care unit. Placement of catheters is often indicated and allows for precise therapy and titration

Table 5.3 Catheter sizes affect flow rates

Intravenous catheter	Rate of flow with gravity (mL/min)	Rate of flow with pressure (mL/min)
14 g 5 cm cannula	236	384
16 g 5 cm cannula	155	334
18 g 4.5 cm cannula	98	153
16 g distal port triple lumen cvl	69	116
Sheath introducer (8 g)	200	333
Intraosseous (tibia)	83	154
MAC[a]	483	

Adapted from Reddick et al. [37]
[a]*MAC* multi-lumen access catheter

of medications. Hemodynamic monitoring is standard in most intensive care settings. Most clinicians will utilize at least one or a combination of devices to validate clinical findings.

Arterial catheters provide continuous arterial pressure and access for repeated blood sampling. Indications for invasive arterial monitoring consist of hypotension, clinically significant hypertension, or therapies requiring vasoactive medications. Arterial catheters can guide fluid responsiveness. Variations in arterial pressure during positive-pressure ventilation correspond with venous return. Pulse pressure variation is the difference between systolic and diastolic arterial blood pressure. Ventricular filling fluctuates in states of decreased preload. Thereby, the pulse pressure variation during the respiratory cycle conveys the likelihood of cardiac output augmentation by volume replacement. The caveat is that this is only useful in the mechanically ventilated patient with tidal volumes ≥8 mm/L with a normal cardiac rhythm. Thus, this may not be ideal in tenuous patients requiring lung protective ventilation. Pulse contour analysis functions as an approximation of cardiac output as it takes into account stroke volume and the compliance of vessels. This may offer an alternative to pulmonary artery catheters (PAC), but it does not provide a direct measurement [38].

Central venous catheterization (CVC) facilitates large volume resuscitation and offers reliable access for vasopressor administration. The CVC can measure central venous pressure (CVP), which can be obtained from the jugular, subclavian, or femoral vein [39]. CVP gauges right atrial pressure which can function as a surrogate for preload assessment. However, cardiac dysfunction or pulmonary hypertension also increases CVP. In the absence of pulmonary or cardiac dysfunction, a CVP of less than 10 mm Hg may suggest fluid responsiveness. Multiple measurements should be obtained, and there is more value in trends. The CVC also serves as a site for central venous blood sampling. Central venous oxygenation ($ScvO_2$) can serve as a proxy for oxygen delivery, consumption, and cardiac output [39]. Trends have more utility for individual patients, and corroboration with other modalities such as cardiac ultrasound is encouraged.

Although the utility of PAC in patient outcomes has been challenged, it can be helpful in the appropriate patient population [40, 41]. PAC supplies information on right atrial, pulmonary artery, and pulmonary artery occlusive pressure or wedge pressure (PAWP). The PAWP should reflect the left atrial pressure. There are a number of limitations for PAC especially in the background of respiratory failure. Elevated PEEP can falsely elevate PAWP. PAWP can also be affected by valvular abnormalities and arrhythmias. The PAC enables measurement of cardiac output through thermodilution and can allow for direct assessment of mixed venous oxygen saturation (SvO_2). $ScvO_2$, obtained from the CVC, is an approximation of SvO_2. SvO_2 is generally higher than $ScvO_2$ in healthy patients but is lower in the critically ill. The myocardium is an important site of oxygen extraction and this is not reflected in $ScvO_2$.

5.6 Refractory Shock

Despite aggressive efforts, 7% of critically ill patients will fail to respond to maximum therapy [42]. Refractory shock is defined as failure to achieve a blood pressure goal despite vasopressor therapy, need for rescue therapy, or need for high vasopressor doses [43]. In managing these patients, all causes of shock should be reconsidered and exonerated. Shock classification will guide therapeutic options.

5.6.1 Adjuncts to Resuscitation

Circulatory collapse affects delivery and pharmacokinetics of drugs delivered, making delivery options limited. Subcutaneous and even peripheral venous administrations can be unpredictable. Despite central venous delivery, acidemia will render vasopressors ineffective. Severe organ dysfunction especially renal and liver hypoperfusion can disrupt drug clearance.

Bicarbonate infusion is frequently employed to counteract severe metabolic acidosis. Unfortunately, bicarbonate has some untoward consequences, namely, hypocalcemia and worsening intracellular acidosis by the diffusion of CO_2 through cell membranes. Both of these effects result in reduced myocardial contractility [44]. The administration of sodium bicarbonate requires the elimination of the excess CO_2 via minute ventilation which can exacerbate acute shock and respiratory failure.

Tris(hydroxymethyl)aminomethane or THAM is a biologically inert amino alcohol and proton acceptor [45]. It is considered an alternative to sodium bicarbonate infusion. THAM is excreted by the kidney as an ammonia by-product. This has the theoretic advantage in the setting of ARDS or severe respiratory failure. THAM does not affect serum potassium, but this can be particularly hazardous in the setting of acute kidney injury or massive transfusion which is often accompanied with hyperkalemia [46].

Refractory distributive shock results from an impaired vascular response to catecholamines. If sepsis is a consideration, empiric antibiotics should be broadened, and an active investigation for an uncontrolled source should be entertained. First- and second-line vasopressors should be optimized. There is much evidence supporting vasopressin as an effective agent with norepinephrine in sepsis. There is equipoise to titrating vasopressin if the patient remains refractory [47]. Glucocorticoids should also be considered [48]. Other potential therapeutic agents include calcium chloride, methylene blue, hydroxocobalamin, ascorbic acid, thiamine, and angiotensin II [42].

In patients with refractory cardiogenic shock, veno-arterial extracorporeal membrane oxygenation (VA ECMO) is the most frequently employed option in management. Refractory cardiogenic shock describes the patient with progressive organ dysfunction as the result of insufficient cardiac output despite maximized inotropic

support [49]. While ECMO is effective in the treatment of severe acute respiratory distress syndrome (ARDS) defined as PaO_2:FiO_2 ratio <100, respiratory failure need not be present for consideration of VA ECMO for refractory cardiogenic shock. VA ECMO should be used in the context of specific goals. Ideally, it should serve as a bridge to recovery, transplantation, or destination therapy such as LVAD implantation. Extracorporeal cardiopulmonary resuscitation or ECPR provides VA ECMO to patients who have cardiac arrest that is initially refractory to resuscitation. The cause of cardiac arrest must be potentially reversible. Patients must be carefully selected and expectations must be clearly delineated. A proposed criteria for ECPR suggests that patients have a witnessed arrest with bystander CPR. Patients should be less than 75 years and no ROSC before 10 min or after 1 h [50]. In the background of dysfunction of multiple organ systems, ECMO may not be considered practical, and outcomes are disappointing. Additionally, patients who have required prolonged mechanical intubation (>10 days) by the time of cannulation do not appear to benefit significantly [51]. Other relative contraindications include contraindications to anticoagulation, severe aortic regurgitation, or aortic dissection.

5.7 Conclusion

Management of circulatory failure is complex. Early identification affects outcomes and prevents organ dysfunction. It is imperative to determine the cause of shock as this drastically affects management options. Treatment should be organized and tailored to each specific patient keeping in mind their age and significant comorbidities. Resuscitation should be guided by the surgeon, but active communication with colleagues and specialists is often necessary. Refractory shock is a dreaded outcome in the patient with circulatory failure, but familiarity with additional adjuncts can provide time to discover a reversible cause. ECMO and ECPR are only indicated in very specific patients, and its role in resuscitation remains under investigation.

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6 Brain Injury in the ACS Patient: Nuts and Bolts of Neuromonitoring and Management

Edoardo Picetti, Sandra Rossi, Marcus Ottochian, and Deborah M. Stein

6.1 Introduction

Traumatic brain injury (TBI), defined as a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury (https://www.cdc.gov/traumaticbraininjury/index.html), is a leading cause of mortality and disability worldwide [1, 2]. In recent years, the epidemiology of TBI has been changing [2, 3]. In high-income countries, we observe an increase in the number of elderly people with TBI, mainly after falls. This category of patients, generally with preexisting diseases, is frequently taking antiplatelet and/or anticoagulation drugs. In low-income and middle-income countries, we observe an increase in the number of young individuals with TBI, mainly related to road traffic incidents. In polytrauma patients, TBI is frequently associated with extracranial injuries [4]. For this reason, every emergency-trauma surgeon should have a basic knowledge about TBI. With this in mind, the objective of this chapter is to provide concise and practical information about TBI pathophysiology, monitoring, and management. Furthermore, given its importance, a brief discussion about the brain death determination and management of the potential organ donor will be provided.

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6.2 Pathophysiology

The brain is protected from direct blows to the head by the presence of the layered barrier of the scalp, skull, and meninges. The elasticity of the cerebral tissue and the space provided by a thin layer of cerebrospinal fluid (CSF) allow the brain to also withstand shear forces and sudden displacements caused by accelerations and decelerations. A mechanical force applied to the head that exceeds these protective properties will result in a TBI. In blunt trauma, accelerations and decelerations can stretch and compress the cerebral tissue beyond its elastic properties. In penetrating trauma, brain tissue is directly disrupted by a foreign object. Its kinetic energy can also propagate through the brain as a centrifuge wave causing further damage. Shock waves created by an explosion can similarly propagate and disrupt brain tissue in a similar way. The overall result is a sudden loss of the integrity of vascular and neural cells leading to hemorrhages and parenchymal injuries and known as *primary brain injury*. This triggers a multitude of molecular cascades that evolve independently and long after the initial insult. The complicated interplay of inflammation, parenchymal edema, ischemia, and many other processes unfolding over many hours and ultimately leading to further brain tissue loss is known as *secondary brain injury* [5–9]. Brain injuries can be also be classified as localized or diffuse. In clinical practice, both types coexist [10–13].

Localized primary injuries can involve any single anatomical entity, but—especially in moderate or severe TBI—rarely occur in isolation. There are known inflammatory, metabolic, and circulatory repercussions involving adjacent areas that make them prone to develop further tissue loss [5, 14–16].

Skull fractures can be linear or depressed. Linear fractures don't cause any direct injury to the underlying meninges and brain but should raise the suspicion of an underlying parenchymal or vascular injury. Careful examination of the CT scan is needed to distinguish a nondisplaced linear fracture from normal suture lines and vessel grooves. With depressed fractures, the disrupted bone margin or its fragments can directly lacerate the underlying vessels, meninges, and brain tissue. The presence of facial and orbital fractures should be suspected when instability of the facial bones or an orbital rim step-off is appreciated on palpation of the face. Upper facial injuries are more often associated with an underlying brain injury [17]. The presence of ecchymosis in the periorbital area (raccoon's eyes) or mastoid area (Battle's sign) can be evidence of a basal skull fracture. This should also be suspected in the case of CSF otorrhea, hemotympanum, and CSF rhinorrhea [6]. During blunt trauma the surface of the brain can impact the bony prominences and ridges of the cranial cavity. This leads to the development of small ill-defined "ecchymosis"—focal cortical contusions—at the site of impact (coup) and/or on the opposite side of the brain (countercoup). Although the extravasated blood is the most prominent feature visible on CT scan, it is important to keep in mind that an equivalent but less visible neuronal damage is taking place at the same site and in surrounding areas in the form of both a primary and secondary injury. Cortical contusions can be relatively small and scattered along a portion of the cortical surface or coalesce to form a lesion extending deeper under the cortex [5–13]. Larger collections of blood

(>2 cm) located deeper in the brain are termed *deep intracerebral hemorrhages (ICH)*. The amount of energy causing these lesions is high, and an associated diffuse injury should be suspected as well as the development of significant secondary brain injury. These blood collections also tend to increase in size and can, in up to 10% of severe TBI patients, extend to the ventricles. The presence of an *intraventricular hemorrhage* implies a more severe injury and is associated with a poor outcome [5–13]. Clinicians should also be aware of the possible development of *delayed traumatic intracerebral hemorrhages (DTICH)*. As the name implies, these are not visible on initial imaging and only appear on follow-up scans [18].

An *epidural hematoma (EDH)* is formed when blood accumulates between the dura mater and the inner table of the skull. This is most typically caused by a trauma to the temporal area of the skull causing a tear of the middle meningeal artery. The initial trauma can be asymptomatic or cause only a brief loss of consciousness followed by temporary resolution of symptoms. This period between the initial injury and the sudden subsequent deterioration is termed "lucid interval." The brisk arterial bleeding in fact causes a rapid expanding hematoma with severe mass effect, a sudden increase in intracranial pressure (ICP), and rapid neurological deterioration. On imaging, they appear as biconvex collections of blood located between the bone and the brain and associated with a skull fracture in around 75% of cases. Being located outside of the dura, they are not limited by the presence of venous sinuses or dural structures like the falx and tentorium but do not cross the sutures. Epidural hematomas can also be occasionally due to the damage to a dural venous sinus in the occipital posterior or anterior middle cranial fossa or at the vertex [5–13].

Blood can also collect in the subdural space, between the dura and arachnoid mater, giving rise to a *subdural hematoma (SDH)*. This is thought to be caused by an injury of the bridging veins that cross the subdural space carrying blood from the brain to a dural venous sinus. Older individuals are especially prone to developing such injuries. This is likely due to the fact that an aging brain gradually decreases in size, progressively stretching the bridging veins and making them more vulnerable to shearing forces. SDH can develop after a minor trauma and can be very indolent (chronic or subacute SDH). It can also be arterial in origin and recurrent (acute on chronic). The fluid collection is often a mixture of blood and CSF leaked from the arachnoid. On CT, it typically appears as a large high-density (when new) or low-density (when old) crescent-shaped lesion [5–13].

Traumatic subarachnoid hemorrhages (tSAH) occur when blood collects in the subarachnoid space. On CT scan, these appear as thin high-density collections covering the surface of the gyri and filling the sulci and basal cisterns. Some degree of cerebral vasospasm has been described in patients with tSAH using surveillance transcranial Doppler ultrasonography or angiography. This tends to develop by day 2, peak at around day 7, and resolve by day 14. Less than one in five patients who develop vasospasm has some evidence of a corresponding clinical deficit [5–13, 19].

An example of diffuse primary injury is a widespread disruption of the long axons that traverse and constitute the white matter. These typically occur in the setting of severe blunt trauma from motor vehicle collisions, falls, or explosions as a result of shear forces from a rotational acceleration. Although the resulting damage

evolves over many hours after the initial event, this *diffuse axonal injury* (*DAI*) is traditionally classified as a primary injury. There is now evidence that axonal damage is not the immediate result of the mechanical rupture of axons but is instead a more complicated process that takes up to 48 h to fully unfold. The stretching of axons disrupts the cytoskeleton and cell membrane causing an unregulated influx of calcium at the nodes of Ranvier. The rise in intracellular calcium activates proteolytic enzymes that further digest the already compromised cytoskeleton. The result is an interruption of axonal transport and an eventual axotomy, apoptosis, and Wallerian degeneration. The areas of the brain that are most vulnerable to this type of injury are also rich in critical neural circuits: the white matter connecting the cortex to the rest of the brain, the corpus callosum which connects the two hemispheres, the brainstem, the basal ganglia, and the thalamus. Diffuse damage to these structures can lead to devastating consequences [5–13, 20, 21]. These types of injury can lead to dense coma and a poor neurological outcome [1]. DAI can be deceptively inconspicuous on the initial CT scan, but its occurrence can be suggested by the presence of its vascular counterpart: petechial white matter hemorrhages. These are punctiform blood extravasations, the result of injury to multiple small blood vessels within the white matter. The endothelial damage that causes them is thought to be analogous to the cellular membrane damage that occurs in DAI [5–13, 22].

Trauma patients can suffer a diffuse brain injury even in the absence of a TBI as a result of a traumatic cardiac arrest. The central nervous system is notoriously vulnerable to ischemic insults. Without perfusion, local reserves of ATP only last only 5 min, and oxygen is depleted in about 20 s. The result is anoxic brain injury. This appears on CT as a loss of definition of white/gray matter on CT. It is associated with a poor prognosis [23].

Primary brain injuries can potentially be prevented, but—because of their instantaneous occurrence—they are for the most part out of the reach of any current medical treatment. What needs to be appreciated is that the original injury initiates a multitude of pathological cascades threatening the surviving brain. Secondary brain injury is the result of all these subsequent events and the main focus of TBI management. It starts immediately following the injury as a result of the disruption of cellular structures and evolves independently from the original injury unfolding over many hours and days. While some neurons might have been irreversibly lost as part of the primary injury, many more are threatened by the development of secondary injuries and are potentially salvageable. The responsibility of every healthcare provider involved in the care of TBI patients is to be cognizant of this evolving process and to take every possible step to limit it or—at the very least—not to aggravate it. This means following some basic principles consistently at all times from the field to the emergency department and the intensive care unit. Maintaining an adequate cerebral perfusion pressure (CPP) and oxygenation are two well-established examples of how salvageable brain tissue can be preserved.

The pathophysiological pathways involved in the development and evolution of secondary brain injuries are complicated and interrelated: inflammation, ischemia, loss of autoregulation, vasospasm, edema, necrosis, apoptosis, meningitis, and seizures are only few examples of the numerous processes involved.

Secondary brain injury can be described as happening on many levels. While at the core of a severe traumatic lesion, severe ischemia and necrosis prevail, while other mechanisms are at play in the surrounding tissue and the rest of the brain. At a cellular level, the membrane disruption causes an influx of calcium with activation of the calpain system. The calpain system is responsible for an unregulated intracellular proteolysis and also for triggering apoptosis. Damage to the mitochondria decreases the cellular energy production and exacerbates the oxidative stress accelerating the molecular pathways leading to apoptosis. The traumatic impact can also cause a massive depolarization with cellular influx of potassium and release of glutamate. Glutamate is also released by damaged neurons. This phenomenon is known as excitotoxicity. The resulting overactivation of NMDA receptors triggers a cellular inflow of calcium and sodium with a subsequent depletion of ATP in an effort to reestablish the electrolyte balance and an additional decrease in mitochondrial function. An increase in the pentose phosphate pathway and a decrease in pyruvate and ATP production compound this "energy crisis" and lead to further cellular loss [5, 24, 25].

At a macroscopic level, recruitment of inflammatory cells with production of oxygen radicals and further cell loss can be observed. Impaired autoregulation of the vascular system leads to relative ischemia. In addition to inflammation and impaired perfusion, it is the development of *brain edema* and the resulting increase in ICP that are major determinants in the evolution of the injury and the main focus of clinical management. Brain edema near the core of the traumatic lesion is generally vasogenic and cytotoxic in nature, occurring mainly as a consequence of the BBB disruption and cell death. The extracellular potassium released from the damaged cells is taken up by astrocytes located in the periphery of the lesion. Water, driven by the osmotic gradient, enters these cells, leading to what is known as ionic edema. While the presence of the rigid skull provides protection from a primary brain injury, it also does not allow for the brain to swell without a corresponding increase in ICP. The consequence is a compartment syndrome leading to ischemia and brain tissue herniation with compression of critical structures in the brain stem [26].

The *Monro-Kellie hypothesis* illustrates the dynamic relationship between the space occupied by the brain tissue (1.4 L), the CSF (150 mL), and the blood (150 mL). Since the intracranial space is constant, an increase in one of these components will lead to a decrease in the others. The increase in brain volume determined by the development of brain edema or an intracranial blood collection initially leads to a decrease in CSF and venous blood. Once the limit of these compensating mechanisms has been reached, the ICP starts to rise. The increase in ICP eventually prevents arterial blood to reach the cranial cavity and also causes displacement of brain tissue. The CPP is the difference between the mean arterial blood pressure (MAP) and the ICP (CPP = MAP − ICP). The CPP is the gradient that drives the perfusion of the brain. A decrease in MAP and an increase in ICP can both result in a fall in the CPP. A certain level of CPP is needed to maintain cerebral blood flow (CBF). If the CPP falls below 60–70 mmHg, the compensatory mechanisms of the cerebral circulation, which may already be impaired as the result of the brain injury itself, become ineffective and tissue ischemia ensues [5–9].

Further local pathological events threatening the recovery from a TBI include the development of seizures, hydrocephalus, meningitis, and vascular complications such as carotid or vertebral artery dissection, the development of a carotid-cavernous fistula, fat embolism, and dural sinus thrombosis. The clinician needs to maintain a high index of suspicion for the development of any of these local complications, especially in the event of a sudden clinical deterioration [5–9].

One last key aspect to keep in mind when caring for a severe TBI patient is that up to 60% of them have an associated injury to some other body region. This can influence the evolution of the secondary brain injury. One of the many examples is the development of acute respiratory distress syndrome (ARDS) following severe lung contusion leading to hypoxemia. At the same time, a brain injury can by itself trigger complications involving other organ systems. Some examples are neurogenic pulmonary edema, cardiac dysrhythmias, systemic coagulopathy from leakage of brain tissue factor (thromboplastin), and diabetes insipidus from pituitary failure. Many more of such complications have been described, and they can all threaten the recovery from a TBI [5–9].

6.3 Neuromonitoring

In the setting of TBI, particular attention should be paid to avoidance of secondary insults such as hypoxia and hypotension, as these are known to be associated with increased mortality and worse neurological outcomes [27]. Additionally, care should be taken to maintain motion restriction of the cervical spine as cervical spine injuries are commonly associated to TBI [5, 6, 28].

Assessing and monitoring the neurological system is carried out once the initial resuscitation is complete and all life-threatening processes have been or are being addressed. The initial and repeated neurologic examination remains the basic tool for assessing and following the progression of any neurological injury. The stratification of a TBI is based on the results of the physical examination and CT scan findings [10, 29]. In particular, the Glasgow Coma Scale (GCS) should be calculated as soon as this is feasible and prior to sedating or intubating the patient if this is safe and possible [30]. Assessing the GCS will also help in determining if the patient should be intubated and—while eliciting the motor component of the GCS in all limbs—allows for a brief spinal cord injury assessment. The initial neurological exam should also include the assessment of the pupillary reflexes bilaterally. All these findings should be clearly documented and communicated by the pre-hospital team to the receiving hospital staff and then again thereafter every time patient care is passed on to a new provider and at regular time intervals [5, 6, 28]. On arrival to the hospital, after completion of the primary survey and after the patient has been sufficiently resuscitated, a more detailed neurological examination should be carried out as part of the secondary survey, and a non-contrast CT scan of the brain and the cervical spine is generally obtained as soon as this is feasible and safe. The initial neurological exam and CT scan findings will inform the trauma team on the need for any immediate surgical intervention [6]. Repeat neurological examinations should then be carried

out at regular intervals and at least hourly or sooner if a deterioration is suspected. The head CT is also repeated at least once after a few hours (generally 6 h) or sooner if needed and thereafter as clinically indicated in patients with significant intracranial findings on initial imaging. Other diagnostic tests such as electroencephalogram (EEG) and magnetic resonance imaging (MRI) may also be valuable under certain circumstances but are rarely needed acutely following TBI.

Once the patient is admitted to the intensive care unit (ICU), the focus shifts toward preventing and managing the development of secondary brain injury. Many systemic and local factors contribute to this such as hypoxemia, hypotension, fever, etc. (secondary insults). Standard ICU monitoring, including pulse oximetry and continuous arterial blood pressure measurement via an intra-arterial catheter, should be utilized. A Foley catheter should also be inserted to monitor the urinary output [31].

The development of tissue edema is the common consequence of most secondary brain injury pathways and leads to intracranial hypertension (IH). IH counteracts the systemic arterial pressure attempting to perfuse the brain, and this is quantified by measuring the CPP (MAP-ICP). In a severely injured brain, cerebral hypoperfusion may be compounded by an already compromised cerebral vascular autoregulation. IH also causes the brain to herniate leading to compression and the catastrophic loss of function of critical structures such as the brainstem. Even short periods of intracranial hypertension and cerebral hypoperfusion, when repeated in time, lead to a progressive worsening outcome. For these reasons monitoring and management of ICP has become central to the ICU care [26, 31–34]. Although there are a growing number of reports on noninvasive techniques, invasive monitoring remains the current standard of care. There is no good quality evidence to support any specific indications for the placement of an ICP monitor, and this remains a highly debated topic. A recent multicenter randomized clinical trial failed to show any advantage in ICP monitoring in the management of severe TBI [35]. A neurosurgeon should always be involved early in the care of a patient with a severe TBI, and ICP monitoring is still recommended in potentially salvageable patients with an abnormal CT scan and a GCS of 8 or less after resuscitation [36].

Patients presenting with brain contusion in which sedation interruption for neurological assessment may be detrimental and patients who undergo a decompressive craniectomy may benefit from ICP monitoring [37, 38].

Careful consideration should also be given to ICP monitoring in hypotensive patients, those with clinical signs of increased ICP including anisocoria and unilateral or bilateral posturing, and those whose clinical deterioration is likely due to intracranial hypertension. The ultimate decision to place an ICP monitor should be taken in concert with the neurosurgeon and the neurointensivist and tailored to the specific clinical scenario [36].

The two commonly employed devices to monitor the ICP are placed either in the brain parenchyma [intraparenchymal monitor (IPM)] or in one of the lateral ventricles [external ventricular drain (EVD)]. The former modality is diagnostic only, while the latter, allowing for the drainage of CSF, is therapeutic as well. A tiered approach to ICP-lowering therapies is recommended and should be driven by institutional guidelines [37].

Complications of invasive ICP monitoring include track hemorrhage, meningitis, and malposition. There does not appear to be an increase in infections when ICP monitors are placed in the ICU compared to the OR. The risk for infection does increase with duration of monitoring, at least during the first week. The use of prophylactic antibiotics reduces this risk, but it is not clear if these should be only administered peri-procedurally or for as long as the device is in place [39]. The incidence of clinically significant hemorrhage varies across the literature but seems to be low (<0.5%) for patients with IPM. It is common practice to correct any coagulopathy prior to insertion of an ICP monitor. There is no consensus of when it is safe to start pharmacological deep vein thrombosis (DVT) prophylaxis, and this needs to be based on an individualized benefit-risk assessment. If not contraindicated, pharmacological DVT prophylaxis should probably be started within the first 72 h after insertion of the device [39–41].

In the TBI setting, an ICP of more than 20 mmHg is considered abnormal, and a sustained value of more than 22 should prompt some type of intervention [36]. The development, duration, and magnitude of IH are independent predictors of a worse outcome [42–45]. In patients with contusions close to the midbrain, a lower threshold may need to be considered [46].

Besides displaying the ICP level as an isolated absolute value expressed in mmHg, continuous monitoring allows the visualization of the ICP waveform which offers useful information about brain compliance. When the ICP is transduced, the waveform has a few distinguishable components. The normal ICP waveform has physiological variations that can be distinguished based on their frequency. Pulse waveforms have the same frequency as the patient's heart rate and an amplitude of about 1–4 mmHg. They display a steep systolic upstroke and a slower downstroke with three discrete peaks of decreasing height. The first and highest peak—P1—is the result of the arterial pressure being transmitted by the choroid plexus to the ventricular CSF and is called "percussive wave." Its height is related to the systemic arterial blood pressure. The second peak—P2—is called "tidal wave," and its size is thought to be inversely related to cerebral compliance: a prominent P2 should raise the suspicion for a decreased compliance of the brain as would be seen in the setting of elevated ICP. The last peak—P3 or "dicrotic wave"—is due to the slight increase in systemic arterial pressure caused by the closure of the aortic valve and being transmitted to the intracranial space. The other physiological variations of ICP are synchronous with the patient's breathing, and they have an amplitude of 2–10 mmHg [42].

When analyzing the ICP trend over a period of many minutes, it is possible to identify other pathological patterns. The best known example is A waves, also known as plateau waves. These are sustained increases in the ICP lasting up to 20 min and reaching an amplitude of more than 50 mmHg. When they resolve, the ICP does not decrease to its previous level and resets to a new higher baseline. Such sustained increases in the ICP are signs of a greatly compromised vascular autoregulation and can lead to severe drops in the CPP and to herniation [47].

Cerebral autoregulation is the ability of the cerebral arterioles to change their muscular tone and diameter in order to guarantee an adequate blood flow

despite changes in the systemic blood pressure and metabolic demands of the brain tissue. The cerebral circulation is able to maintain a constant blood flow of 40–50 mL/100 g/min despite changes in the MAP in the range of 50–150 mmHg. Hypertension causes arteriolar vasoconstriction, while hypotension causes arteriolar vasodilatation. A decrease in tissue pH, as can be seen in the case of ischemia, causes cerebral vasodilatation and an increase in blood flow. On the contrary, the alkalemia caused by hyperventilation causes vasoconstriction, a decrease in blood supply to the brain with the transient potential advantage of decreasing the intracranial blood volume and therefore the ICP [48, 49]. The preservation of an effective cerebral autoregulation can be approximated by the measurement of the pressure-reactivity index (PRx) which expresses the dynamic relationship of changes in the ICP in response to variations in the arterial blood pressure over a period of many minutes [42].

Weaning from the ICP monitor can be done once the ICP and clinical status have been consistently stable for a number of days. If the patient has an EVD, the drain is closed after a period of increasing drain height. A repeat CT is typically obtained the following day. If this shows the presence of a hydrocephalus or if the ICP rises above 20 mmHg for more than 5 min or if there is a clinical deterioration, the drain is reopened [5, 6, 39].

The development of new unprovoked seizures is common following severe TBIs with a reported incidence of 22%; nonconvulsive seizures are slightly more frequent than convulsive ones [50]. Risk factors are the presence of a subdural hematoma, a skull fracture, a history of loss of consciousness or amnesia lasting more than 24 h, and age over 65 [51]. Electroencephalography (EEG) is the gold standard for detecting the presence of seizures and helpful in titrating antiepileptic medications. It can be performed as a "spot" exam or as a continuous recording. Besides being helpful in detecting the presence of seizure activity, it can also aid in the prognostication process [34].

The interstitial biochemical environment can be directly sampled through the use of cerebral microdialysis. A catheter is inserted in the brain parenchyma, and a solution, similar in composition to cerebrospinal fluid, is circulated inside the catheter. A semipermeable membrane separates this solution from the interstitial space. This prevents the solution from spilling into the brain tissue but allows solutes, such as glucose, glutamate, lactic acid, pyruvate, and cytokines, to move from the interstitial space into the lumen of the catheter and be collected. The solution is then retrieved and analyzed. An increase in the lactate to pyruvate ratio (LPR)—for example—can indicate the shift toward anaerobic metabolism dictated by the presence of ischemia or by a maladaptive dysfunction of the glycolytic pathway as seen following TBI. In TBI this is also associated to increased mortality [52].

As mentioned above, the brain is very sensitive to drops in oxygen delivery. The brain tissue oxygen (BtO2) tension can be measured directly using probes inserted into the parenchyma. The frontal lobe on the side of the most severe injury is generally chosen. If there is a diffuse injury, the nondominant side is chosen instead. The measurement obtained is a regional one and does not necessarily reflect the

oxygenation of other areas or of most of the brain. Following severe TBI brain hypoxemia, defined as a BtO2 tension of <10 mmHg for more than 15 min, correlates with worse outcomes (OR 4.0; 95% CI 1.9–8.2) and increased mortality (OR 4.6; 95% CI 2.2–9.6) [53]. Strategies aimed at improving oxygen delivery by augmenting the CPP with the use of norepinephrine have been shown to significantly increase the BtO2 tension [54].

Global cerebral oxygen utilization can also be measured by jugular bulb oximetry in which an oximetry probe is placed in the jugular vein. The normal jugular vein saturation of oxygen (SjVO2) is above 60%. The presence and duration of episodes of desaturation, defined as a SjVO2 of <50% for 10 min, has been associated with a worse outcome [55].

Occasionally a clinician may be interested in assessing for the development of reactive cerebral vasospasm leading to brain hypoperfusion. This can be achieved by performing a transcranial Doppler ultrasonography (TCD) and measuring the cerebral blood flow velocity. Vasospasm is a well-documented complication of spontaneous aneurysmal subarachnoid hemorrhages (SAH) but can also happen following traumatic brain injuries, especially if a tSAH is present. In this case the onset tends to be earlier and the duration shorter when compared to vasospasm associated to spontaneous SAH [19].

6.4 Management

This section is focused on the management of post-traumatic IH. Elevated ICP is associated with worse outcome [56, 57], and for this reason it must be quickly recognized and treated.

Regarding the management of severe salvageable TBI patients, three points should be kept in mind:

1. In the case of intracranial hematomas requiring urgent surgical evacuation (to prevent/treat brain shift, compression, and herniation), early neurosurgical consultation is mandatory. Trying to treat an emergent surgical problem with medical therapy can be very harmful for the patient. For surgical therapy, please refer to "Guidelines for the Surgical Management of TBI" edited by the Brain Trauma Foundation (BTF) [58] [available at: www.braintrauma.org/guidelines/guidelines-for-the-surgical-management-of-tbi#/].
2. Any therapy for ICP control has pros and cons that every provider should keep in mind [37, 59, 60].
3. In addition to treatment of elevated ICP, the CPP should be optimized to maintain an adequate CBF considering patient's age and comorbidities (i.e., arterial hypertension) [36].

A stepwise approach to the treatment of IH is recommended [37], where the level of therapy in patients with elevated ICP is increased step by step, reserving more aggressive interventions which are generally associated with greater risks/

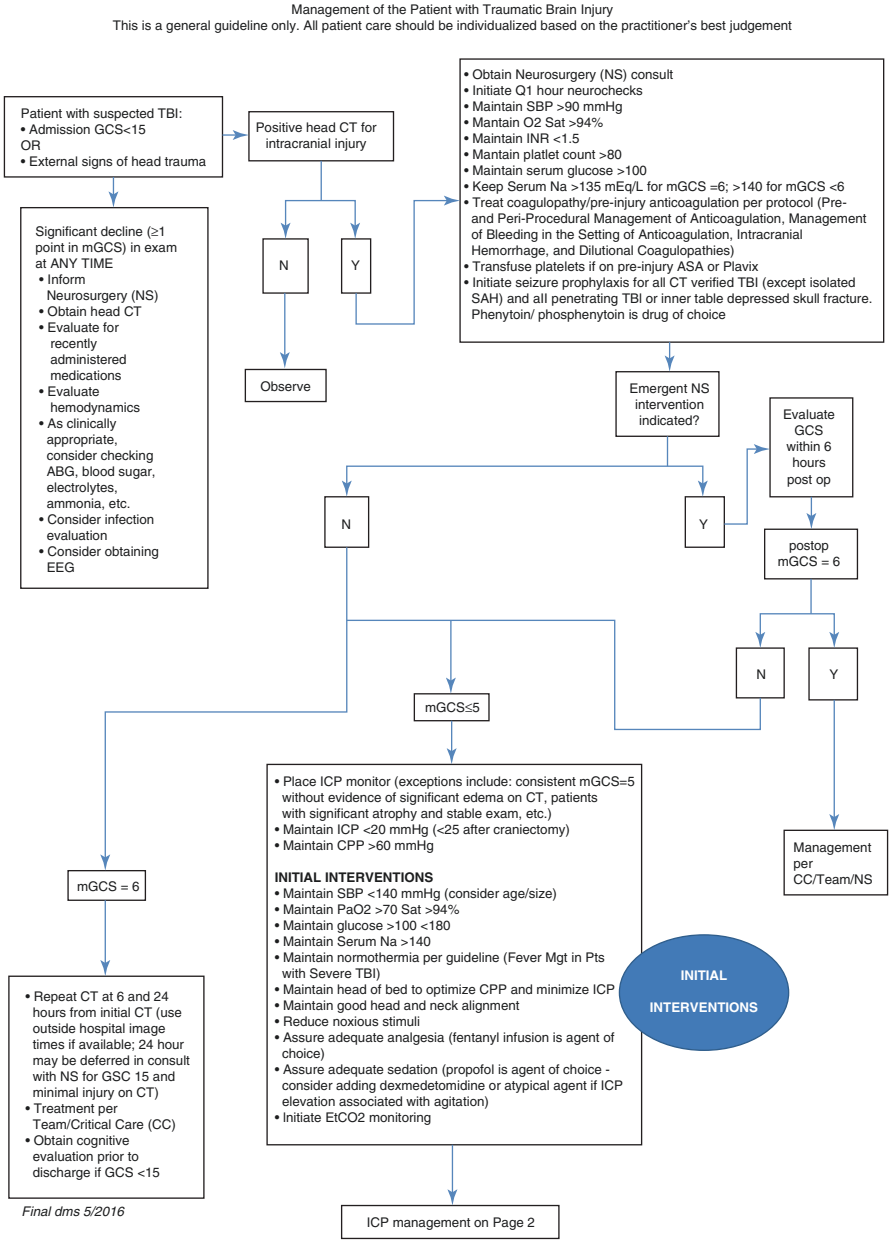

Fig. 6.1 The R Adams Cowley Shock Trauma Center algorithm for management of patients with severe TBI

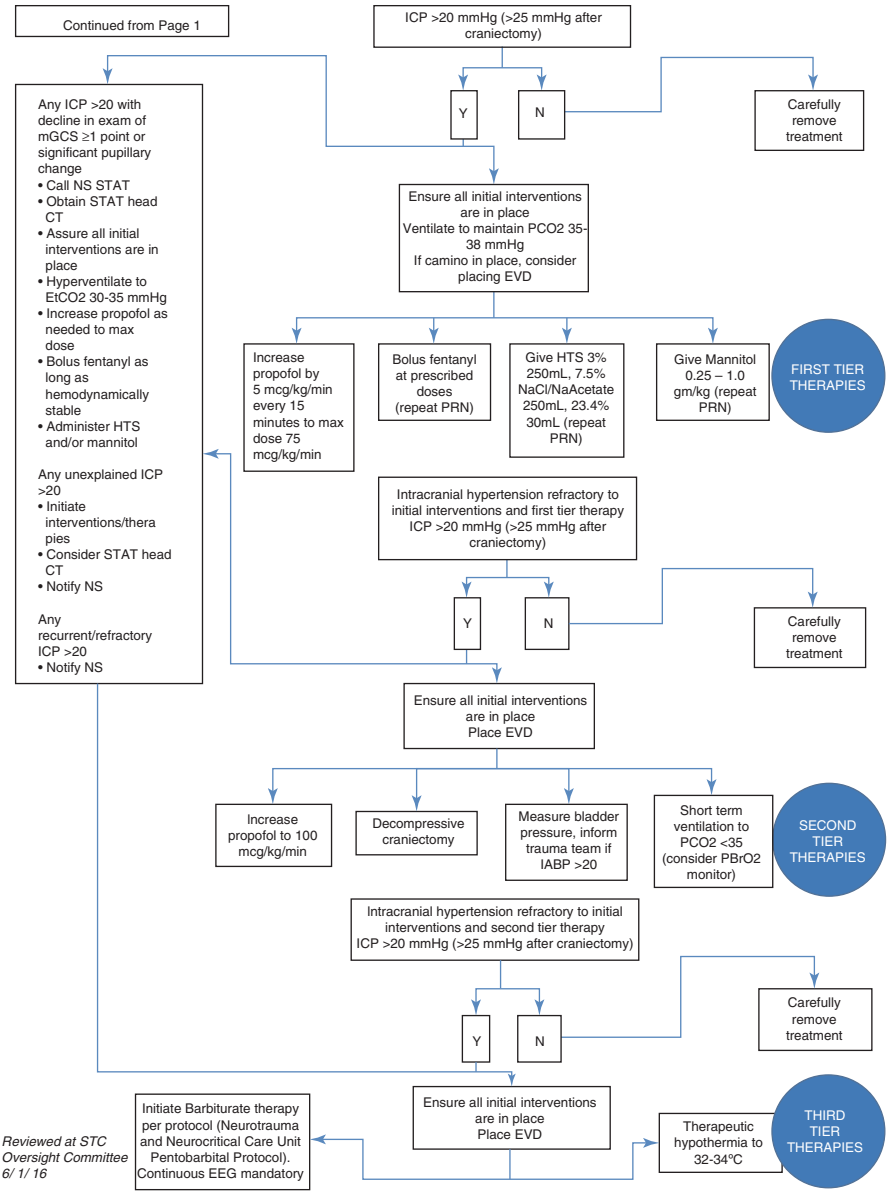

Fig. 6.1 (continued)

adverse effects when no response is observed (Fig. 6.1; Table 6.1). The availability of advanced multimodal neuromonitoring (i.e., brain tissue oxygen monitoring, cerebral microdialysis, etc.), providing a more comprehensive understanding of the injured brain, might better optimize individualized treatment decisions, but outcome studies are lacking [2, 61].

Table 6.1 Approach to intracranial hypertension (Parma ICU protocol)

0—Basic	
– Head position	At least 30° from horizontal plain
– Neck position	Midline
– Sedation/analgesia	
– Normothermia	BT < 37.5 °C
– PaO2	80–100 mmHg
– PaCO2	35–40 mmHg
1—First-tier therapies	
– CSF withdrawal	If EVD available for ICP monitoring
– Osmotherapy	Mannitol, hypertonic saline Serum osmolarity <320 mOsm/L Serum Na < 150–155 mEq/L
– Increase sedation	
– PaCO2	30–35 mmHg
2—Second-tier therapies	
– PaCO2	25–30 mmHg
– Hypothermia	BT 35–36 °C
– Barbiturate coma	
– Decompressive craniectomy	In the case of frontotemporoparietal DC (not <12 × 15 cm or 15 cm diameter)

BT body temperature, *EVD* external ventricular drain, *ICP* intracranial pressure, *Na* sodium, *DC* decompressive craniectomy, *PaO2* arterial partial pressure of oxygen, *PaCO2* arterial partial pressure of carbon dioxide

Note:

- ICP goal: < 20 mmHg
- In some cases neuromuscular blocking agents might be added to sedation
- Cerebral perfusion pressure (CPP) [mean arterial pressure—intracranial pressure] should be maintained between 60 and 70 mmHg

6.4.1 Sedation/Analgesia

In the ICU, sedative and analgesic drugs are routinely utilized for the control of (1) pain, (2) anxiety, (3) agitation, and (4) patient-ventilator interaction [62]. Moreover, sedatives exert specific cerebral protective effects [63, 64]. Sedative agents reduce in a dose-dependent manner the cerebral metabolic rate of oxygen (CMRO2) and consequently the CBF with a parallel decrease in cerebral blood volume (CBV). The CBV reduction is associated with a decrease in ICP. In addition, an appropriate sedative and analgesic strategy decreases pain and agitation which may exacerbate IH. Sedation also may reduce the occurrence of seizures. Characteristics of some sedatives and analgesic drugs frequently utilized in neuro-ICU (NICU) are reported in Table 6.2. Sedation/analgesia could be individualized considering potential benefits (in correlation with the severity of brain injury and the difficulty in ICP control) and risks and side effect profile. Excessive sedation, prolonging ICU stay, is associated with increase morbidity and mortality [62]. The BTF currently recommends the use of propofol as a level IIb recommendation for the control of ICP, despite no demonstrated improvement in mortality or 6-month outcomes [36].

Table 6.2 Sedatives and analgesics characteristics

Sedatives	*Characteristics*
Midazolam BD IV: 0.05–0.2 mg/kg CI IV: 1–4 mcg/kg/min	• GABA-R agonist • Rapid onset • Modest decrease in MAP • Accumulation (slow recovery) in the case of: 1. Kidney failure 2. Prolonged infusion without interruption • ↑ ICU delirium
Lorazepam BD IV: 0.05–0.15 mg/kg CI IV: 0.01–0.1 mg/kg/hr	• GABA-R agonist • Slow onset/slow recovery • Modest decrease in MAP • Cost-effective in the case of long-term sedation without the necessity to perform a reliable neurol. exam
Propofol BD IV: 0.5–1 mg/kg CI IV: 1–3 mg/kg/hr	• GABA-R agonist • Rapid onset/fast recovery • Marked decrease in MAP (esp. hypovolemia) • ↑ TG and calories (1 mL propofol = 1 kcal) • Don't exceed 4 mg/kg/h for 48 h for the risk of propofol infusion syndrome*
Analgesics	*Characteristics*
Fentanyl BD IV: 1–2 mcg/kg CI IV: 50–100 mcg/hr	• μ-R agonist • Rapid onset • Modest decrease in MAP • Accumulation (slow recovery) in the case of: 1. Hepatic failure 2. Prolonged infusion
Morphine BD IV: 0.1 mg/kg CI IV: 20–40 mcg/kg/hr	• μ-R agonist • Onset velocity < fentanyl/slow recovery • Modest decrease in MAP • Accumulation in the case of: 1. Hepatic failure 2. Renal failure • Histamine release
Remifentanil BD IV: not recommended CI IV: 0.05–0.2 mcg/kg/min	• μ-R agonist • Rapid onset/fast recovery • Marked decrease in MAP (no bolus) • Hyperalgesia at the end of infusion

Abbreviations: *BD* bolus dose, *IV* intravenous, *CI* continuous infusion, *R* receptor, *MAP* mean arterial pressure, *ICU* intensive care unit, *TG* triglycerides

*Low heart rate, metabolic acidosis, high serum lactate, high creatine phosphokinase (CPK), heart failure

6.4.2 Cerebrospinal Fluid (CSF) Drainage

CSF drainage is a simple and effective approach in the management of intracranial hypertension especially when an EVD is already present for ICP monitoring [37]. When an EVD catheter is utilized for CSF drainage, some points should be considered [39, 65–67]:

1. Excessive drainage may expose patients to an increased risk of intracranial hemorrhage.
2. During CSF drainage, it's not possible to monitor ICP, unless a double reading catheter (fluid coupled + fiberoptic) is used; undetected episodes of intracranial hypertension have been described during continuous drainage of CSF.
3. In the case of a diffuse swollen brain, the ventricles may collapse, limiting the usefulness of EVD (see Point 2).
4. EVDs, especially if maintained for more than 2 weeks, are associated with an increased risk of central nervous system (CNS) infection.

6.4.3 Osmotherapy

Hyperosmolar agents, such as mannitol and hypertonic saline, are generally effective in ICP reduction through several mechanisms [68]:

– Reduction in blood viscosity through volume expansion (immediately after the start of infusion, short lived); this leads to a cerebral vasoconstriction with an associated decrease in CBV.
– Increase in plasma osmolarity. In this way, a gradient across the intact BBB is created and water removed from the normal brain tissue. The efficacy of hyperosmolar agents depends on the integrity of BBB. This effect lasts for several hours and ends once the osmotic equilibrium is restored.

Hypertonic saline is available in a variety of formulations, with 3% being the most commonly used. Mannitol is associated with a significant rebound effect, typically when high repeated doses are used. Characteristics of mannitol and hypertonic saline are reported in Table 6.3. Until now, high-quality trials showing the superiority of an agent with respect to another have not been published, but a few series and meta-analyses have demonstrated that hypertonic saline may be superior [69].

Table 6.3 Characteristics of hyperosmolar agents[a]

	Mannitol 18%	Hypertonic saline (HS) 3%
Modality of administration	Bolus	Bolus/CI
Dosage	0.25–1 g/kg every 4–8 h Generally 100–250 mL In the case of herniation 500 mL	100–250 mL every 4–8 h
Osmolarity	1098 mOsm/lt	1027 mOsm/lt
Adverse effects	Hypovolemia Kidney failure	Hypernatremia
Clinical practice	Good option in the case of hypervolemia (diuretic effect)	Good option in the case of hypovolemia

CI continuous infusion

[a]In terms of effects, it's generally important to compare agents with the same osmolarity (e.g., mannitol 18% vs. HS 3%)

6.4.4 Hyperventilation and Induced Hypocapnia

Hypocapnia induced by hyperventilation (increase in minute ventilation with mechanical ventilation) reduces ICP [70, 71]. Precisely, low arterial carbon dioxide levels (PaCO2) result in CSF alkalosis; this increase in CSF pH induces a cerebral vasoconstriction with concurrent reduction in CBF and CBV. Over time (generally within 24 h), CSF pH and CBF gradually return to normal level; therefore the effect of hyperventilation is temporary. The reduction in ICP linked with hyperventilation is associated with the risk of development of cerebral ischemia [70–72]. In this regard, if utilizing hyperventilation, it is advisable to have additional monitoring for the detection of cerebral ischemia (i.e., jugular venous oximetry, brain tissue oxygenation, etc.). Empiric hyperventilation is not recommended [36]. Profound hypocapnia (PaCO2 25 mmHg) could be utilized transiently (temporary measure associated with other therapies), facing with a patient with brain herniation waiting an emergency neurosurgical procedure (i.e., subdural hematoma evacuation) [71].

6.4.5 Hypothermia

Mild hypothermia (32–35 °C) has been utilized in clinical trials for ICP control (long-term hypothermia) and for neuroprotection (short-term hypothermia; duration <48 h) [73]. Some mechanisms of action and potential side effects of mild hypothermia are reported in Table 6.4 [74, 75]. Despite its effectiveness on ICP control, hypothermia was associated with worse neurologic outcome in clinical trials [76]. Hypothermia must be considered an "extreme" therapy in the management of refractory IH. It has been utilized in selected centers, able to adequately recognize and treat its side effect. Prevention and aggressive treatment of fever, however, are recommended due to the association of hyperthermia and poor outcomes [77].

6.4.6 Barbiturate Coma

Barbiturates act by reducing cerebral metabolism and, accordingly, CBF [37, 64]. In this way, a proportional decrease in CBV is obtained with reduction in ICP [37, 64]. Considering their serious side effects (Table 6.5), barbiturate coma is generally reserved for refractory IH after the failure of other therapies [37, 64]. Doses, monitoring, and potential side effects related to barbiturate coma are reported in Table 6.5. If barbiturates are to be used, monitoring with continuous EEG may be useful.

6.4.7 Decompressive Craniectomy

Decompressive craniectomy (DC) is a surgical procedure that, by removing of a part of the skull and opening the dura mater (generally by duraplasty), increases cranial

Table 6.4 Some mechanisms of action and side effects of mild hypothermia

Mechanisms of action	
– ↓ Cerebral metabolism (↓ CBF and CBV with associated ↓ ICP)	
– ↓ BBB permeability	
– ↓ Free radical production	
– ↓ Excitoxic substances and pro-inflammatory cytokine production	
– Apoptosis prevention	
– ↓ Epileptic activity and cortical depolarization (anti-seizures effect)	
Side effects	*Comment*
• Hypovolemia (cold diuresis)	Hemodynamic monitoring
• Electrolytes disturbances IND.: ↓ K, Mg, P, and Ca REW.: ↑ K	Check electrolytes (every 4–6 h during IND. and REW.)
• Coagulation abnormalities (impairment of PLTs' function and coagulation cascade)	Check coagulation and PLTs' function (especially in patients with cerebral hematomas/contusions) Consider POCT[a], if available
• Shivering	Check the body/skin of the patient and eventually administer sedatives and/or analgesics and/or NMBAs, etc.
• ↑ Infection risk	Loss of fever as sign of infection ↑ Infection surveillance
• Hyperglycemia (insulin resistance)	Check serum glucose (every 2–4 h)
• Pressure ulcers (cutaneous vasoconstriction, etc.)	↑ Cutaneous surveillance
• ↓ Drugs clearance	Consider in the case of: – Neurologic ex. – Delayed awakening – Prognostication

Notes: During REW. pay attention to intracranial hypertension (rebound phenomenon); REW. rate 0.1–0.2 °C/h

CBF cerebral blood flow, *CBV* cerebral blood volume, *ICP* intracranial pressure, *K* potassium, *Mg* magnesium, *P* phosphorus, *Ca* calcium, *IND.* induction, *REW.* rewarming, *h* hour, *PLT* platelet, *POCT* point-of-care testing, *NMBA* neuromuscular blocking agent, *ex.* examination

[a]Thromboelastometry (ROTEM) and thromboelastography (TEG)

volume to accommodate brain swelling [78, 79]. In this way, the skull is converted from a closed box (with finite volume) to an open box [78, 79]. DC is very effective in ICP reduction, but recent trials [80, 81] have shown differences in neurological outcome. In the DECRA trial [80], DC (bifrontal, diffuse brain injury, utilized for modest ICP increase) decreased ICP and ICU stay but was associated with more unfavorable outcomes. In the RESCUE-ICP trial [81], DC (mainly monolateral, utilized for refractory severe IH) resulted in lower mortality but higher rates of vegetative state, lower severe disability, and upper severe disability. A better profile was observed in patients aged ≤40 years. DC is associated with several complications such as central nervous system and wound infections, cerebral hematomas, CSF disturbances (e.g., hydrocephalus), etc. [82]. As other "extreme" therapies (hypothermia, barbiturate coma), primary DC should be reserved for selected patients with refractory IH.

Table 6.5 Barbiturate coma: doses, monitoring, and side effects

Barbiturates	*Doses*
Pentobarbital	– Loading dose: 30–40 mg/kg over 4 h – Maintenance: 2–3.5 mg/kg/h
Thiopental[a]	– Loading dose: 3 mg/kg bolus followed by 10–20 mg/kg over 1 h – Maintenance: 3–5 mg/kg/h
Side effects	*Monitoring*
– Arterial hypotension	Consider S-G catheter, echocardiography, etc.
– Hypokalemia (induction), hyperkalemia (weaning)	Serum K monitoring every 4–6 h
– Increase risk of infections	↑ surveillance
– Impaired gastrointestinal motility, bowel ischemia	↑ surveillance
– Adrenal insufficiency	Serum cortisol monitoring, ACTH stimulation test
During barbiturate coma: – Pupillary light reflex can disappear – Nutrition requirements can be reduced – EEG/BIS monitoring can be performed to monitor cerebral electrical activity/depth of anesthesia but generally barbiturate dosage should be titrated to ICP control	

h hour, *ICP* intracranial pressure, *S-G* Swan-Ganz, *K* potassium, *ACTH* adrenocorticotropic hormone, *EEG* electroencephalogram, *BIS* bispectral index™

[a]Weaning after 24–48 h of ICP control, initially consider reduction of 500 mg/12 h and after, looking at the ICP, more rapid (dosage halved every 12 h)

6.5 Determination of Brain Death and Management of the Potential Organ Donor

The irreversible complete loss of all brain activities, including the ones controlled by the brain stem, is termed neurologic death (previously known as brain death). Neurologic determination of death implies cessation of life equivalent to the one seen in terminal cardiorespiratory arrest. This has clearly important ethical and clinical implications, and practitioners should be familiar with the local pertinent legislation on this topic [83].

In the typical scenario, after sustaining a severe TBI, a patient presents with coma and radiologic findings of severe injury. Despite appropriate medical and surgical interventions, there is a progressive cessation of all discernible neurological responses. The loss of central nervous reflexes, such as pupillary constriction in response to light, spontaneous breathing, or coughing during suction, indicates the involvement of the brainstem and an imminent evolution toward neurologic death.

Since most of the organs currently transplanted come from patients with neurologic death, it is important that the local organ procurement organization (OPO) is informed early in the process. It is also critical that a clear distinction is maintained between the team caring for the patient and the OPO at all times. It is generally not appropriate for the clinician caring for the patient to discuss organ donation as this may be perceived as a conflict of interest [83, 84]. A scrupulous approach is needed

in order to determine neurological death, and clinicians should be familiar with the local guidelines, as local institutional policies in the United States dictate the appropriate procedures to determine death by neurological criteria. There are also differences in recommendations for pediatric patients based on age of which the provider should be aware.

The process starts with methodically ruling out any other possible factor contributing to the loss of neurological function. The radiologic imaging should clearly substantiate the clinical picture. The presence of any significant physiologic, metabolic, or endocrine derangements should be ruled out and corrected. Examples are hypotension, adrenal insufficiency, myxedema coma, hypothermia, and hyponatremia. A toxicological exam should rule the presence of any neuro-depressive substance.

Once all these issues have been addressed, the formal exam revolves around determining the loss of all cortical and brain stem function. The loss of cortical function is confirmed by the presence of a GCS of 3. The loss of brainstem function is determined by checking for the presence of the pupillary, oculocephalic, oculovestibular, corneal, gag, and cough reflexes. The last step of the examination consists in performing an "apnea test." The rationale of this exam is to verify the presence or absence of spontaneous breathing in response to a rise in the blood CO2. The loss of this very primitive reflex is considered a proof of a severe widespread damage of the brain stem. In practice, the patient is first preoxygenated with 100% oxygen for at least 10 min. An initial ("baseline") arterial blood gas (ABG) is then obtained. The patient is then disconnected from the ventilator, and passive oxygenation is achieved by placing a plastic cannula into the endotracheal tube to deliver 100% oxygen at 6 L/min. At this point the patient's chest needs to be closely observed for any respiratory effort. If there is any clinical decompensation, such as hypotension or hypoxemia, this should be immediately addressed, and the apnea test should be abandoned. If the patient's vitals remain stable, after 8–10 min another ABG is drawn, the test is terminated, and the patient is connected back to the ventilator. Neurologic death is confirmed if during the apnea test, there is no evidence of any respiratory efforts despite a rise in arterial PCO2 to 60 mmHg or 20 mmHg above the baseline as documented by the two ABGs. Alternatively, carbogen testing has also become standard in some centers, in which the patient remains on low minute ventilation and mechanical ventilation and exogenous CO2 is administered. As stated in the 2010 update of the American Academy of Neurology guidelines, there has never been a neurological improvement in a patient in which neurological death is determined following these criteria over many years. If the patient is not able to tolerate an apnea test or if there is any component of the clinical exam which cannot be performed, a confirmatory study, like nuclear cerebral blood flow test, can be obtained [85, 86].

If the patient is deemed to be a potential organ donor, in agreement with their previous wishes or the family consent, active management is continued following the common principles of ICU care with the goal of preserving physiological homeostasis. The patient should be mechanically ventilated applying lung protective strategies; the MAP should be maintained above 60 mmHg and the urinary output

(UOP) above 1 mL/Kg/h. The loss of brain function leads to a loss of neuroendocrine control. In the case of persistent hypotension, besides ruling out other causes of worsening shock, empiric endocrine replacement therapy should be instituted. A vasopressin infusion is indicated if hypotension persists despite adequate fluid resuscitation. If shock persists or if the cardiac ejection fraction (EF) is below 45%, a thyroxine (T4) infusion should be considered. A high UOP (>150 mL/h) is suggestive of diabetes insipidus. The presence of hypernatremia and an inappropriately diluted urine (specific gravity <1005 and urine osmolality <200) confirm this diagnosis, and the patient should be started on desmopressin (DDAVP) [83, 84].

6.6 Resources

Regarding the treatment of the TBI patients, we recommend to refer to the fourth edition of the *Guidelines for the Management of Severe Traumatic Brain Injury* edited by the Brain Trauma Foundation [36] and the American College of Surgeon's Trauma Quality Improvement Program's Best Practices in the Management of Traumatic Brain Injury (https://www.facs.org/~/media/files/quality%20programs/trauma/tqip/traumatic%20brain%20injury%20guidelines.ashx).

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7 Renal Failure in the ACS Patient: Understanding Appropriate Fluid Management and Renal Replacement Therapy

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7.1 AKI in the Surgical Patient

7.1.1 Epidemiology

Acute kidney injury (AKI) is common in hospitalized patients, complicating approximately 7% of all admissions [1]. Of patients admitted to the intensive care unit (ICU), up to 57% will develop AKI [2]. Patients admitted to a surgical ICU are at particular risk, as they possess significant risk factors including sepsis, shock and surgery [3]. It is therefore not surprising that some report an incidence of AKI of up to 88% in surgical patients with septic shock [4]. In critically ill patients with higher stages of AKI, up to two-thirds will require some form of renal replacement therapy (RRT), representing approximately 10% of all patients admitted to the ICU [5, 6].

The development of AKI is associated with an important increase in morbidity and mortality. In fact, even minimal elevations in serum creatinine (0.3 mg/dL) are independently associated with an increase in mortality [7]. Furthermore, the increase in mortality appears to be directly proportional to the severity of AKI. For example, in critically ill patients requiring RRT, mortality approaches 70% [8]. AKI is also a significant source of morbidity as it is associated with an increased length of stay and healthcare-related costs [9, 10]. Long-term, AKI is associated

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with an increased incidence of chronic kidney disease (CKD) and progressive CKD [11–15]. However, even in patients requiring RRT during their hospitalization, 56% of survivors will recover by discharge, and up to 78% will normalize their creatinine by 1 year [11, 12].

The epidemiology of AKI in the surgical population has been particularly difficult to elucidate as the definitions put forward by leading surgical societies have lacked sensitivity. For example, the American College of Surgeons Committee on Trauma defines AKI as a serum creatinine above 3.5 mg/dL, whereas the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) defines AKI based on the need for RRT or a postoperative elevation of creatinine above 2 mg/dL [16, 17]. In a large cohort study of surgical patients, only 7% of patients with AKI met the ACS NSQIP definition of AKI. This is clinically relevant, as an additional 30% of patients met a more sensitive consensus definition of AKI, and this diagnosis is translated to an increase in patient mortality [18].

7.1.2 Aetiology of AKI

Common aetiologies of AKI in the surgical patient include sepsis, hypovolaemia, ischemia, rhabdomyolysis and medication-/contrast-induced. One notable cause in ACS patients is the abdominal compartment syndrome, arising from intra-abdominal hypertension leading to renal congestion and ischemia, seen in patients with severe abdominal sepsis, trauma, pancreatitis, large-volume resuscitation and high intrathoracic pressure ventilation [19].

7.1.3 Definitions

Various definitions of AKI have been proposed over the last few decades. The most commonly accepted definitions use measurements of serum creatinine and urine output over a specific time frame [20]. The RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease), AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease: Improving Global Outcomes) classification systems all utilize these parameters to provide a staging system where increasing severity is associated with worse outcomes [20–23] (Table 7.1). These staging criteria have been validated in a wide range of patient populations and demonstrate a consistent correlation between severity of AKI and prognosis [24–27].

It must be emphasized however that these definitions rely on the measurement of serum creatinine as a surrogate of glomerular filtration rate (GFR). Although serum creatinine is easily measurable and widely available, its use in critically ill patients presents a number of limitations [28]. Firstly, as in all populations, serum creatinine changes are delayed after an AKI event [29]. In addition, altered rates of production from a catabolic state and increases in total body water leading to increased volumes

Table 7.1 A comparison of the RIFLE, AKIN and KDIGO criteria for the severity of AKI [20, 21, 23]

	RIFLE	AKIN	KDIGO	RIFLE, AKIN and KDIGO
	Serum creatinine			Urine output
1 or risk	Creatinine 1.5× Or GFR decrease >25%	Creatinine ≥26.4 μmol/L Or Creatinine 150–200% (>1.5 to 2.0×)	Creatinine 1.5–1.9× Or Creatinine + ≥26.4 μmol/L	<0.5 mL/kg/h ≥ 6 h
2 or injury	Creatinine 2× Or GFR decrease >50%	Creatinine 200–300% (>2.0 to 3.0×)	Creatinine 2.0–2.9×	<0.5 mL/kg/h ≥ 12 h
3 or failure	Creatinine 3× Or Creatinine ≥354 μmol/L with acute increase ≥44 μmol/L Or GFR decrease 75%	Creatinine >300% (>3.0×) Or Creatinine ≥354 μmol/L with acute increase ≥44 μmol/L Or RRT	Creatinine 3× Or Creatinine ≥354 μmol/L Or RRT	<0.3 mL/kg/h ≥ 24 h Or Anuria ≥12 h
Time interval	<1 to 7 days	<48 h	<7 days	

of distribution further limit creatinine measurements [30]. Finally, various drugs that are commonly used in the ICU can alter creatinine levels through impairment of renal tubular secretion without truly impairing GFR. Thus, creatinine measurements lack both sensitivity and specificity in this setting [31]. Even 24-h urine collections for creatinine clearance have significant limitations in the ICU setting [30].

Urine output is a more sensitive marker of AKI and is easily measured in the ICU setting as most patients have a urinary catheter and 1:1 nursing. Urine output still presents limitations however, as urine output may persist until kidney function almost ceases. Furthermore, oliguria may be an appropriate physiological response to hypovolaemia, a postoperative state, and following trauma as a result of ADH release. Finally, in obese patients, the use of total weight rather than ideal body weight to calculate appropriate urine output may lead to the overdiagnosis of AKI [29].

Novel markers are currently being developed and show promise in detecting AKI earlier than serum creatinine. These include markers of kidney function (e.g. serum cystatin C) or renal damage (e.g. Kim-1, NGAL, TIMP2 and IGFBP3) [6]. Various imaging modalities, most notably functional renal magnetic resonance (MR), can assess both renal morphology and function [32]. A more detailed discussion of emerging diagnostic modalities is beyond the scope of this chapter. Nevertheless, until these novel measurements are validated and widely available, serum creatinine and urine output will remain the key components of the definition of AKI.

7.2 Fluid Management in the AKI Patient

7.2.1 Principles of Fluid Management

The physiological rationale for administration of fluids in critically ill patients is to restore tissue perfusion and oxygenation. The two most common indications for fluid administration in ICU patients are hypotension (59%) and oliguria (18%) [33]. While fluids are clearly of benefit in hypovolaemic states and may be a preventative measure against AKI, there are many forms of AKI that are considered volume-unresponsive, in particular AKI caused by nephrotoxin exposure or renal inflammation [34]. In these latter situations, indiscriminate use of fluids carries the risk of de novo or worsening of AKI by fluid overload and may even impair renal recovery after AKI [29, 35]. Furthermore, it is highly likely that the effects of fluid therapy are dependent on the phase of critical illness, i.e. resuscitation, optimization, stabilization and de-escalation [36, 37]. At present, there are no generally accepted rules regarding fluid management in the ICU patient; however this is an area of active research. In the meantime, the principles of a fluid challenge over a short time period, assessing volume responsiveness using dynamic measures and avoiding indiscriminate fluid administration are of paramount importance.

7.2.2 Vasopressors

Given the loss of autoregulation in AKI, it is imperative to maintain systemic haemodynamic stability to maximize renal perfusion. Current guidelines recommend titrating vasopressors to a MAP of 65–70 mmHg in patients with septic shock and suggest a higher target MAP (80–85 mmHg) in patients with pre-existent hypertension [38]. These targets are derived from the SEPSISPAM trial, where, although the investigators did not demonstrate a difference in mortality, in the subset of patients with chronic hypertension, a higher MAP was associated with decreased incidence of AKI stage 2 and need for RRT [39]. A subsequent meta-analysis also demonstrated no difference in 28-day mortality between MAP targets but showed that those treated with a higher MAP for more than 6 h had a higher risk of mortality and persistent organ dysfunction [40]. Given these discordant results, it is unclear if a higher MAP is of benefit in certain patient populations in the setting of septic shock.

Regarding the choice of vasopressor, norepinephrine (along with volume correction) is recommended as the first choice [41]. Vasopressin may have some renal-protective effects, although this requires further validation [42]. Angiotensin II, a vasopressor that has direct effects on renal microcirculation, shows promise in patients with refractory shock requiring RRT. In fact, a post hoc analysis of the ATHOS-3 trial demonstrated a higher proportion of patients alive and free of RRT when treated with angiotensin II in addition to standard therapy [43]. Low-dose dopamine, initially thought to promote renal perfusion through a vasodilatory effect, has not been shown to improve outcomes in AKI and is not recommended [44, 45].

A recent RCT evaluating fenoldopam, a selective dopamine-1 receptor agonist, in a cardiac surgery population with AKI was stopped prematurely when it failed to reduce the need for RRT and 30-day mortality but increased hypotension rates [46].

7.2.3 Type of Resuscitation Fluids

Isotonic crystalloids remain the preferred choice for resuscitation, although albumin may be used in those circumstances where the patient has already received a large volume of crystalloid [47, 48]. Synthetic colloids, on the other hand, such as hydroxyethyl starches (HES), gelatins and dextrans are not recommended. HES increase the rates of AKI, RRT and mortality in patients with sepsis [49, 50]. Gelatins have also been shown to increase the incidence of AKI compared to crystalloids or albumin [51].

The type of isotonic crystalloid to use is an area of active debate and stems from safety concerns of isotonic saline causing a hyperchloraemic metabolic acidosis leading to renal vasoconstriction, an increased incidence of AKI and higher mortality. Balanced solutions (e.g. Ringer's lactate), however, are not without potential drawbacks. These include relative hypotonicity to serum, the development of metabolic alkalosis and hyperkalaemia as well as a signal to increased transfusion requirements [52]. A meta-analysis of 11 RCTs failed to show any difference in the incidence of AKI, need for RRT or mortality between balanced crystalloid and isotonic saline for fluid resuscitation [53]. However, this study had many limitations, and caution is required in interpreting the results. The SPLIT trial was the largest trial included in the meta-analysis and was performed in a predominantly surgical population. Although there was no difference in primary outcome defined as AKI by RIFLE criteria, there was a 1% absolute difference in mortality (non-significant) favouring the balanced solution group. Since the SPLIT trial, two RCTs have been published in heterogenous ICU populations (SALT and SMART) addressing the same question [54, 55]. The SALT trial did not demonstrate a difference in the composite outcome of death, dialysis or persistent renal dysfunction within 30 days between fluid strategies. Importantly, in this trial as well as in the SPLIT trial, patients received relatively small volumes of study fluid, and serum chloride levels were not measured [54]. The largest study to date and the one likely to influence clinical practice is the SMART trial, a pragmatic RCT conducted in over 15,000 patients admitted to 5 ICUs in the United States [55]. The balanced crystalloid group received a median of 1000 mL (0–3210 mL) and the saline group a median of 1020 mL (0–3500 mL) within the first 30 days. Fewer patients in the balanced crystalloids group had a measured plasma chloride concentration greater than 110 mmol/L (24.5% vs. 35.6%, $p < 0.001$) or a plasma bicarbonate concentration less than 20 mmol/L (35.2% vs. 42.1%, $p < 0.001$). The primary outcome, a composite of death, new RRT or persistent renal dysfunction at 30 days, was lower in the balanced crystalloids group (14.3% vs. 15.4% $p = 0.04$, odds ratio 0.91 [0.84–0.99]), largely driven by a difference in mortality and need for RRT.

At present, it is recommended that isotonic crystalloid be used as the initial resuscitation fluid in the absence of haemorrhagic shock [56]. Experts recommend balanced isotonic solutions for large-volume resuscitations given the evidence outlined above; however, isotonic saline can still be used in small volumes with close monitoring of serum chloride levels and acid-base status, with avoidance of hyperchloraemia [38].

7.2.4 Diuretics

Although not necessarily causal, a positive fluid balance is associated with decreased rates of renal recovery and increased mortality in patients with AKI [57–61]. In fact, some trials have suggested improved renal outcomes with a fluid restrictive approach [62, 63]. Thus, recent attention has focused on the role of diuretics in AKI especially in the stabilization and de-escalation phases of critical illness. Although diuretics have been associated with an increase in urine output, in established AKI, they have not been shown to have an impact on the duration of AKI, the need for RRT or mortality [64–67]. They may, however, predict AKI progression as there is evidence that a lack of appropriate response to a one-time dose of diuretic (as defined by a urine output of 100 cc/h for 2 h post furosemide 1–1.5 mg/kg) in early AKI predicts progressive AKI in critically ill patients [68]. Certainly if the patient is volume overloaded (>10% of admission body weight) and is not responsive to diuretics in the setting of AKI, the initiation of RRT should be strongly considered.

7.3 Mitigating Renal Injury in the ACS Patient

7.3.1 Medications

One of the important management principles in AKI is the prevention of secondary injury from nephrotoxic agents. The most notable agents in critically ill patients include non-steroidal anti-inflammatory agents (NSAIDs), vancomycin, aminoglycosides and amphotericin B [31]. Furthermore, it is imperative to dose adjust all renally excreted medications in order to ensure proper therapeutic levels while minimizing nephrotoxicity.

7.3.2 Metabolic Factors

Although the primary mechanism is unclear, there is evidence that tight glucose control may be reno-protective and may reduce the incidence of AKI and the need for RRT [69–71]. The European Society of Intensive Care Medicine recommends a blood glucose level below 180 mg/dL (10 mmol/L) to avoid the nephrotoxic effects of hyperglycaemia [38].

Adequate nutritional support is important but can be challenging; traditional modes of assessment (e.g. prealbumin) may be less accurate in AKI as it is a pro-inflammatory and hypercatabolic state [72, 73]. It is recommended that all patients at risk of developing AKI or with AKI should receive adequate nutrition, preferably enterally [38].

7.3.3 Contrast Agents

Computed tomography scans are ubiquitously performed in critically ill patients; thus a commonly encountered agent is intravenous contrast. It is important to note that recent evidence has questioned the association between intravenous contrast and the development of AKI in emergency medicine and ICU patients [74, 75]. In a recent cohort study of 6877 critically ill patients, intravenous contrast administration was not associated with an increase incidence of AKI or mortality in patients with a pre-CT eGFR greater or less than 45 mL/min. There was an increased need for dialysis in the cohort with a pre-CT eGFR ≤45 mL/min; however it is not known if this reflects local practice patterns or other unknown factors [76].

Nonetheless, there is significant interest in prevention strategies for contrast-induced nephropathy (CIN). In the critically ill, the evidence remains limited, and most recommendations are extrapolated from non-ICU populations. The use of nonionic low-osmolar or iso-osmolar contrast agents is clearly less nephrotoxic than the infusion of high-osmolar contrast [77]. The PRESERVE trial addressed the utility of *N*-acetyl cysteine (NAC) and type of intravenous fluid (saline versus bicarbonate) in over 5000 patients at risk of CIN. There was no difference in the primary composite outcome of death, RRT or a creatinine >50% over baseline at 90 days between NAC and placebo, thus definitively establishing that NAC is ineffective to prevent CIN. There was also no difference observed between intravenous saline and bicarbonate; thus it appears that either fluid strategy is acceptable to prevent CIN. Finally, although not well studied in the ICU population, the use of prophylactic RRT does not appear to decrease the incidence of contrast-induced nephropathy [78].

If a contrast study is necessary in the critically ill patient, guidelines suggest proceeding without delay [38]. If time allows, isotonic crystalloid can be administered; however, the preventative effect against CIN is unknown.

7.3.4 AKI Bundles

In an effort to better manage AKI, there has been some interest in developing AKI bundles of care, similar to those previously developed in the management of sepsis and ventilator-associated pneumonia. Although the evidence is limited, the implementation of AKI bundles show promise in improving processes of care and patient outcomes. The specific components of the individual bundles differed slightly per study; however, the core components were similar, including a focus on medication

review, fluid balance, diagnosis (e.g. urinalysis and imaging) and following serum creatinine [79]. The introduction of these bundles has been associated with improved processes of care, including AKI recognition, assessments of fluid status, use of investigations and the discontinuation of nephrotoxic medications [80–83]. When implemented within 24 h of an AKI episode, these bundles are also associated with less progression to higher AKI stages and lower in hospital mortality [84, 85].

7.4 Renal Replacement Therapy

7.4.1 Indications

Once the diagnosis of AKI has been established in the critically ill patient, the intensivist must decide whether RRT is indicated. Classically, the indications for RRT have been reactive and late in the course of AKI (Table 7.2). Moreover, many of these indications are highly subjective and nonspecific. In fact, international surveys of practice patterns in the implementation of RRT show highly variable results [86, 87]. More recently, the concept of RRT has moved away from "replacement" late in the disease process and more towards early "renal support" [88].

To standardize RRT initiation, both a personalized "demand versus capacity" approach and an approach based on AKI stage have been proposed. The "demand versus capacity" approach has been described by the Acute Dialysis Quality Initiative (ADQI) work group and states that acute RRT should be considered when the individual's metabolic and fluid demands exceed total kidney capacity and should not be solely based on renal function or AKI stage [89]. Regarding the timing approach, two meta-analyses did not show any benefit of early initiation in terms of survival or length of stay [90, 91]. The two largest timing of initiation trials were included in the most recent meta-analysis [90]. In the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial, there was no difference in 60-day mortality between patients with stage 3 AKI in the early (at randomization) versus late (awaiting an acute indication for RRT) initiation arms [92]. Conversely, in the Early Versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN) trial, early institution (within 8 h of diagnosis of KDIGO stage 2 disease) of RRT in patients led to a 15.4% reduction in 90-day mortality as compared to the delayed group (RRT initiated within 12 h of stage 3 or no initiation at all) [93]. The long-term outcomes in the early initiation group of the ELAIN trial have recently been reported and remain favourable at 12 months of follow-up [94].

Table 7.2 Common acute indications for renal replacement therapy

Refractory metabolic acidosis
Refractory hyperkalaemia
Dialysable toxins
Complications of uremia (pericarditis, encephalopathy)
Fluid overload

Given the discordant findings of these trials, which can partially be explained by heterogeneous populations, small sample sizes and differences in study definitions and design, the results of the ongoing Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury (STARRT-AKI) trial (ClinicalTrials.gov Identifier: NCT02568722) will hopefully help clarify this question. In the meantime, current guidelines remain vague, recommending emergent RRT in the presence of life-threatening fluid and metabolic derangements and consideration for earlier RRT depending on the clinical context (e.g. volume status) [56].

7.4.2 Modalities of RRT

Multiple modalities of RRT are commonly used in the critical care setting. All represent extracorporeal circuits that remove water and solute from the body through a semipermeable membrane. These include intermittent haemodialysis (IHD), sustained low-efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). CRRT includes continuous venovenous haemodialysis (CVVHD), continuous venovenous haemofiltration (CVVH) or continuous venovenous haemodiafiltration (CVVHDF).

The nomenclature of these therapies refers to the process through which solute removal occurs, i.e. diffusion (haemodialysis), convection (haemofiltration) or a combination of both (haemodiafiltration). During diffusive clearance, small solutes (e.g. sodium and urea) move down their concentration gradient across a semipermeable membrane [95]. To maximize concentration differences, dialysis flows in the opposite direction or countercurrent to the blood flow. With convective clearance, a pressure gradient is applied across the dialyser membrane resulting in bulk flow of water and dissolved solutes across the dialyser membrane in an iso-osmolar fashion, a concept referred to as “solvent drag”. Because a large amount of volume can be lost with this form of clearance, a replacement solution is often infused into the patient or machine circuit (pre- and/or post-filter). Convection is more effective in the clearance of middle-size molecules (i.e. inflammatory cytokines). The amount of clearance depends upon the modality chosen. Table 7.3 outlines the differences between intermittent haemodialysis, SLEDD and CRRT.

The choice of modality in critically ill patients remains controversial. In fact, when comparing intermittent HD to CRRT, RCTs have failed to show a mortality difference [96, 97]. Although meta-analyses have confirmed this finding, there is emerging evidence that CRRT may be associated with an improvement in long-term renal recovery in critically ill patients with AKI [98, 99]. When comparing haemofiltration and haemodialysis, there does not seem to be a difference in mortality or long-term RRT dependence; however, there is evidence that haemofiltration may increase the clearance of inflammatory cytokines, which may have a theoretical advantage in sepsis [100]. Ultimately, the choice of RRT modality relies largely on local practice, expertise and resources.

Table 7.3 Comparison of various techniques of renal replacement therapy [6, 124]

	CRRT	IHD	SLED
Duration	Continuous	4 h	6–12 h
Frequency	Continuous	3×/week	3–6×/week
Dialysate flow rates (mL/min)	100–200	250–350	100–200
Dose of dialysate	20–25 mL/kg/h	500–800 mL/min	100–300 mL/min
Urea clearance (mL/min)	30	150	80
Efficiency	Low	High	Moderate
Haemodynamic effects	Minimal	Significant	Moderate
Control of volume status	+++	+	++
Anticoagulation need	High	Low	Moderate
Toxin removal	Slow	Fast	Moderate
Costs	High	Low	High initially, low subsequently

CRRT continuous renal replacement therapy, *IHD* intermittent haemodialysis, *SLED* sustained low-efficiency dialysis

7.4.3 Vascular Access

Once the decision is made to implement RRT, a well-functioning vascular access must be established. In critically ill patients, access for RRT is often obtained urgently through a temporary large-bore non-tunnelled central venous catheters (CVC) inserted at the bedside. KDIGO has published guidelines regarding vascular access site, in order of preference: (1) right internal jugular, (2) femoral, (3) left internal jugular and (4) subclavian, although the evidence for this recommendation has not been graded [56]. Whenever possible, the subclavian (and probably the left internal jugular) site should be avoided to reduce the risk of central vein stenosis as this will compromise potential future permanent vascular access. It is recommended that ultrasound guidance be used for all non-tunnelled haemodialysis line insertions and that the catheter tip be positioned to achieve ideal blood flows (i.e. internal jugular lines should terminate in the right atrium and femoral catheters in the inferior vena cava) [56, 101]. Regardless of site, the same infection-control bundles of care for standard CVC insertion should be implemented [6].

Previously, concerns were raised regarding the femoral site as observational evidence reported an increase in infectious complications. The Cathedia study found that the internal jugular and femoral access sites were equivalent in terms of infectious complications in critically ill bed-bound patients, although the risk at the femoral site was dependent on patient BMI with lower infection rates in patients with a BMI <24.2 and higher if the BMI >28.4 [102–105]. The quality of delivered RRT was equivalent; however if patients required higher blood flows (e.g. for intermittent therapies), the jugular site was superior [103]. Thus, the femoral site is a reasonable second access site in non-ambulatory patients with a low BMI. It is also favoured in patients with a tracheostomy present or planned in the near future [6, 102, 106].

7.4.4 Dosing of RRT

The intensity (i.e. dose) of continuous therapies remains a debated topic and is not standardized across critical care units. It was initially thought that high-dose CRRT (i.e. effluent volume >35 mL/kg/h) was associated with increased survival based upon the landmark study of Ronco et al. [107]. Since then, two large multicentre RCTs have refuted the findings of this study. In the Acute Renal Failure Trial Network (ATN) trial, there was no difference in 60-day mortality between the lower-intensity (defined dose of intermittent haemodialysis three times per week and CVVH at 20 mL/kg/h) and higher-intensity (intermittent haemodialysis and sustained low-efficiency dialysis six times per week and CVVH at 35 mL/kg/h) groups [108]. The largest trial to date is the Randomized Evaluation of Normal versus Augmented Level of Renal Replacement (RENAL) study where 1508 critically ill patients were randomized to low- (25 mL/kg/h) versus high (40 mL/kg/h)-dose groups in CVVHDF mode [109]. There was no difference in 90-day mortality or any prespecified outcomes between dose intensity groups. Importantly, in both the ATN and RENAL studies, there was also no difference observed in long-term renal recovery between low- and high-intensity groups. As such, it appears that increasing the dose of RRT above 20–25 mL/kg/h does not provide any additional benefit and current recommendations therefore advocate this threshold [56]. It is important to note that discrepancies often exist between the prescribed and the delivered dose due to interruptions in treatment time (e.g. patient transport or filter clotting). Thus to minimize this discrepancy, it is general practice to prescribe a 20% higher (ideal) weight-based dose to ensure the patient receives the recommended minimum dose of dialysis.

7.4.5 Anticoagulation

During all forms of renal replacement therapy, blood flows through synthetic dialyser membranes and circuits. Thus, there is a high risk of thrombus formation and subsequent dialyser dysfunction resulting in decreased clearance. Strategies utilized to minimize risk of thrombus formation include straight catheters with minimal side holes, the use of pre-filter fluid replacement in CVVH and CVVHDF modes of CRRT, proper nurse training in the early recognition of filter dysfunction and anticoagulation of the circuit [110]. While it is common not to use anticoagulation on CRRT in critically ill post-surgical patients, if the filter is clotting, either heparin or citrate can be used if the patient's status allows. Both are effective anticoagulants but also have unique clinical concerns. Heparin requires systemic anticoagulation and is associated with increased bleeding, develops resistance over time in critically ill patients and promotes a pro-inflammatory state [111]. Furthermore, there is also a risk of heparin-induced thrombocytopenia (HIT). The use of citrate circumvents some of these problems as it is locally infused pre-filter into the dialyser circuit chelating calcium, which provides regional anticoagulation. Citrate also inhibits

platelet and granulocyte activation upon membrane contact, which increases biocompatibility of the dialyser membrane [6]. To avoid hypocalcaemia, calcium is infused into the patient; thus close monitoring of serum total and ionized calcium levels is required [6]. Citrate accumulation can occur in states of severe acute liver failure and cardiogenic shock and is generally avoided in these circumstances [112]. Signs of citrate toxicity include an anion gap metabolic acidosis, increasing calcium infusion requirements and a high total calcium to ionized calcium level [112]. Other common side effects caused by metabolism of citrate are hypernatremia and metabolic alkalosis, which are managed by changing the composition of base in the dialysate and/or replacement solutions.

A meta-analysis in critically ill patients comparing heparin and citrate anticoagulation for CRRT demonstrated that citrate was associated with a decreased incidence of bleeding (compared to systemic heparin) and HIT, as well as a longer dialysis circuit and filter life. The type of anticoagulant used did not influence patient survival [113]. KDIGO guidelines recommend the use of citrate in CRRT rather than heparin in patients without a clear contraindication, although at the time of this publication, the use of citrate in CRRT is not approved by the US Food and Drug Administration (FDA) [56].

7.4.6 Special Populations

Although equipoise often exists in the choice of modalities of RRT in the critically ill, there are specific patient populations for which further evidence exists.

In haemodynamically unstable patients, CRRT has commonly been the preferred modality because of more precise control of fluid and solute shifts. There is evidence however that intermittent modalities may be well tolerated in this patient population with less aggressive ultrafiltration and lower blood and dialysate flows [114]. A 2006 RCT of CRRT versus IHD in patients with multi-organ dysfunction showed adequate haemodynamic tolerance in the IHD group, as long as strict practice guidelines were followed [96]. In haemodynamically unstable patients with severe lactic acidosis, CRRT may minimize pH variations and their concomitant haemodynamic effects [115].

In acute liver failure with concomitant AKI, there are concerns that rapid shifts of solutes, notably urea, may lead to a hypo-osmolar state. The intracellular shift of water ultimately increases the risk of cerebral oedema and increased ICP. In a small observational study in this specific patient population, the use of IHD as compared to CRRT both increased ICP and decreased cerebral perfusion pressure (CPP) [116]. A small follow-up RCT performed at the same institution also confirmed these results [117]. As such, in acute liver failure patients, it appears that CRRT may indeed be safer than IHD and is recommended by the US Acute Liver Failure Study Group [118].

With these concerns related to the interdependence of solute shifts and ICP, it would be logical that CRRT may be preferred over IHD in patients with any concern for increased ICP, notably acute neurological injuries. Although there is no

direct evidence comparing RRT modalities in acute neurological disease, given the physiological plausibility, CRRT may be preferred in patients at risk of increased ICP [119].

In septic patients, RRT has been hypothesized to be beneficial in removing circulating cytokines and therefore blunting the inflammatory cascade. Two RCTS have examined the use of CVVH in severely septic patients and failed to demonstrate improved outcomes or even a decrease in inflammatory markers [120, 121]. In the multicentre high volume in intensive care (IVOIRE) RCT, higher-volume haemofiltration (70 mL/kg/h) was compared to lower-volume (35 mL/kg/h) in patients with septic shock. There was no difference in 28-day mortality, haemodynamic profile or organ dysfunction [122]. The EUPHRATES trial evaluated the use of polymyxin B haemoperfusion in critically ill adults treated for endotoxemia and refractory septic shock. Although the investigators found no difference in overall mortality at 28 days between groups, in the subgroup with endotoxin activity assay >0.6 but less than 0.9, there was a signal to decreased mortality, improved haemodynamic parameters and a decreased need for RRT [123]. More studies using adsorptive technologies are expected in the future.

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8 Acute Hepatic Failure in the ACS Patient: Nuts and Bolts of Pathophysiology and Therapy

Bruno M. Pereira

8.1 Background

Acute liver failure (ALF) is a poor prognosis state defined as an acute and severe hepatic lesion with encephalopathy, in patients without previous liver disease. Trey and Davidson [1], in 1970, proposed the most widely accepted definition in which acute hepatic failure (AHF) manifests with the development of encephalopathy within 8iweeks from the onset of the disease. In another classification [2], two terms were used: sub-fulminant hepatic failure is one in which encephalopathy occurs 2 to 12 weeks after jaundice begins, while fulminant hepatic failure is one in which encephalopathy sets in before 2 weeks. Afterward [3], three terms were used to characterize the syndrome, subacute, acute, and superacute hepatic failure, according to the time elapsed between jaundice and the onset of encephalopathy (Table 8.1). The etiology, much more than the time of disease, will define its prognosis. It is important to emphasize that acute liver failure is a syndrome in which, in addition to the liver, other organs can be affected, such as the brain, kidneys, lungs, and bone marrow, as well as circulatory system and immune system. There are numerous causes of AHF, such as viral hepatitis, the use of drugs, metabolic diseases, toxic exposure, ischemia, and a range of diseases listed in Table 8.2. The careful investigation of all possible etiologic agents of AHF, however, is not always successful, and about 40% to 50% of the cases are without determined etiology [4]. The liver plays a key role in the synthesis of proteins, metabolism of toxins and drugs, and in modulation of immunity. In critically ill patients, hypoxic, toxic, and inflammatory insults can affect hepatic excretory, synthetic, and/or purification functions, leading

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Table 8.1 AHF classification

Author	Definition	Onset time of encephalopathy (after jaundice in weeks)
Bernuau et al. [2]	Fulminant HF	0–2
	Sub-fulminant HF	3–12
O'Grady et al. [3]	Superacute HF	0–1
	AHF	2–4
	Subacute HF	5–12

Table 8.2 AHF etiologies

Infectious diseases	Rifampicin
Viral hepatitis: A, B, and combinations	Tetracycline
Cytomegalovirus	Dissulfiram
Herpes simplex	Reye syndrome (acetylsalicylic acid)
Epstein-Barr	Ketoconazole
Paramyxoviruses	Non-hormonal anti-inflammatory
Adenovirus	Antithyroid, hydantoin, alpha-methyldopa
Dengue	
Yellow fever	Ischemic/hypoxia
Metabolic diseases	Venoclusive disease
Wilson's disease	Primary hepatic dysfunction posttransplant
αr1-antitrypsin deficiency	
Galactosemia	Ischemic hepatic shock
Drugs and toxins exposure	Heart failure
(a) Dose related	*Miscellaneous*
Acetaminophen	Autoimmune hepatitis
Amanita phalloides (death cap)	Lymphoma
Yellow phosphorus	Acute steatosis in pregnancy
(b) Idiosyncratic	Hyperthermia
Isoniazid, halothane	Partial hepatectomy

to systemic complications such as coagulopathy, increased risk of infection, hypoglycemia, acute kidney injury, and brain dysfunction in severe cases. Because of the lack of specificity of standard laboratory investigations, identifying liver injury or dysfunction in critically ill patients remains a significant challenge.

Both hepatitis A and acute hepatitis B, for instance, can progress to AHF in variable percentages, usually <1% of cases. Hepatitis E, although of rare prevalence, causes AHF in pregnant women. Viruses alone do not appear to cause hepatic injury, and the more severe evolution of infection appears to be a consequence of the host's more vigorous immune response [5]. In the case of hepatitis B, according to some studies, either mutations of the pre-core region or reactivation of chronic latent hepatitis B or the use of immunosuppressant or chemotherapy may occasionally lead to AHF triggering [6]. Another factor that may precipitate AHF in patients with hepatitis B is superinfection with the delta virus. In hepatitis C, the occurrence of AHF is controversial, being more accepted that superinfection with other viruses or other causes would be possible triggers [7]. The use of drugs with an unpredictable reaction may be another cause of AHF. Acetaminophen, a drug with a predictable

Table 8.3 Key points of AH injury, AH dysfunction, and AHF in the ACS patient

	Hypoxic hepatitis • Hypoxemia • Reduced blood flow • Anemia	Sepsis	Parenteral nutrition	Drugs
AH injury	Hepatocellular (high AST, AST)		Cholestatic (high ALP, GGT)	
AH dysfunction	Synthetic dysfunction (high bilirubin, INR) • Frequent • Associated with increased mortality		Elimination dysfunction (low ICG-PDR) • Determined noninvasively at bedside • Associated with increased mortality	
AHF	Hepatic dysfunction with *encephalopathy* • Coagulation disorders • Jaundice • Intracranial hypertension • High risk of mortality without liver transplantation			

hepatotoxic effect, has been reported worldwide as one of the most frequent causes of AHF in both adults and children above 3 years [8]. Several infrequent causes such as Wilson's disease, Budd-Chiari syndrome, or malignant liver infiltration also need to be investigated prior to labeling AHF as an indeterminate cause.

There is a great heterogeneity of criteria used to define the consequences of liver insults. This increases the difficulties for the assistant physician to properly interpret hepatic biochemical abnormalities. Hepatic dysfunction refers to derangement of pathways related to synthetic or clearance function, including international normalized ratio (INR) and bilirubin. Hepatotoxicity refers to hepatic injury and dysfunction caused by a drug or another noninfectious agent [9]. AHF designates liver injury that results in life-threatening hepatic synthetic dysfunction and brain dysfunction (encephalopathy) (Table 8.3).

8.2 Pathophysiology

AHF leads to severe functional deficiency of the liver, with alteration of its entire metabolism. The metabolic capacity of endogenous substances such as hormones, bilirubins, vitamins, and even drugs is depleted, requiring extreme caution in the prescription of drugs, especially those dependent on hepatic metabolism and potentially hepatotoxic. When present, increased brain levels of gamma-aminobutyric acid (GABA), for instance, elevate the sensitivity of patients to benzodiazepines in brain receptors, which contraindicates the use of this group of drugs in patients with acute or chronic liver disease [10]. Although serum ammonia levels are often not related to the degree of encephalopathy or the severity of hepatitis, this substance is of fundamental importance in the pathogenesis of severe hepatic failure. Several experimental evidence show that ammonia is a neurotoxic substance, which can produce seizures, coma, and death. Hyperammonemia has toxic synergism with all the metabolic changes described in hepatic dysfunction. The toxic synergism

of these different substances results in the inhibition of Na^+ and K^+ ATPase, which plays an important role in the transmission of nerve impulses [11].

Changes in carbohydrate metabolism are mainly manifested by hypoglycemia. Regarding protein synthesis, although albumin may be normal at the onset of the clinical condition due to its longer half-life, other short half-life proteins such as alpha-1 and alpha-2 globulins rapidly decline. Several blood-clotting factors, synthesized in the liver and having short half-lives, are also decreased in AHF, such as factor V and prothrombin activity.

Kupffer cells remove bacteria from the circulation, ingest endotoxin, and modulate the immune response through the release of pro-inflammatory mediators. The malfunction of Kupffer cells in AHF allows the free transit of microorganisms and endotoxins from the intestine, which reach the blood circulation, worsening metabolic functions and favoring the installation of infections and the release of cytokines with serious circulatory consequences, aggravating even more the disease [12].

Hypoxic hepatitis (HH) such as ischemic hepatitis, hypoxic hepatopathy, shock liver, or hypoxic liver injury results from inadequate oxygen delivery to the liver and is defined as liver injury as a consequence of a cardiovascular insult followed by a sudden transient elevation of aminotransferases greater than tenfold above baseline with no other identified cause of liver damage. HH often is characterized by the triad of acute elevation in serum aminotransferases, rapid elevation in INR, and altered renal function. This can be caused by inadequate oxygen in blood (hypoxemic hypoxia), inadequate blood flow (ischemic hypoxia), or lack of carrying capacity (anemic hypoxia). Indeed, ischemic hypoxia of the liver can be caused by increased venous pressures, as well as decreased arterial pressures. The centrilobular hepatocytes are particularly vulnerable to hypoxia, so the primary injury is centrilobular necrosis (Fig. 8.1). Patients with unrecognized preexisting liver disease might be more susceptible to hypoxic injury. In this condition, elevation in liver enzymes may be difficult to

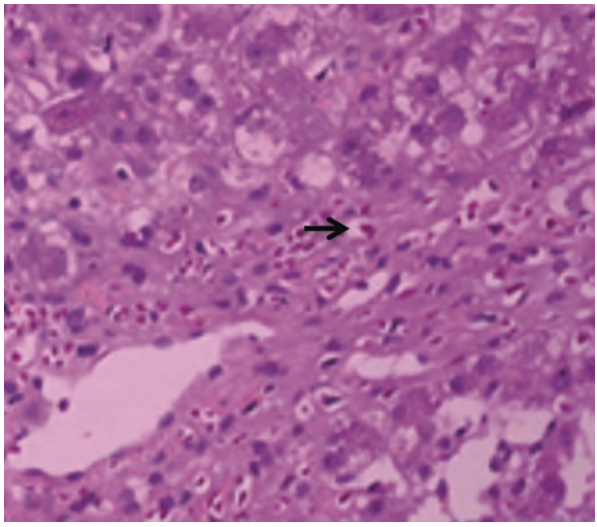

Fig. 8.1 Histologic example of hypoxic hepatitis (HH). Perivenular hepatocyte necrosis with cell loss, moderate congestion (arrow), and acidophil bodies (from the Pathology Department of the University of Campinas)

interpret in cases of previous biochemistry abnormalities. In ICU patients, the prevalence of hypoxic hepatitis has been estimated to be between 1% and 12% [13]. The conditions most frequently associated with the development of hypoxic hepatitis in the acute care surgery patient are hypovolemic or septic shock, cardiac failure (congestive and acute), and global hypoxia. In patients with septic shock, it has been associated with high in-hospital mortality (more than 80%) [14, 15].

Focusing specifically on sepsis for a moment, it is important to highlight that several factors may contribute to the development of hepatic dysfunction during sepsis. The two most common causes of hepatic dysfunction in sepsis are the mentioned above HH and sepsis-associated cholestasis. During the initial phase of septic shock, the impairment of hepatic perfusion may result in HH, resulting in direct hepatocellular injury. Hepatocellular injury is defined by injury to hepatocytes, which can be either a reversible disturbance or cell death. It is characterized by elevation of intracellular enzymes (aminotransferases) involved in α-amino group regulation. AST and ALT are cleared in the sinusoidal cells of the liver, and serum concentrations reflect hepatocyte turnover and clearance. During liver injury, hepatocellular permeability is increased, and consequently AST and ALT are released from the intracellular space into plasma. The duration of elevation depends upon the severity of hepatic insult and the half-life of the enzyme [16]. Clinical studies indicate that liver injury can also develop despite an increase in splanchnic blood flow that increases proportionally to cardiac output. This is likely because there is increased splanchnic oxygen consumption so less oxygen reaches the liver through the portal system, or another flow-independent mechanism may explain hepatic dysfunction in patients with septic shock. It is also possible that the initial injury of the centrilobular regions leads to swelling in this region and a specific loss of flow in the critical area.

In cases of functional sepsis-associated cholestasis, increased intestinal permeability as a complication of sepsis can lead to endotoxin translocation from the intestinal lumen into the portal circulation. Endotoxin activates Kupffer cells, which in turn secrete pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 cells, which in turn mediates through its inhibitory effects interleukin-6 (IL-6). This inflammatory process alters hepatocyte or cholangiocyte uptake of bile acids, intracellular architecture, transporter systems, and cellular junctions and reduces secretion of bile [17].

The clinical setting may be insidious or rapid and progressive, leading to the failure of multiple organs and systems. With that said, the mainstay of clinical management of liver injury in the acute care surgery patient at the ICU is therefore related to early diagnosis and correct identification of etiology. Figure 8.2 proposes the first measures to follow in patients with AHF presenting with SIRS, scenario that can be observed on the ACS patient in the ICU. The first symptoms are not specific—nausea, malaise, and fatigue. The most striking symptom is encephalopathy, which may appear before or after jaundice. It is important to consider differential diagnosis of non-hepatic causes of neurological disorders, such as meningitis, barbiturate, or benzodiazepine poisoning, reversible by the administration of a specific antagonist (flumazenil). Several extrahepatic factors may contribute to encephalopathy such as hypoglycemia, hyponatremia, uremia, hypoxia, and

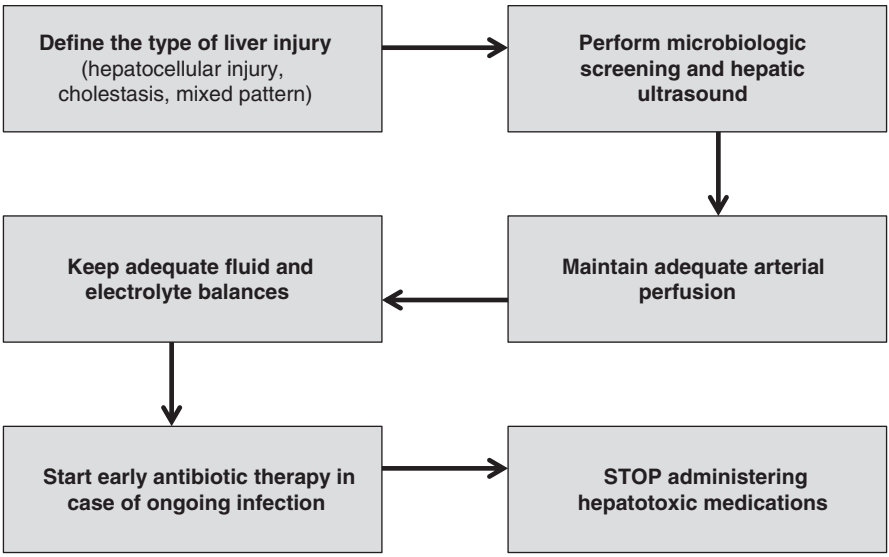

Fig. 8.2 First measures to follow in patients with AHF presenting with SIRS

sepsis. Clinically, sepsis-induced hepatic dysfunction may be suspected in septic patients with biochemical cholestasis. However, the differential diagnosis of hyperbilirubinemia in this setting is broad and includes cold agglutinin-associated hemolytic anemia, drug-induced hemolysis, and transfusion reactions. This makes static laboratory blood tests unreliable in the assessment of hepatic function. The use of dynamic methods, such ICG-PDR monitoring, may in the future help to detect and monitor suspected hepatic dysfunction more reliably and earlier in septic patients [17].

The evolution of encephalopathy is classically described in four stages, beginning with behavioral alterations, sleep-wake disorders, and space disorientation. Alternations from one degree to another can occur in hours, evolving to more advanced stages such as precoma and hepatic coma.

In concomitance with the development of neuropsychic alterations of hepatic encephalopathy, it is common to establish infections, renal insufficiency, and hemorrhages, being possible on this scenario to characterize multiple organ failure syndrome. In addition to these non-specific data, the onset of cerebral edema is unique to AHF, which is a frequent cause of mortality [18].

Cerebral edema and multiple organ failure are indeed the leading causes of AHF mortality. Cerebral edema manifests clinically when intracranial pressure (ICP) exceeds 30 mmHg, accompanied by arterial sustained or not hypertension and muscular hypertonia. Eventually, one may find decerebrate posturing, pupil dilation less reactive to light, papilledema, headache, vomiting, and opisthotonus. These signs may be masked by the use of neuromuscular blockers [19].

Hypoglycemia occurs in 40% of AHF patients and has a multifactorial etiology. It may be related to impaired hepatic glucose release, altered hepatic gluconeogenesis,

Table 8.4 Prognostic factors of fulminant hepatic failure

Static factors		Bad prognosis
	Age	<10 or >40 years old
	Etiology	Hepatitis (except A)
		Drugs (except acetaminophen)
Dynamic factors	Bilirubin level	>18 mg/dL
	Prothrombin T	>100 s
	Factor V	<20%
	Hepatic steatosis	Grade IV
	Hepatocellular necrosis	Extensive
	Complications	Present

and increased serum insulin concentration in severe hepatic disease. Bleeding due to coagulopathy is not frequent, and upper gastrointestinal tract hemorrhage secondary to acute peptic erosions is more often observed.

Infections are present in 80% of the cases, resulting from deficiency of Kupffer cell function, intestinal bacterial translocation, leukocyte dysfunction, reduction of opsonization and complement, as well as the release of endotoxins and immunosuppressive cytokines. Invasive procedures, such as venous catheters and intubation in AHF patients, are important gateways for different infections [20]. Multiple organ failure, one of the main contraindications to liver transplantation, is manifested by hypotension with peripheral vasodilation, pulmonary edema, acute tubular necrosis, and disseminated intravascular coagulation. Renal insufficiency often occurs in AHF, and it is sometimes difficult to differentiate between simple intravascular volume depletion and acute tubular necrosis, typical of multiple organ failure.

AHF prognostic factors may be static or dynamic. The patientstiage and the etiology of the fulminant HF have been considered as static prognostic factors. Both hepatitis A and acetaminophen intoxication are considered to have a better prognosis, with mortality rates around 50%. On the other hand, cases of viral etiology, classified as non-A–E, as well as several medications, tend to have a worse prognosis [21] (Table 8.4).

8.3 Therapy

Specific therapy can only be applied since an etiologic identification of AHF has been done. In acetaminophen poisoning, for instance, the use of *N*-acetylcysteine should be appointed as early as possible within the first 10–24 h. In patients who experience acute liver failure, *N*-acetylcysteine has indeed an expanded role. Intravenous *N*-acetylcysteine is associated with improved transplant-free survival in patients with early encephalopathy caused by nonacetaminophen acute liver failure, including drug-induced liver injury, autoimmune hepatitis, hepatitis B, and indeterminate etiologies [22]. Except for patients requiring invasive procedure and those with active bleeding, platelets or fresh frozen plasma systematic, *N*-acetylcysteine administration should be avoided. In patients with acute failure, increased INR and/or low platelet count are not necessarily associated with excess risk of bleeding, in part because of compensatory mechanisms [23]. INR is a marker of the synthetic

function of the liver and constitutes an important prognosis marker used in several scoring systems. In addition, fresh frozen plasma alone does not allow adequate correction of coagulopathy and exposes patients to the risk of volume overload and transfusion-related acute lung injury (TRALI).

The treatment for herpes simplex-induced AHF is the administration of acyclovir [24]. In hepatitis B evolving with AHF, oral antiviral use is indicated with lamivudine (at standard doses), although other rapid-acting antivirals such as entecavir are promising [25].

Correction of factors that may lead to hepatic injury and encephalopathy worsening, such as hemorrhage, hypoxia, and hemodynamic, hydroelectrolytic, or acid-base metabolism, is urgent and mandatory. The treatment of these patients is multidisciplinary, covering different professionals, besides the hepatologist and liver transplant surgeons. Table 8.5 presents the set of therapeutic measures to be taken in the case of AHF. Some specific interventions have been tested on AHF, but since their efficacy has not been proven, its use is not recommended. Among them we have the use of corticosteroids, which probably increases the risks of septicemia. Infusion of insulin and glucagon should stimulate hepatic regeneration, but, like activated charcoal and prostaglandins, they have not been effective [26]. There are no controlled studies regarding the efficacy of lactulose in AHF patients and should be avoided when cerebral edema is present as part of the effort to minimize any type of stimulation. Lactulose does not prevent coma, as it depends on the degree of liver damage.

Table 8.5 Therapeutic guidance in the different clinical manifestations of fulminant hepatic failure

Complication	Therapeutic guidance
Hepatic encephalopathy	Hypoproteic diet (branched-chain amino acids or vegetable proteins) Avoid sedatives Intestinal enema Lactulose (?)—avoid in case of cerebral edema
Cerebral edema	Monitor ICP Avoid movements Avoid nasotracheal aspiration 45° bed headboard elevation Mannitol
Hypoglycemia	Constant glycemic control Glucose serum in continuous infusion
Renal failure	Dialysis Hemofiltration
Respiratory failure	ABGureatory onin Endotracheal intubation Mechanical ventilation
Hypotension	Dopamine
Infection	Regular source screening Antibiotic therapy
Bleeding	FFP/platelets Coagulation factors (use thromboelastogram for guidance) H_2 blockers/PPI
Kingckecollege criteria	Hepatic transplant

The level of consciousness must be rigorously evaluated in short intervals of time in order to follow up the deepening of coma. As patients have intense catabolic states and require adequate caloric intake, protein intake should be controlled. Depending on the state of consciousness, the nutritional access may be by nasogastric tube. To avoid malnutrition, which worsens the general condition of the patient, enteral or parenteral nutrition (PN) should be started early in the coma patients. The balanced solution rich in branched-chain amino acids has been recommended [27, 28]. Regarding parenteral nutrition indeed, in a prospective study that included more than 3000 critically ill patients, Grau et al. found that acute hepatotoxicity (defined as cholestasis, hepatocellular injury, or a mixed pattern) occurred more frequently in patients receiving PN than in those receiving enteral nutrition (30 and 18%, respectively). Daily caloric intake greater than 25 kcal/kg appears to be one of the most important factors predictive of PN-associated hepatotoxicity, along with total quantity of PN and sepsis [28]. Early enteral nutrition is preferably recommended when patient's clinical state allows it.

Central venous catheter placement is required for both central blood pressure monitoring and adequate infusion administration. Swan-Ganz catheter use is controversial, and although it facilitates monitoring of fluid overload, allowing occluded pulmonary capillary pressure to be maintained at about 12 mmHg, it is often not recommended and getting less and less used due to bedside ultrasonography advances. Daily cultures of blood, urine, secretions, and catheters should be performed, as 30% of infected patients with AHF do not show fever or leukocytosis. The most frequent sites of infection in AHF are blood stream (bacteremia), respiratory tract, urinary tract, and catheters. Treatment with systemic antibiotics is of fundamental importance, with third-generation cephalosporins being the most used to date as initial approach.

Continuous intravenously administration of 10% glucose is recommended whenever AHF is suspected, to keep glucose levels above 60 mg/dL.

Respiratory alkalosis and hypocapnia arise as a result of hyperventilation and infections, which often accompany the clinical setting of AHF. If respiratory failure is suspected, in addition to monitoring the arterial gases and making the desired corrections, intubation and mechanical ventilation should be performed.

To prevent cerebral edema, the head of the bed should be elevated to 45°. Mannitol (100–200 mL at 20% rapid infusion) continues to be indicated as the first line in the treatment of intracranial hypertension and cerebral edema. However, it should be used with caution in the presence of renal failure. In oliguric and/or refractory mannitol patients, the decrease in ICP can be obtained with thiopental infusion, which promotes cerebral vasoconstriction. Mild hypothermia (32–33 °C) is an exception procedure that prevents cerebral edema and has already been successfully used in humans as a bridge for liver transplantation [29].

In the presence of renal failure, hemodialysis may be required when hyperpotassemia, hyperosmolarity, or fluid overload occurs, and slow hemodialysis may be indicated, depending on the patient's condition.

In patients with spontaneous bleeding in gastrointestinal tube mucosa or with cerebral hemorrhage, correction of coagulation factors or replacement of platelets/fresh plasma should be attempted whenever necessary. The use of thromboelastogram is recommended. Blockade of gastric acidity can be done with the proton pump inhibitors or H2 blockers. Table 8.5 summarizes the main attitudes to be taken in the different AHF complications.

Bioartificial systems of hepatic support are constituted by hepatocyte cultures in resins and filters. Analogous to hemofiltration, the patient's plasma is perfused through these devices into direct contact with liver cells, which would maintain the functions of a normal liver. However, the amount of hepatocytes and their viability, as well as any functions not performed by Kupffer cells, will determine the efficacy of the treatment [30]. Hepatocyte transplantation is another alternative that has been advocated, although its usefulness is similar to the previous ones.

These procedures are intended to keep the individual alive and to give the liver time to regenerate itself and delay liver transplantation or for avoidance. In order to support the complex hepatic metabolic functions, these systems have been shown to be limited and expensive, which makes their current use difficult.

Extracorporeal albumin dialysis was used in patients with cirrhosis and acute-on-chronic liver failure, with the goal of removing albumin-bound toxins such as bile acids, nitric oxide, and metals [31].

Liver transplantation is the definitive treatment, capable of effectively saving the lives of these patients, with imminent risk of death. However, it is not easy to judge the timing of the transplant appointment.

The most widely used AHF liver transplantation criteria in the world is King's College criteria [32]. When AHF is induced by the overuse of acetaminophen, the pH can be kept in less than 7.3, regardless of the degree of encephalopathy. In other causes of AHF, the indication for liver transplantation may be only in the prolongation of prothrombin time over 100 s or in the association of at least three of the following criteria: age <10 or >40 years, non-hepatitis A to E, unpredictable reaction to medications, duration of jaundice greater than 7 days before encephalopathy, prothrombin time extended by more than 50 s, or total bilirubin above 18 mg/dL.

In some diseases, such as metabolic diseases, Wilson's disease and alpha1-antitrypsin deficiency, the transplantation has an effective curative character.

Acute and uncontrolled infections, irreversible cerebral edema, multiple organ failure, very advanced age, and extensive venous thrombosis are contraindications to liver transplantation.

8.4 Conclusion

Acute liver injury and hepatotoxicity occur frequently in critically ill patients and affect prognosis. The main causes of acute liver injury on the acute care surgery patient include shock, sepsis, and drugs. Synthetic dysfunction may complicate liver injury and lead to systemic complications and occasionally to acute liver failure. Despite poor specificity, routine laboratory biochemistry, such as aminotransferases,

bilirubin, INR, and factor V, may help to detect liver injury but remains of limited value in evaluating hepatic function. The development of novel techniques to assess hepatic function at the bedside potentially may help to standardize the definition of acute liver injury or dysfunction. Currently, supportive therapy for most patients remains the mainstay of therapy.

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9 Shock, Resuscitation, and Fluid Therapy Strategies in Acute Care Surgery: From Pathophysiology to Practice

Barclay T. Stewart and Ronald V. Maier

9.1 Introduction

Among the chief responsibilities of an acute care surgeon is early identification of shock and directing appropriate fluid resuscitation for patients suffering from surgical emergencies. This means that, in addition to the surgical decision-making and mastery of surgical techniques, the surgeon must also be facile with shock physiology and fluid resuscitation strategies to achieve optimal patient outcomes. To provide surgeons with the conceptual tools necessary to perform these responsibilities, this chapter presents a review of the principle physiologic derangements that occur during shock, clinically pertinent fluid physiology, and the evidence regarding fluid resuscitation in acute care surgery.

9.2 Shock Pathophysiology

Normal cellular and organ function requires sufficient oxygen delivery and rapid removal of potentially toxic metabolites. In hypovolemic and shock states, oxygen delivery and removal of metabolites from tissues are insufficient. If shock persists, irreversible cellular injury and organ failure may occur. Therefore, it is imperative that patients with shock are quickly and accurately diagnosed and appropriate fluid resuscitation is initiated without delay to rapidly restore homeostasis. The pathophysiology outlined below describes normal oxygen kinetics and the cellular response to hypoxia common to all shock states. These principles below underlie the basis for fluid resuscitation.

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9.2.1 Normal Oxygen Kinetics

Aerobic metabolism utilizes oxygen in the combustion of carbohydrates, amino acids, and fats to create energy and release carbon dioxide. The respiratory function of blood delivers oxygen to and removes carbon dioxide from tissues. Carbon dioxide transport efficiency is markedly greater than that of oxygen; thus, the clinical focus is on adequate oxygen delivery.

Blood contains both dissolved and hemoglobin-bound oxygen. The dissolved component is termed the partial pressure of arterial oxygen (PaO_2). PaO_2 represents only a small fraction of the total oxygen content in blood and is more useful when considered a measure of pulmonary gas exchange efficiency [1]. Blood oxygen content is primarily determined by hemoglobin concentration as described by the following equation:

$$CaO_2 = \left(1.34 \times Hb \times SaO_2\right) + \left(0.003 \times PaO_2\right)$$

In this equation, 1.34 is the oxygen-binding capacity of hemoglobin (mL/g), Hb is the concentration of hemoglobin (g/dL), SaO_2 is the oxygen saturation (mL/dL), 0.003 is the solubility coefficient of oxygen in blood (mL/100 mL/mmHg), and PaO_2 is the partial pressure of oxygen in arterial blood (mmHg). This equation demonstrates that anemia (low Hb) has a markedly greater impact on oxygen content of blood than does hypoxemia (low PaO_2). In addition, under most clinical conditions, PaO_2 greater than 80–100 mmHg will produce a SaO_2 of 100%. Given that the amount of oxygen dissolved in blood is such a small fraction of total oxygen content, it can be eliminated from the equation above to give a simplified equation:

$$CaO_2 = \left(1.34 \times Hb \times SaO_2\right)$$

The body has several mechanisms to limit dysoxia and mitigate shock, such as increasing cardiac output, increasing oxygen uptake by hemoglobin, and improving oxygen extraction from hemoglobin. Oxygen delivery (DO_2) is the volume of oxygen that reaches the systemic capillary beds in milliliters per minute. The equation for DO_2 is:

$$DO_2 = CO \times \left(1.34 \times Hb \times SaO_2\right) \times 10$$

or

$$DO_2 = CO \times CaO_2 \times 10$$

where CO is the cardiac output (L/min), 1.34 is the oxygen-binding capacity of hemoglobin (mL/g), Hb is the concentration of hemoglobin (g/dL), and SaO_2 is

the arterial oxygen saturation (mL/dL). The multiplier of 10 converts the oxygen content into mL/L.

Oxygen uptake (VO_2) is the volume of oxygen that dissociates from hemoglobin in the capillary beds and moves into tissue in milliliters per minute. Since oxygen is not stored in tissues, VO_2 is a direct measure of oxygen consumption. The Fick equation for VO_2 is:

$$VO_2 = CO \times 1.34 \times Hb \times \left(SaO_2 - SvO_2\right) \times 10$$

SvO_2 is the venous oxygen saturation (mL/dL). This calculated VO_2 does not account for oxygen uptake by the lungs, which can be up to 20% in critically ill patients. To provide a more accurate measurement of whole-body VO_2 and account for pulmonary VO_2, a metabolic cart can be used, which measures the fractional concentration of oxygen in inhaled (F_IO_2) and exhaled gas (F_EO_2):

$$VO_2 = \left(\text{minute ventilation}\right) \times \left(F_IO_2 - F_EO_2\right)$$

Under normal physiologic conditions, only 20–25% of oxygen delivered to capillaries is taken up into the tissues. The oxygen extraction ratio (O_2ER) compares oxygen delivery to oxygen uptake [2]:

$$O_2ER = VO_2 / DO_2 = \left(SaO_2 - SvO_2\right) / SaO_2$$

A decrease in DO_2 is initially compensated for with an increase in O_2ER to maintain VO_2. This mechanism will sustain a stable VO_2 until the O_2ER reaches approximately 50%, at which point oxygen extraction from hemoglobin is maximized [3]. Beyond this threshold, further decreases in DO_2 will decrease VO_2, and anaerobic metabolism will ensue. In addition, maintenance of extraction efficiency for cellular metabolism is dependent on normal mitochondrial respiratory function, which can also be impaired under specific conditions, such as sepsis.

SaO_2 is monitored by pulse oximetry, and SvO_2 is monitored by measurement of either the mixed venous oxygen saturation via a pulmonary artery catheter or the central venous oxygen saturation, $ScvO_2$, via a central venous catheter. Clinically, these indirect measures of tissue oxygenation allow calculation of O_2ER, which may be useful for assessing the degree of shock and effectiveness of resuscitation.

9.2.2 Cellular Response to Hypoxia

During aerobic metabolism, cells generate energy in the form of adenosine triphosphate (ATP) from glucose and oxygen in the mitochondrial membrane. When oxygen is not available, mitochondrial respiration is disrupted, and cells convert to anaerobic metabolism, which leads to inefficient energy generation, depletion of

ATP stores, accumulation of lactate, and acidemia. Early cellular injury associated with anaerobic metabolism is characterized by impairment of the sodium and calcium pumps and cellular swelling. Cellular swelling further impairs capillary perfusion, which potentiates the anaerobic microenvironment [4]. Initially, the insults that result from anaerobic metabolism are reversible; however, prolonged hypoxia leads to cell death.

Resuscitation during shock states results in rebound production and accumulation of cytotoxic reactive oxygen and nitrogen species that contribute to reperfusion injury. This cytopathic dysoxia stimulates the innate immune system via the release of proinflammatory cytokines and activation of the complement system, which leads to indiscriminant and excessive inflammation that causes bystander cellular injury.

Ultimately, if resuscitation and restoration of normoxia is delayed, irreversible cellular injury occurs and is characterized by disruption of the plasma membrane, release of lysosomal enzymes, and cellular necrosis. Given the derangements associated with dysoxia, timely diagnosis and treatment of shock are imperative to prevent cellular dysfunction and organ failure and achieve optimal outcomes when caring for these critically ill patients.

9.3 Fluid Physiology

The most common shock states encountered by acute care surgeons are the result of hypovolemia, hemorrhage, and sepsis. The treatment common to each of these states is fluid resuscitation. In order to understand the recommendations for fluid resuscitation, an overview of fluid physiology, fluid solutions, and excessive resuscitation is required.

9.3.1 Fluid Compartments

About 50–60% of an adult's total body weight is water [5]. The relationship between total body weight and total body water (TBW) is relatively constant and reflects body fat. Lean tissues (e.g., muscle) and solid organs have higher water content than fat. Therefore, younger and leaner patients have proportionally more TBW than older, frail, and/or obese patients. Obese patients have 10–20% less TBW than patients with a normal body mass index (BMI), and significantly malnourished patients have 10% more TBW [6].

TBW is divided into three compartments: intravascular fluid, interstitial fluid, and intracellular fluid (ICF) (see Fig. 9.1). Intravascular and interstitial fluid comprise the extracellular fluid compartment (ECF), which is about one third of TBW. Intracellular fluid comprises the remaining two thirds of TBW.

The ECF is balanced with sodium, the major cation, and chloride and bicarbonate, the major anions (see Fig. 9.2). The electrolyte composition of the intracellular fluid compartment is comprised predominantly by the cations, potassium and magnesium, and the anions, phosphate and sulfate. The electrolyte gradient between the

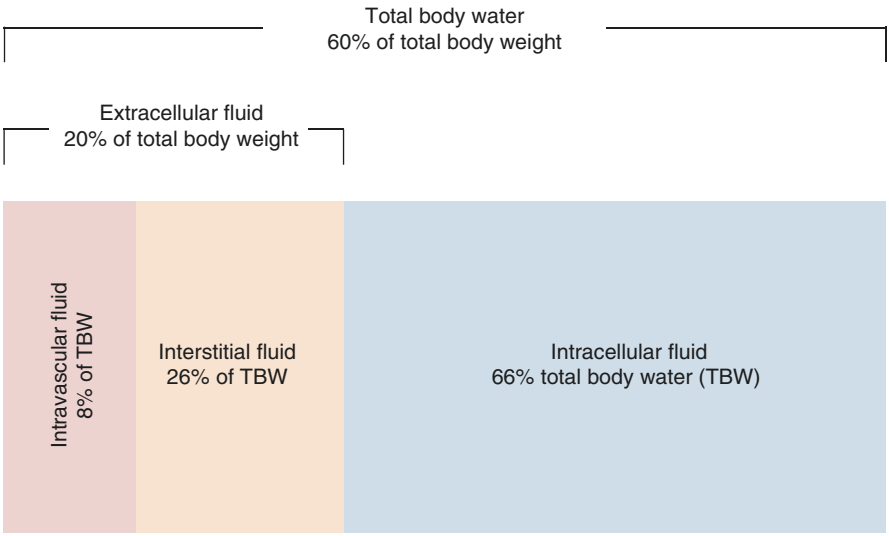

Fig. 9.1 Fluid compartments of the body. *TBW* total body water

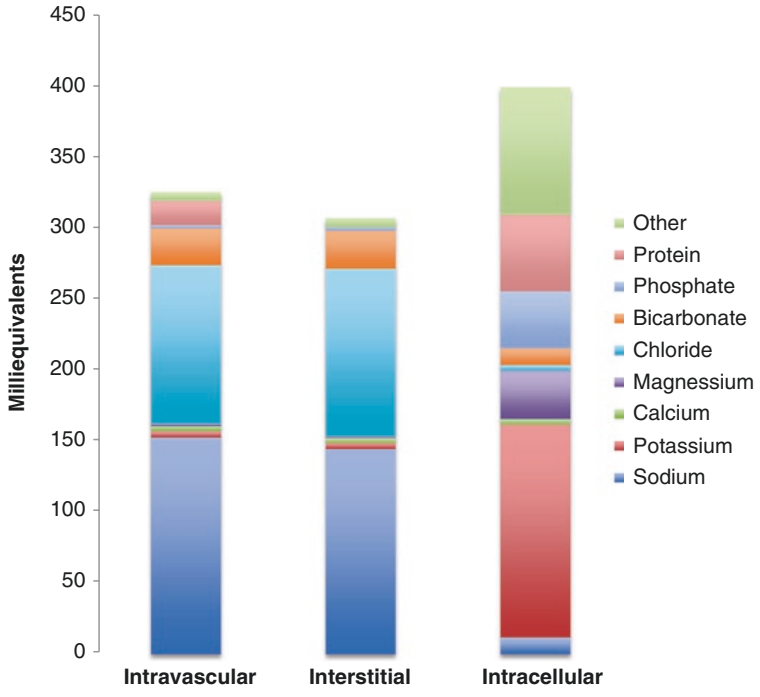

Fig. 9.2 Electrolyte and other solute concentrations of the fluid compartments of the body

ECF and ICF is maintained by sodium-potassium pumps within the cell membrane; however, water is freely diffusible. Resultantly, a given volume of water increases the volume of all compartments but minimally affects an individual compartment.

The properties of sodium confine it predominantly to the ECF and make it intimately associated with water. Therefore, sodium-containing resuscitation fluids are distributed throughout the ECF and add to the volume of both the intravascular and interstitial spaces without adding water to the intracellular fluid compartment. Given the relative proportions of each fluid compartment, resuscitation with sodium-containing fluids expands the interstitial compartment approximately three times more than the intravascular compartment.

9.3.2 Paradigm of Fluid Physiology

For more than a century, it has been assumed that fluid physiology, volume resuscitation, and clinical edema formation were governed solely by Starling's principle of microvascular fluid exchange [7]. Starling's principle states that capillary hydrostatic pressure and interstitial protein oncotic pressure drive transendothelial filtration and a counteracting absorptive force is exerted by plasma protein oncotic pressure and interstitial hydrostatic pressure. However, fluid resuscitation does not result in the ECF expansion expected from Starling's model [8]. In recent years, research has demonstrated the existence and function of the endothelial glycocalyx layer (EGL) in fluid physiology, and Starling's equation has been revised. Familiarity with this paradigm allows the surgeon to better understand the plight of resuscitation fluids and more accurately predict ECF expansion during resuscitation.

The EGL is a web of membrane-bound glycoproteins and proteoglycans on the luminal side of endothelial cells (see Fig. 9.3) [9]. The web contains numerous glycosaminoglycans that constitute the depth and volume of the layer. The fluid within the EGL is a constituent of the intravascular fluid compartment, but it does not circulate. Further, the EGL has a protein concentration gradient between that of plasma and the endothelial clefts that regulate passage of fluid, electrolytes, and proteins [10]. The EGL excludes red blood cells but is semipermeable to anionic macromolecules (e.g., albumin, immunoglobulins) whose size and structure determine their ability to penetrate the layer [8].

Disruption of the EGL, termed compaction or shedding, results in an increase in the plasma concentrations of the glycosaminoglycans that comprise EGL. Thus, high plasma concentrations of these molecules are thought to represent EGL injury, which occurs during rapid fluid infusion, sepsis, shock, diabetes, acute hyperglycemia, surgery, and trauma [11]. When the EGL is damaged, fluid, electrolytes, and proteins are able to pass into the interstitial fluid space more easily, resulting in interstitial edema and fluid sequestration [8].

In contrast to Starling's principle, fluid, electrolytes, and proteins are returned to circulation not through postcapillary venules but via the lymph system [12].

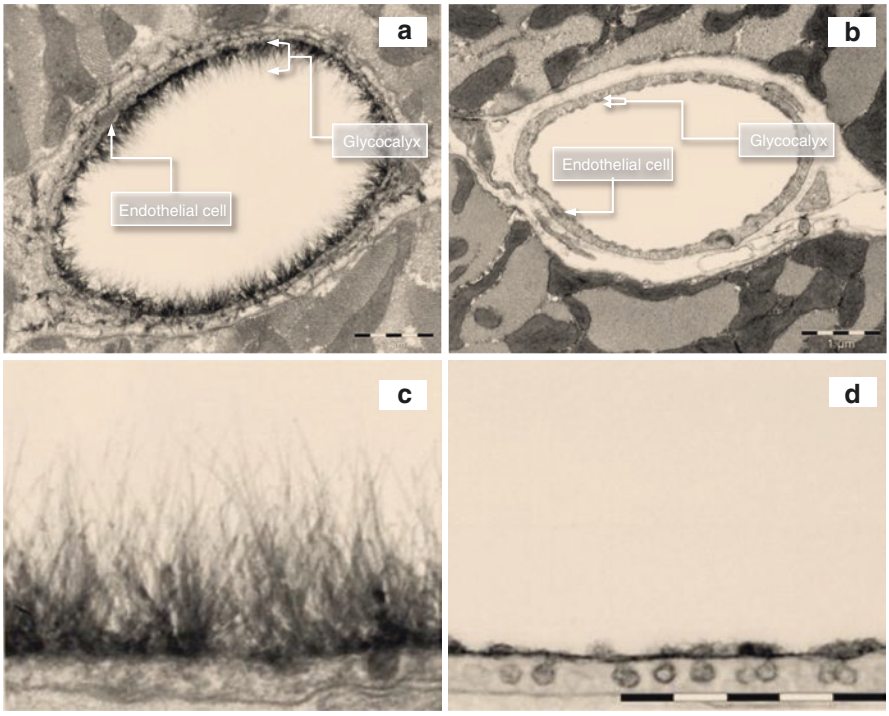

Fig. 9.3 Representation of the endothelial glycocalyx layer in normal and injured states. (**a**) Representative of normal endothelial glycocalyx layer (EGL); (**b**) representative of damaged EGL such as in times of shock; (**c**) magnification of normal EGL; (**d**) magnification of damaged (i.e., contracted) EGL such as in times of shock. Figure adapted from van der Berg et al. The Endothelial Glycocalyx Protects Against Myocardial Edema. Circulation Research (2003) 92(6):592–4 (copyright Wolters Kluwer Health, Inc.)

Studies that described this model demonstrated several types of capillary beds (e.g., sinusoidal, liver, spleen, bone marrow; fenestrated, endocrine, choroid plexus, gut mucosa; non-fenestrated, nervous system, muscle, connective tissue, lung; in-line fenestrated, glomerular) [8]. Although transfused macromolecules (e.g., albumin, dextran) do not easily penetrate an intact EGL or fenestrated capillary beds, they pass easily into the interstitial space through a damaged EGL and sinusoidal capillaries in the liver, spleen, and bone marrow.

It should be noted that an increase in the proportion of the cardiac output going to damaged or sinusoidal capillary beds will increase the escape rate of proteins and transfused albumin from plasma to the interstitial space. Given that there is no significant absorption of interstitial fluid to the plasma due to these increases in oncotic pressure in the interstitium, one can understand why colloid-based resuscitation (e.g., albumin, dextran) does not prevent or improve tissue edema or result in a sustained expansion of intravascular volume.

9.3.3 Exchange of Fluids and Electrolytes

An average-sized adult requires about 2 L of water per day [6]. Daily water losses include approximately 1 L in urine, 250 mL in stool, and 600 mL in insensible losses (e.g., via the skin and respiration). Insensible water and electrolyte losses are increased by fever, hypermetabolic states, and hyperventilation during compensation for metabolic acidosis.

The average-sized adult consumes about 3–5 g of salt per day, and the kidneys regulate sodium balance. With hyponatremia or hypovolemia, the kidneys modulate sodium excretion to as little as 1 mEq/day or as much as 5000 mEq/day to achieve normonatremia and preserve TBW. Sweat and respiration fluids are hypotonic (i.e., having a lower osmotic pressure than intracellular fluid); therefore, sweating and hyperventilation usually result in only a small sodium losses. Gastrointestinal losses are relatively isotonic and can be replaced by an appropriately matched volume of isotonic salt solutions.

9.3.4 Changes in Body Fluids

Changes in fluid and electrolyte balance may be classified into disturbances of (1) volume, (2) concentration, or (3) composition [6]. Although these chances often occur concurrently, each is a distinct entity with unique mechanisms and demands individual assessment and correction during resuscitation.

Isotonic gain or loss of salt solution results in ECF changes, with little effect on intracellular fluid volume. If free water is gained or lost from the ECF, water will pass between the ECF and ICF until the salt or solute concentration (i.e., osmolality) is equalized across the compartments. Unlike with sodium, the concentration of other ions in the ECF can be altered without significant change in osmolarity, producing only a change in fluid composition.

9.3.4.1 Volume Homeostasis

Hypovolemia in the acute care surgical patient is most often caused by hemorrhage, profound fluid losses (e.g., prolonged nasogastric suction, vomiting, diarrhea, large wounds), fluid sequestration (e.g., acute pancreatitis, bowel obstruction), and excessive diuresis.

Acute actual or relative volume loss activates the atrial stretch receptors and baroreceptors in the aortic arch and carotid bodies (see Fig. 9.4). Upon activation of these receptors, their inhibitory effect on the autonomic nervous system is interrupted, and a surge of sympathetic stimulation leads to a compensatory response of the cardiovascular system. Release of adrenaline produces β_1-adrenergic receptor stimulation that results in an increased heart rate and stronger contractility to enhance cardiac output and maintain oxygen delivery. Concomitantly, α1-adrenergic receptor stimulation causes peripheral vasoconstriction and increased systemic vascular resistance that maintains afterload and perfusion pressure, measured by mean arterial pressure (MAP). These autoregulatory mechanisms shunt blood away from the skin, kidneys, and splanchnic circulation to preserve blood flow to the heart and brain.

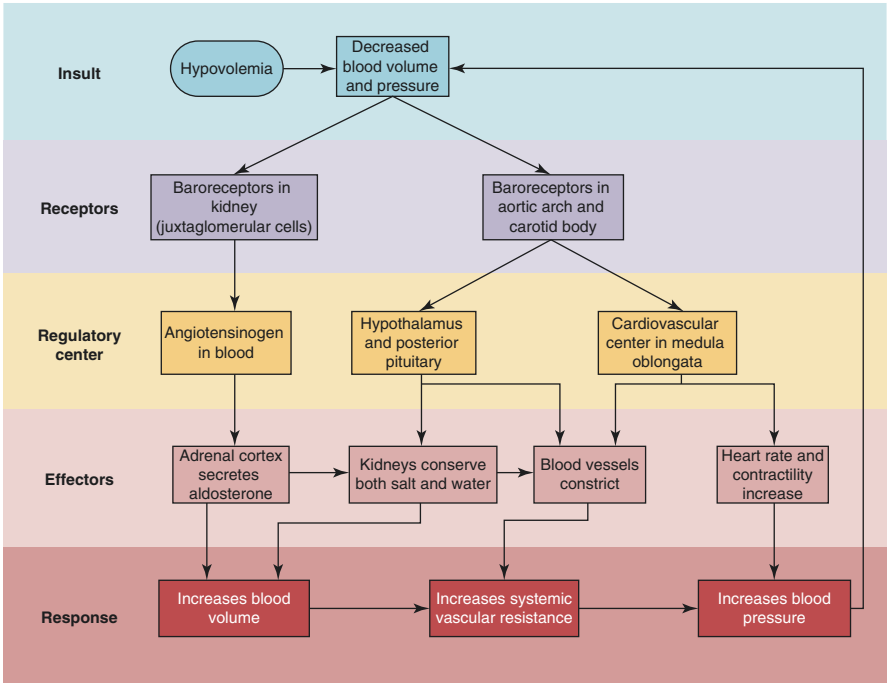

Fig. 9.4 Physiologic responses to actual or relative hypovolemia

Reduced blood flow to the kidneys activates the renin-angiotensin-aldosterone system. Renin is released from the juxtaglomerular cells and catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I to angiotensin II, which is a potent vasoconstrictor and stimulates aldosterone release. Aldosterone acts to restore intravascular volume by increasing sodium reabsorption in the nephron, in turn increasing water reabsorption. In the short run, oliguria in the patient with hypovolemic shock is an acute renal success, not acute renal failure. However, prolonged renal hypoperfusion results in depletion of renal ATP stores with subsequent acute renal injury, renal failure, and, at times, paradoxical urine production despite systemic hypovolemia.

Additionally, acute volume loss leads to central activation of the hypothalamic-pituitary-adrenal axis. Stimulation of the hypothalamus leads to the release of corticotrophin-releasing hormone (CRH) and activation of the pituitary gland to release adrenocorticotropin hormone (ACTH). ACTH stimulates the adrenal cortex to release cortisol. Cortisol potentiates positive cardiovascular hemodynamics (e.g., increased inotropy and chronotropy) and creates a generalized catabolic state characterized by glycogenolysis, lipolysis, gluconeogenesis, and insulin resistance. Elevation in circulating glucose levels provides a critical energy source to maintain cardiac and brain function during shock states and creates an osmotic effect to draw interstitial fluid into the intravascular space. However, this process may also produce an inappropriate osmotic diuresis.

9.3.4.2 Concentration Homeostasis

Disturbances in TBW are reflected by changes in plasma sodium concentration. Hypo- and hypernatremia are commonly encountered by the acute care surgeon and are worthy of a brief discussion.

Hyponatremia

Hyponatremia occurs in the setting of a relative excess of extracellular water to sodium and is strongly associated with perioperative morbidity and mortality [13]. Extracellular fluid volume can be high, normal, or low. In the surgical patient, sodium concentration is typically decreased from either sodium depletion or dilution (see Fig. 9.5).

Sodium depletion and hyponatremia are the consequence of either decreased intake or increased losses of sodium-containing fluids and are commonly accompanied by an ECF deficit. Causes in the surgical patient include decreased sodium intake (e.g., nothing by mouth status, enteral feeds), gastrointestinal losses (e.g., vomiting, nasogastric decompression, diarrhea), and renal losses (e.g., diuresis, kidney disease).

Sodium dilution and hyponatremia often result from excess free water and are commonly accompanied by high ECF volume status. Excessive water intake, iatrogenic free water administration (e.g., hypotonic intravenous fluids, enteral flushes), and medications (e.g., angiotensin-converting enzyme inhibitors) can cause hyponatremia. Patients with infection, injury, or pain are prone to increased secretion of antidiuretic hormone (ADH) with the physiologic effects described above. However, the effects of ADH are usually self-limited since both hyponatremia and volume expansion decrease ADH secretion.

Hyperosmolar hyponatremia may occur in the setting of excess solute relative to free water (e.g., significant hyperglycemia, mannitol infusion). Hyponatremia may appear to be present when there are extreme elevations of plasma lipids or proteins (i.e., pseudohyponatremia), but with no actual decrease in extracellular sodium relative to water.

Ordered evaluation for hyponatremia generally allows accurate diagnosis of the inciting etiology. Hyperosmolar causes, including hyperglycemia or mannitol infusion and pseudohyponatremia, can be easily excluded. Next, depletion and dilution causes of hyponatremia are assessed. In the absence of kidney disease, depletion is associated with low urine sodium levels (<20 mEq/L), whereas renal sodium wasting shows high urine sodium levels (>20 mEq/L) [6]. Depletion states typically require measured fluid resuscitation. Dilution causes of hyponatremia are associated with hypervolemic states. A normal volume status in the setting of hyponatremia should prompt an evaluation for syndrome of inappropriate secretion of ADH.

Hypernatremia

Hypernatremia results from either a loss of free water or a gain of sodium relative to water (see Fig. 9.6). Like hyponatremia, ECF volume can be high, normal, or low. Hypervolemic hypernatremia in the surgical patient is typically caused by iatrogenic administration of sodium-containing fluids or, less commonly, mineralocorticoid excess (e.g., hyperaldosteronism) [6]. Urine sodium concentration is

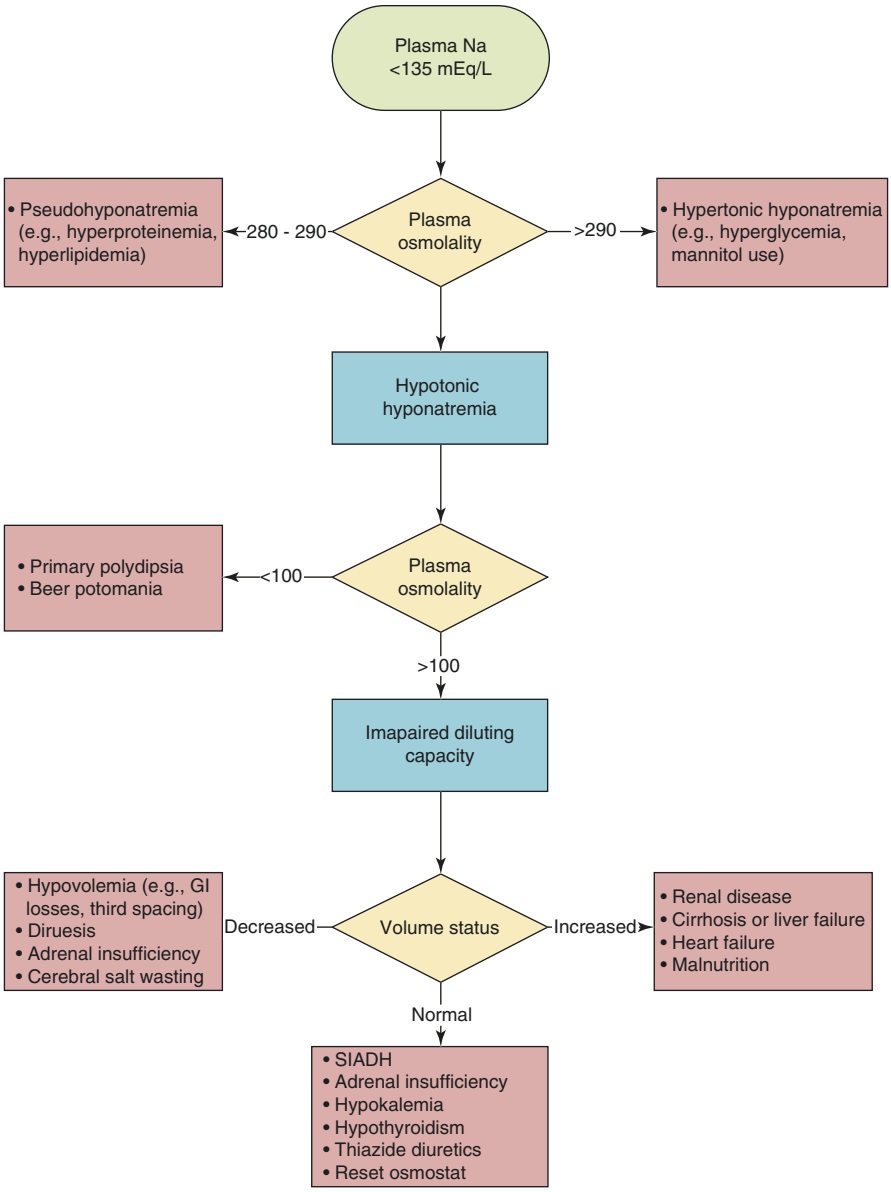

Fig. 9.5 Hyponatremia diagnosis algorithm. *GI* gastrointestinal, *SIADH* syndrome of inappropriate antidiuretic hormone secretion

typically >20 mEq/L, and urine osmolarity is >300 mOsm/L. Normovolemic hypernatremia results from renal causes or from relatively small-volume gastrointestinal or insensible losses. When hypovolemia is present, urine sodium concentration is <20 mEq/L, and urine osmolarity is <700 mOsm/L. However, nonrenal water losses can occur secondary to relatively isotonic gastrointestinal fluid losses (e.g.,

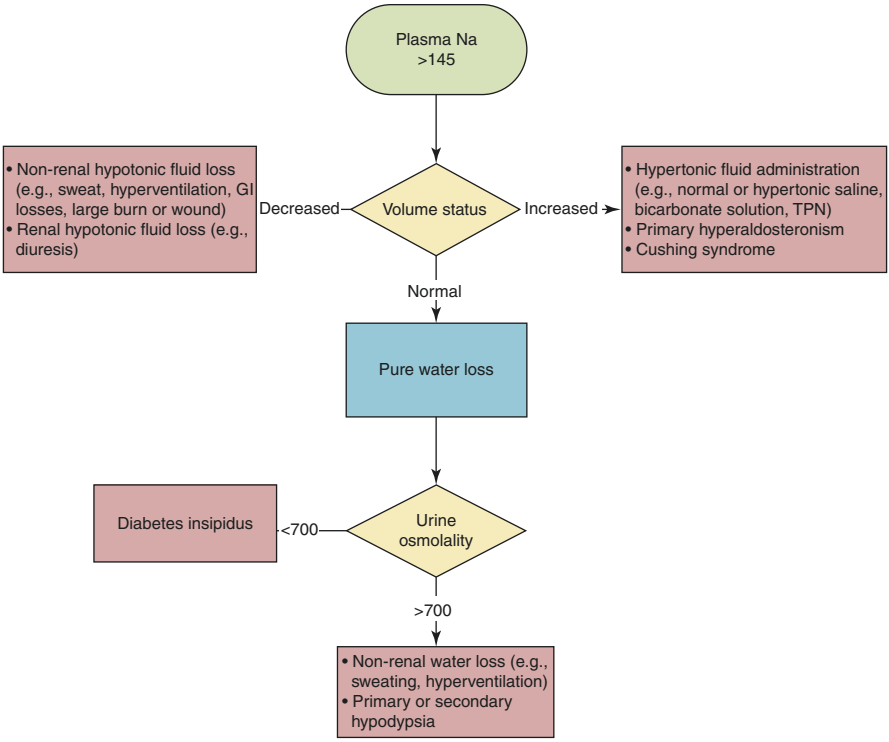

Fig. 9.6 Hypernatremia diagnosis algorithm. *GI* gastrointestinal, *TPN* total parenteral nutrition

prolonged nasogastric suction, vomiting, diarrhea) or insensible losses. With nonrenal water loss, urine sodium concentration is <15 mEq/L, and the urine osmolarity is >700 mOsm/L.

9.3.4.3 Fluid and Electrolyte Composition Homeostasis

Disturbances in potassium, calcium, phosphate, chloride, and magnesium are typically unrelated to changes in TBW. However, they often occur in surgical patients and resuscitation due to losses of blood and electrolytes in body fluids; fluid resuscitation; stress response to infection, surgery, or injury; changes in acid-base status; renal failure; and transfusions. Discussion of the causes, evaluation, and management of electrolyte abnormalities are beyond the scope of this chapter. However, electrolyte homeostasis is an important responsibility of the surgeon (see Table 9.1).

9.4 Resuscitation Fluids

Fluid resuscitation is a ubiquitous intervention in acute care surgery. While the selection and use of resuscitation fluids is founded in physiologic principles, the clinical practice is largely determined by clinician preference, institutional protocols, and

Table 9.1 Causes, manifestations, and treatment for electrolyte composition disorders

	Causes	Manifestations	Treatment
Hypokalemia	Low intake; nonrenal losses (e.g., vomiting or nasogastric drainage, diarrhea, sweating, burns or large wounds); renal losses (e.g., diuresis, steroid therapy, magnesium deficiency); redistribution (e.g., alkalosis, insulin, adrenergic agonist)	Muscle weakness and cramps, ileus, dysrhythmias, bradycardia	Potassium repletion; exercise caution in patients with renal dysfunction
Hyperkalemia	Endogenous (e.g., renal failure, acidosis, rhabdomyolysis, tissue injury); exogenous (e.g., supplementation, potassium-sparing diuretics, ACEi or ARB, mineralocorticoid antagonists, NSAIDS, penicillin, B-blockers, succinylcholine, heparin, insulin deficiency)	Muscle and abdominal cramps, decreased cardiac contractility, dysrhythmias, ventricular fibrillation and arrest	Removal (e.g., kayexalate, oral or rectal sorbitol, dialysis); shift (e.g., glucose and insulin administration, bicarbonate infusion); cardiac stabilization with intravenous calcium
Hypocalcemia	Citrated blood transfusion, pancreatitis, rhabdomyolysis, hypomagnessemia, hypoparathyroidism, vitamin D deficiency, renal disease, hyperphostatemia	Paresthesias, muscle cramps, tetany, bronchospasm, torsades de pointes	Calcium ± magnesium and vitamin D repletion
Hypercalcemia	Acute renal failure, medications (e.g., thiazide diuretics, lithium), malignancy, endocrine causes (e.g., hyperparathyroidism)	Muscle weakness, constipation, hypertension, polyuria, kidney stones, neuropsychiatric symptoms, cardiac arrest	Repletion of associate volume deficit followed by diuresis; dialysis
Hypophosphatemia	Refeeding syndrome, alkalosis, burns or large wounds, hypomagnessemia, hypokalemia, diarrhea, vitamin D deficiency, diuretic use, hypercalcemia, intestinal malabsorption,	Muscle weakness, decreased cardiac contractility, neuropsychiatric symptoms, immunosuppression, platelet dysfunction	Phosphate repletion

(continued)

Table 9.1 (continued)

	Causes	Manifestations	Treatment
Hyperphosphatemia	Endogenous (e.g., rhabdomyolysis, hemolysis, intestinal infarction, acidosis); exogenous (e.g., excessive administration, phosphate enemas, vitamin D intoxication); renal causes (e.g., renal failure, magnesium deficiency)	Neuromuscular hyperactivity, prolonged QT interval, seizures, cardiac arrest	Phosphate binders, calcium if concurrent hypocalcemia, dialysis
Hypochloremia	Low intake, vomiting or nasogastric drainage, diarrhea, sweating, burn or large wound, alkalosis	Muscle cramps, seizures, dysrhythmias	Fluid resuscitation and concomitant electrolyte repletion
Hyperchloremia	Normal saline infusion, hypernatremia, acidosis, renal failure, brain injury	Lethargy, muscle weakness, neurological depression, hyperventilation, decreased cardiac contractility, dysrhythmias	Treatment of underlying condition
Hypomagnessemia	Poor intake, diarrhea, renal losses (e.g., diuresis, intrinsic renal disease), osmotic agents (e.g., mannitol, hyperglycemia), hypercalcemia, hypokalemia, pancreatitis, diarrhea, catecholamine excess, burn or large wound, citrated blood transfusion	Hyperreflexia, paresthesias, muscle cramps, neuropsychiatric symptoms, bronchospasm, hypotension, tetany, seizures	Magnesium repletion; correct hypocalcemia if present
Hypermagnesemia	Renal failure, adrenal insufficiency, lithium toxicity, acidosis	Muscle weakness, hyporeflexia, lethargy, bradycardia, hypotension	Treatment of underlying condition; cardiac stabilization with calcium; dialysis

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *NSAIDs* nonsteroidal anti-inflammatory drugs

cost [12]. Systemic reviews of randomized trials have consistently shown that there is little evidence that resuscitation with one type of fluid compared with another reduces mortality or that one solution is more effective or safer than another [14, 15]. However, there is mounting evidence that the types and dose of resuscitation fluid administered may affect patient outcomes in specific populations. Therefore,

the selection and administration of fluid should be based on the patient's current physiology, the underlying condition, and potential toxic effects of additional fluid to capitalize the benefits of appropriate resuscitation while minimizing morbidity and life-threatening adverse effects.

9.4.1 Crystalloid Solutions

Crystalloids are solutions of ions, which determine the fluid's tonicity (e.g., lactated Ringer's, normal saline, PlasmaLyte, hypertonic saline). These solutions are the mainstay of resuscitation given their relatively physiologic pH and electrolyte compositions (see Table 9.2). In general, crystalloids are inexpensive, easy to ship and store, and fairly innocuous in small doses. However, crystalloid solutions pass relatively freely across the vascular endothelium and damaged EGL, often resulting in pronounced ECF expansion during resuscitation with negative consequences on organ systems when given indiscriminately.

9.4.1.1 Lactated Ringer's

Ringer's solution was developed in 1885 to aid the development of an extracorporeal beating heart model [16]. As such, the original solution was an isotonic salt solution that contained calcium required for perpetuation of the cardiac cycle. In the 1930s, Hartmann added lactate to the Ringer's solution to act as a buffer; lactate is metabolized to bicarbonate and CO_2. Lactated Ringer's (LR) is a relatively balanced solution that mimics normal human electrolyte composition and has a pH of 6.5. No human study has demonstrated superiority of LR versus other crystalloid solutions. However, resuscitation with large volumes of LR was less likely to potentiate acidosis and causes hyperchloremia, hyperkalemia, and/or dilutional coagulopathy in animal models of hemorrhagic shock [17, 18]. Data have shown that the R-isomer of lactate is capable of activating

Table 9.2 Characteristics and composition of common resuscitation fluids

	Lactated Ringer's	Normal saline	PlasmaLyte	Albumin (4%)	Hetastarch (6%)	Plasma
pH	6.5	5.0	7.4	7.4	5.5	7.4
Osmolarity	273	308	294	330	308	295
Na^+	130	154	140	150	154	140
K^+	5	–	5	–	–	4
Cl^-	109	154	98	120	154	103
Ca^{2+}	1	–	–	–	–	5
Mg^{2+}	1	–	3	–	–	2
Lactate*	29	–	–	–	–	25
Acetate	–	–	27	–	–	–
Gluconate	–	–	23	–	–	–

*Lactate in lactated Ringer's is rapidly metabolized in the liver to bicarbonate ions (HCO_3^-); bicarbonate cannot be added into solutions because it has a tendency to precipitate; osmolarity presented in mOsm/L

the innate proinflammatory response and aggravating tissue and organ injury, reinforcing use of the L-lactate isomer in LR solutions [19].

9.4.1.2 Normal Saline

Saline solution was developed during the Indian blue cholera epidemic in the 1830s [20]. The solution was designed to be "normal" or isotonic, measured by its ability to not lyse red blood cells. However, normal saline (0.9% sodium chloride) has supraphysiologic amounts of sodium and chloride (154 mEq of each) and is markedly more acidotic than human plasma (pH 5.0). Thus, resuscitation with significant volumes of normal saline causes hyperchloremic metabolic acidosis that compounds the acidemia characteristic of shock states [17]. Renal dysfunction has been attributed to hyperchloremic metabolic acidosis from normal saline resuscitation [21, 22]. Plasma chloride content regulates renal blood flow and may contribute to acute kidney injury [23]. Delivery of chloride to the macula densa drives mesangial contraction and decreases glomerular filtration [24]. A meta-analysis of high- versus low-chloride fluid resuscitation in critically ill patients found an increased incidence of acute kidney injury, but no difference in mortality [25].

9.4.1.3 PlasmaLyte

PlasmaLyte is a family of balanced crystalloid solutions with formulations developed to mimic the pH, osmolality, and electrolyte compositions of normal human plasma [26]. PlasmaLyte has a significant buffer capacity from the addition of lactate, acetate, and gluconate. The use of PlasmaLyte for resuscitation has been shown to result in a lower base deficit and more physiologic chemistry profile compared to the use of normal saline [26]. In general surgical patients, the use of PlasmaLyte has been associated with a lower rate of major complications (e.g., postoperative infection, renal replacement therapy, blood transfusion, and acidosis-related investigations) compared to normal saline [27, 28]. While cost constraints have been reported as barriers to the use of PlasmaLyte, a cost-minimization analysis of PlasmaLyte suggested that the use of it is overall more cost-effective due to less need for electrolyte repletion and lower incidence of ongoing acidemia compared to normal saline [29].

9.4.1.4 Hypertonic Saline

Ongoing concerns about the effect of large-volume resuscitation led to experimentation with small-volume resuscitation using hypertonic saline (e.g., 3%, 5%, and 7.5% sodium solutions). There is no high-quality evidence that the use of hypertonic saline for resuscitation provides short- or long-term mortality benefits to the critically ill [30]. However, the use of low-volume hypertonic saline among patients who underwent damage control surgery resulted in a lower incidence in acute respiratory distress syndrome (ARDS), sepsis, multiple organ dysfunction syndrome (MODS), and mortality [31]. Further, there is some evidence that patients who had hypertonic saline used as a maintenance fluid after damage control laparotomy were more likely to achieve primary fascial closure and were closed more quickly than those who did not receive hypertonic saline [32, 33]. Better evidence is needed before recommending the routine use of hypertonic saline in this population.

9.4.2 Colloid Solutions

Colloid solutions (e.g., albumin, hetastarch, gelatins, dextran) contain macromolecules suspended in salt solutions that were designed to remain within the intravascular fluid compartment under Starling's original assumptions regarding the role of plasma oncotic pressure in fluid physiology (see Table 9.2). However, as described above, the sinusoidal capillary tissue beds and disrupted EGL do not retain large molecules, limiting the theoretical effectiveness of these solutions.

9.4.2.1 Albumin

Albumin was made available with the advent of blood fractionation in 1941 and was used for the first time in large quantities as a resuscitation fluid for patients burned during the attack on Pearl Harbor [34]. Human recombinant albumin is commonly available in 5% and 25% solutions suspended in an isotonic salt solution. Albumin is produced by the fractionation of blood and is heat-treated to reduce the risk of transmission of blood-borne infections; thus, albumin is relatively expensive to produce and distribute compared to other crystalloid and colloid solutions.

A meta-analysis compared albumin with crystalloid solutions in patients with hypovolemic shock, burns, or hypoalbuminemia. Pooled analysis found that the use of albumin-based resuscitation was of no benefit and potentially associated with an increased rate of death compared to crystalloid solutions [35]. Subsequently, a randomized trial examined the safety of 4% albumin for use in critically ill adults [36]. The Saline versus Albumin Fluid Evaluation (SAFE) study of 7000 critically ill patients randomized to 4% albumin or normal saline reported no difference between albumin and saline with regards to 28-day mortality or development of new organ failure. Secondary analyses of results from the SAFE study suggested an association between albumin and death at 2 years among patients with traumatic brain injury [37]. However, albumin resuscitation was associated with a decreased risk of death at 28 days in patients with severe sepsis [38]. In contrast to the SAFE study, the Albumin Italian Outcome Sepsis (ALBIOS) study randomized 1818 patients with severe sepsis to daily administration of 20% albumin targeting a serum albumin level of 3 g/L or crystalloid resuscitation [38]. There were no differences in either 28- or 90-day mortality rates between the two groups. Similarly, the multicenter Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial did not show a mortality difference at 28 days between patients with hypovolemic shock randomized to albumin or saline [39].

Given the additional cost of albumin and a recent meta-analysis reporting no impact of albumin on sepsis-related mortality, the Surviving Sepsis Campaign (SSC) continues to recommend crystalloids as the initial sepsis resuscitation fluid [40]. However, the SSC has advised consideration of albumin when patients require substantial amounts of crystalloids [41].

9.4.2.2 Semisynthetic Colloids

The donor pool and relative cost of albumin prompted the development of semisynthetic colloid solutions (e.g., hydroxyethyl starch [HES], succinylated gelatin,

dextran). Globally, HES solutions are the most commonly used semisynthetic colloids and have gained popularity in the recent past due to their use in military medicine [42]. HES solutions are produced by hydroxyethyl substitution of amylopectin from starches (e.g., sorghum, maize, potatoes) [43]. This substitution protects against hydrolysis by nonspecific amylases in the blood, which has been proposed to prolong the intravascular expansion associated with the volume and increased oncotic pressure provided by the larger molecules. However, when the vascular endothelium and EGL are damaged and leaky, HES accumulates in tissues, such as the skin, lung, liver, and kidney, and has been shown to cause significant adverse effects [12]. Further, large-volume HES resuscitation has been associated with risks of renal injury and coagulopathy [44]. Studies of the use of HES in blunt trauma, burns, and among critically ill patients requiring volume resuscitation suggest a potential correlation with increased risk of renal replacement therapy and mortality [42, 45, 46]. Therefore, the potential harms and cost of HES likely outweigh the benefits of its administration when other solutions are available and suggest that semisynthetic colloids should not be used for volume resuscitation in critically ill patients.

9.4.2.3 Plasma

While plasma is typically considered for patients at risk of or with clinically significant coagulopathy, it has other potential uses in resuscitation. For example, plasma has extreme buffering capacity that can be useful in profound academia and may better maintain and potentially restore damaged vascular endothelium and EGL compared with other solutions [47, 48]. The use of plasma as a resuscitation fluid is limited by its cost and limited donor pool, as well as risks of transfusion reactions (e.g., transfusion-related acute lung injury [TRALI], transfusion-associated circulatory overload [TACO], ABO incompatibility), immunosuppression, and transmission of blood-borne infections. Further, the use of plasma for resuscitation in patients without coagulopathy has been associated with development of sepsis, MODS, and ARDS [49, 50].

Given the aforementioned limitations and risks, solvent/detergent-treated plasma has been introduced that minimizes risk of the transmission of enveloped viruses (e.g., HIV, HBV, and HCV) and is hypothesized to reduce the risk of TRALI [51]; however, solvent/detergent-treated plasma is prohibitively expensive in most settings.

Freeze-dried and lyophilized plasma were developed to lengthen the storage life of plasma and make its transport easy for use in combat settings [52, 53]. These products have demonstrated the same hemostatic properties as fresh plasma after reconstitution. Further, lyophilized plasma is compatible with all blood types and can be stored at room temperature for up to 2 years, and its reconstitution requires less than 6 min [53]. Further research is needed to determine specific indications for such products in the management of civilian patients with severe hemorrhage [54].

9.4.3 Excessive Resuscitation

Early and landmark work in the physiology of shock states identified several perturbations of normal homeostasis, including abnormal capillary permeability,

decreased oncotic pressure, and a loss of intravascular volume into the interstitial fluid compartment [8]. Therefore, pioneers in shock resuscitation advocated for aggressive replacement of the fluid sequestered from the intravascular space in addition to maintenance fluid. This led to the legacy of supraphysiologic resuscitation and excessive resuscitation, which has profound functional consequences on multiple organ systems [55]. Excessive resuscitation in surgical patients is associated with impaired oxygen delivery, preventable cardiopulmonary morbidity, prolonged intensive care unit and hospital stay, prolonged mechanical ventilation, intestinal anastomotic failure, compartment syndromes, increased intracranial pressure in the setting of traumatic brain injury (TBI), MODS, and death [55–62]. Conversely, excessive fluid restriction and fixed, unmonitored fluid resuscitation are associated with hypovolemia, poor oxygen delivery, secondary brain injury in patients with TBI, and overall worsened organ dysfunction [63]. Therefore, it has been inferred that a restrictive but goal-directed fluid resuscitation approach to maintain adequate perfusion in the perioperative period and during shock states will lead to better patient outcomes [64].

9.5 Resuscitation Strategies in Perioperative and Shock States

Although there is a clear benefit for early fluid resuscitation and reversal of tissue dysoxia in patients with hypovolemia and shock, there is mounting evidence regarding the negative effects of excessive resuscitation on multiple organ systems and patient outcomes. As a result, a number of studies on the use of liberal versus restrictive and goal-directed resuscitation strategies have helped guide current practice recommendations. The hallmark physiological derangements, diagnostic approaches, and specific resuscitation strategies for the perioperative and septic and hemorrhagic shock states are reviewed.

9.5.1 Perioperative State

Acute care surgeons are often called upon to guide fluid resuscitation for patients who have suffered significant physiologic insult(s) by an underlying disease state compounded by both pre- and intraoperative fluid losses, the stress response to surgery or trauma, and ongoing fluid losses.

In addition to fluid or blood losses or concurrent sepsis, the stress response to surgery must also be considered when planning fluid resuscitation. The stress response to surgery or trauma is the result of multiple biochemical pathways that facilitate blood volume expansion, glucose availability, organ perfusion, and inflammation. This response is triggered by significant tissue disruption (e.g., injury, pancreatitis), entry into a major body cavity (e.g., abdomen, chest), substantial blood loss, hemodynamic instability, and use of mechanical cardiopulmonary support devices. The response results in the activation of multiple neurohormonal and biochemical cascades, which are the same as those activated by hypovolemia as described above [65]:

- Catecholamines (epinephrine and norepinephrine)—secreted by the adrenal gland in response to sympathetic nervous system stimulation resulting in vasoconstriction, tachycardia and improved myocardial contractility (i.e., increased cardiac output with significant increase in cardiac oxygen consumption), catabolism, and hyperglycemia
- Cortisol—secreted by the adrenal gland in response to hypothalamic-pituitary axis input resulting in gluconeogenesis and potentiation of catecholamine effects
- Vasopressin (antidiuretic hormone or ADH)—secreted by the posterior pituitary gland in response to elevated plasma osmolality, hypovolemia, and circulating stress mediators resulting in renal water retention and intravascular volume expansion
- Aldosterone—secreted by the adrenal gland in response to renin-angiotensin axis activation resulting in renal sodium and water retention and intravascular volume expansion
- Cytokines—released by immune, endothelial, and other cells resulting in both local and systemic inflammatory responses

Although the stress response is designed to restore homeostasis in times of dysoxia and shock, multiple complications may occur. For example, aldosterone can cause potassium wasting; cortisol- and catecholamine-induced hyperglycemia can promote wound infection and dehiscence; and systemic inflammatory responses can predispose to capillary leak, tissue injury, and organ dysfunction (e.g., acute renal failure, ARDS, compartment syndromes) [65].

At times, it can be difficult to determine if the clinical picture portrayed by a patient (e.g., tachycardia, hypotension, oliguria) is the result of hypovolemia and shock or the stress response provoked by the surgery or tissue injury. In the past, postoperative fluid management was focused on resolving these signs and resulted in unnecessary large-volume fluid resuscitation. Recent guidelines have underscored the potential for organ dysfunction caused by a dysregulated host response to injury, infection, or surgery to occur even in resuscitated patients and suggest limiting fluid resuscitation and allowing permissive oliguria when appropriate [66, 67].

Fluid losses in the perioperative period vary with the type of procedure performed, the patient's physiology, the underlying disease for which the procedure was performed, and the severity of the stress response associated with the procedure, injury, and/or disease. Fluid losses to consider include bleeding, drainage, "third spacing," and insensible losses.

Bleeding should always be considered in postoperative patients needing fluid resuscitation. It should be noted that clinical manifestations of bleeding may not be apparent until 15% or more of the patient's circulating blood volume is lost (see Table 9.3). Although fluid resuscitation is indicated to support the bleeding patient initially, blood products and hemorrhage control are the mainstays of treatment. Resuscitation of hemorrhagic shock is discussed in detail below.

Drainage of body fluids contributes to fluid losses, such as that from nasogastric decompression, thoracostomy tubes, and peritoneal drains. Significant hypovolemia and electrolyte disturbances may ensue if not replaced.

Table 9.3 Characteristics and signs classes of hemorrhagic shock

	Class I	Class II	Class III	Class IV
Blood volume, mL	<750	750–1500	1500–2000	>2000
% of blood volume	<15	15–30	30–40	>40
Heart rate, per minute	<100	100–120	120–140	>140
Pulse pressure, mmHg	Normal	Decreased	Decreased	Decreased
Systolic blood pressure, mmHg	Normal	Normal	Decreased	Decreased
Respiratory rate, per minute	14–20	20–30	30–40	>35
Urine output, mL/h	>30	20–30	5–15	Negligible
Mental status	Slightly anxious	Anxious	Confused	Lethargic

Third spacing is the process of capillary leak and extravasation of intravascular fluid to the interstitial space of soft tissues (e.g., skin, fat, muscle), organs (e.g., lung, bowel), and body cavities (e.g., pleural space, peritoneal cavity), potential spaces created by surgery, or the retroperitoneum. Third spacing occurs in response to inflammatory conditions, direct and indirect tissue damage, infections, and massive fluid resuscitation and should be considered during ongoing resuscitation.

Insensible losses due to sweating, hyperventilation, and prolonged exposure of body cavities or wounds to the environment during surgery should also be factored into fluid resuscitation needs. Losses from open abdominal exposure can be estimated at 0.5 to 1 mL/kg/h but vary with the degree of exposure and illness or injury severity. Minimally invasive approaches are associated with less insensible losses but are often poorly tolerated by patients in shock. Postoperatively, insensible losses also occur through large open wounds, such as an open chest or abdomen wound (e.g., wide debridement, burn).

Additional resuscitation needs should be considered for patients who have undergone procedures that result in significant blood loss (i.e., >500 mL or 7 mL/kg) or prolonged anesthesia (i.e., >3 h); demonstrate hemodynamic instability or major organ dysfunction; required large-volume pre- or intraoperative resuscitation (i.e., >30 mL/kg); or have evidence of significant "third space" or ongoing fluid losses (e.g., distal bowel obstruction, large wounds) [68].

9.5.1.1 Fluid Resuscitation Strategy in the Perioperative State

The first step in fluid resuscitation in the perioperative state is estimating the fluid deficit. Preoperative fluid losses should be estimated by history (e.g., recent vomiting, diarrhea, fever, sweating, bleeding) and physical and laboratory evaluation (e.g., vital signs, presence of anxiety, urine output, base deficit). Oliguria must be cautiously interpreted when acute and/or chronic renal dysfunction is present. Intraoperative findings and resuscitation by the anesthesia team should also be considered.

Estimating blood loss during an operation is notoriously difficult and inaccurate [69]. However, attempts should be made to estimate blood loss by summing blood captured by closed suction and sponges and blood loss on the drapes, gowns, and operating room floor. Blood returned to the patient via autotransfusion should be subtracted from the total lost, and the volume of non-captured blood (e.g., retroperitoneal hematoma) and non-blood fluid lost (e.g., ascites, urine, succus) should

be estimated. Generally, some or all of the pre- and intraoperative losses will have been replaced during surgery. However, in the era of damage control surgery, many patients leave the operating room with ongoing need for fluid resuscitation.

The second step is measuring ongoing fluid losses. The volume of losses from decompression and surgical drains can be readily calculated assuming they are functioning appropriately. Scheduled or continuous fluid replacement can be performed depending on the volume of ongoing losses. Lower losses (i.e., <50 mL/h) can be replaced at scheduled intervals, while higher losses should be replaced continuously and without waiting for physiologic decompensation to prompt repeated bolus resuscitation.

Lastly, the volume of fluids being administered in the form of medications, blood products, and enteral or parenteral nutrition must be subtracted from the fluid deficit and ongoing fluid losses and excluded from estimates of fluid resuscitation needed.

Once the fluid losses have been estimated, the total required resuscitation volume can be determined. Given the inflammatory insult caused by infections, surgery, and injury, many acute care surgery patients will require up to three times the estimated fluid deficit to counteract physiologic fluid shifts and capillary leak [70].

Fluid resuscitation can generally be performed through large-bore peripheral intravenous (IV) lines. A liter of fluid can be administered by gravity within 5 min through an 18 gauge peripheral IV. When higher flow rates are needed, a pressure bag or rapid infuser is useful, and central access with an introducer sheath is required. Infusion of larger volumes (i.e., >2 L) of room-temperature fluids can result in hypothermia and potentiate cardiac dysfunction and coagulopathy. Therefore, a fluid warmer should be used during large-volume resuscitation.

Fluid resuscitation frequently proceeds with IV fluid boluses; however, rapid infusion of fluids has been shown to disrupt the EGL and promote capillary leak [8]. Therefore, increasing the rate of maintenance fluid and continuously titrating it to specific goals (e.g., urine output, rate of lactate clearance, lower pulse pressure variation) may be a more effective strategy when possible. Intravenous fluid resuscitation should continue until the fluid deficit is repleted and/or the desired effect on physiological parameters is achieved. Note that patients with cardiopulmonary or renal diseases may require smaller fluid volumes and more invasive monitoring to prevent the negative consequences of excessive resuscitation. Goal-directed fluid resuscitation is discussed in the setting of septic shock below but can be applied to patients in the perioperative period and patients with hypovolemia without septic shock.

9.5.2 Septic Shock

Sepsis is an inflammatory response to severe infection characterized by hypovolemia, vasodilation, and capillary leak treated by early antibiotics and fluid resuscitation. Despite the vital role that fluid resuscitation has in the care of patients with sepsis, fundamental questions regarding which fluid and in what amount remain unanswered.

Patients with sepsis are typically hypovolemic from decreased intake, large-volume intravascular volume losses into the interstitium, and increased insensible losses. In addition, the inflammation related to the immune response to infection alters systematic vascular resistance, venous capacitance, myocardial function, and the EGL, further exacerbating hypovolemia. Resultant decreases in stroke volume and cardiac output imbalance oxygen delivery and demand, precipitating tissue hypoxia, shock, anaerobic metabolism, and lactic acidosis. The rationale for fluid resuscitation in sepsis is to restore intravascular volume, cardiac output, and oxygen delivery.

Rivers' landmark study on the use of early goal-directed therapy (EGDT) in the treatment of severe sepsis and septic shock highlighted the importance of early prompt recognition and treatment of sepsis to prevent ongoing organ insults [71]. The study randomized 263 patients with sepsis and hypoperfusion to either standard therapy or EGDT. Standard therapy involved arterial and central venous catheterization and a protocol targeting CVP of 8–12 mmHg, mean arterial pressure (MAP) at least 65 mmHg, and urine output at least 0.5 ml/kg/h. EGDT included all elements of standard therapy in addition to a catheter measuring central venous oxygen saturation (SvO_2), 6 h of treatment in the emergency department before admission, and protocolized administration of 500 mL of IV crystalloid every 30 min to achieve CVP goals, vasopressors and vasodilators to maintain MAP goals, and blood transfusion or dobutamine to achieve $SvO_2 \geq 70\%$. During the 6 h of intervention, EGDT patients received more IV fluid, red cell transfusions, and dobutamine. In-hospital mortality was 16% lower with EGDT compared to standard therapy. The mortality benefit demonstrated by Rivers' study made early, protocol-driven, goal-directed fluid resuscitation, the preferred strategy for septic shock globally.

Over the last decade, three large, multicenter trials (ProCESS, ARISE, and ProMISe trials) compared EGDT to usual care in which invasive management was optional (e.g., central venous access in ProCESS) or not permitted (e.g., SvO_2 measurement in ARISE) [72–74]. These trials reported no differences in any clinical outcome between EGDT and usual care among the 4201 patients in these trials, calling into question the need for invasive hemodynamic monitoring in the current era of sepsis awareness, aggressive early treatment, and better access to critical care services [23].

After initial resuscitation, the potential benefits of fluid must be balanced against the risks of excessive resuscitation. Observational studies have associated positive fluid balance with additional morbidity and mortality. Multiple trials have reported increased odds of mortality for patients with higher fluid balance after resuscitation compared to those who were maintained more euvolemic [75, 76]. Although these studies were inherently limited by indication bias (i.e., that patients with higher severity of illness may have been more likely to both have fluid administered and die compared to those with a less severe illness), the association calls into question unchecked resuscitation and the potential role of deresuscitation or diuresis. The Fluid and Catheter Treatment Trial (FACTT) controlled post-resuscitation fluid management for 1000 acute respiratory distress syndrome (ARDS) patients, of whom 70% had underlying sepsis [58]. Once adequate resuscitation was achieved,

the fluid strategy that emphasized diuresis and limiting fluid boluses reduced the number of ventilator and intensive care unit days without precipitating cardiovascular or renal dysfunction.

9.5.2.1 Fluid Resuscitation Strategy in Septic Shock

For patients in septic shock, current recommendations advise immediate initiation of resuscitation with a minimum of 30 mL/kg of IV crystalloid fluid administered within the first 3 h [41]. During this resuscitation, serial evaluation with diagnostics and reassessment of responsiveness to fluid should take place. Patients with circulatory failure may require an additional fluid bolus to increase stroke volume. However, the risk of repeated fluid challenges is fluid overload, which has potentially deleterious effects on the function of the heart, lungs, and kidneys leading to increased mortality in patients with septic shock. A study of post-resuscitation fluid boluses in severe sepsis and septic shock demonstrated that repeated fluid boluses did not have a sustained effect on parameters typically associated with improved outcomes (e.g., urine output, $ScvO_2$, lactate) [77].

Serial or continuous assessment of fluid responsiveness is necessary to avoid fluid overload and is best monitored using dynamic hemodynamic indices (e.g., passive leg raise, pulse pressure variation, stroke volume variation) as opposed to static hemodynamic indices (e.g., central venous pressure, pulmonary artery occlusion pressure). The indiscriminate use of fluid challenges without adherence to dynamic physiologic parameters that generates excessive resuscitation in severe sepsis and septic shock is associated with increased need for fluid-related medical interventions (e.g., thoracentesis, paracentesis, diuresis, ultrafiltration), ICU readmission, and mortality [78].

Dynamic hemodynamic indices provide real-time feedback of the relationship between ventricular end-diastolic volume and stroke volume, essentially depicting the patient's movement along the Frank-Starling Curve (see Fig. 9.7). In patients with septic shock and low ventricular end-diastolic volume (i.e., preload), fluid boluses immediately increase stroke volume, effectively improving cardiac output and oxygen delivery. These patients are fluid responsive. Once the ventricular end-diastolic volume has reached the optimal plateau, further fluid resuscitation does not improve cardiac output, and detrimental excessive resuscitation is occurring.

Passive leg raise (PLR) is a diagnostic test used in patients with acute circulatory failure that predicts whether cardiac output will increase with volume expansion (i.e., fluid responsive) [79]. It has been shown to be highly accurate in predicting fluid responsiveness in patients admitted to the ICU [80, 81]. PLR is performed with the patient in a semi-recumbent position, with the patient's trunk at 45° and legs completely horizontal to the floor. A baseline measurement of cardiac output is performed using arterial pulse contour analysis, transthoracic echocardiography (TTE), or esophageal Doppler. While measurement of the arterial pulse pressure alone is correlated with stroke volume, it also depends on arterial compliance and pulse wave amplification and has been shown to be a poor indicator of changes in cardiac output [82]. The bed is then adjusted so that the patient's trunk is horizontal and the legs are lifted to 45°. This maneuver shifts approximately 300 mL of

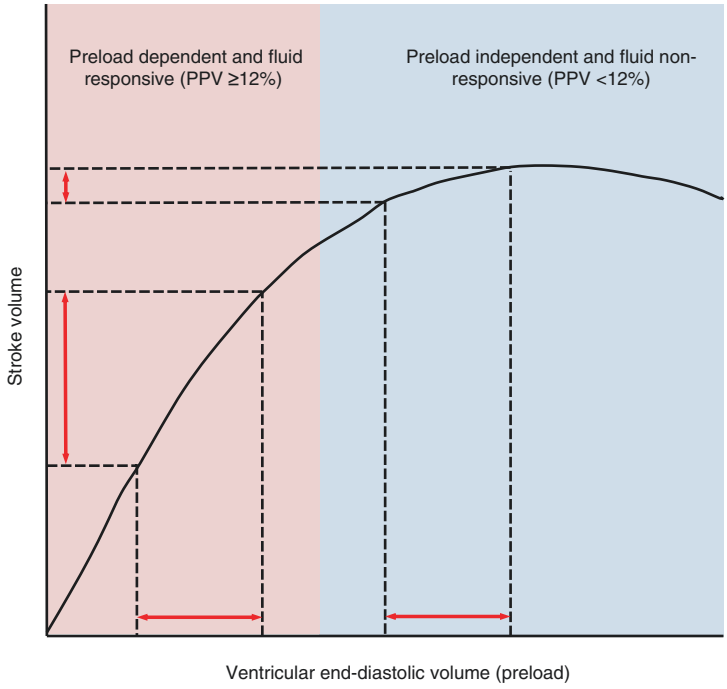

Fig. 9.7 Frank-Starling curve and fluid responsiveness. *PPV* pulse pressure variation

venous blood from the lower abdomen and extremities to the right heart, effectively increasing cardiac preload within 1 min. The second measurement of cardiac output is performed real-time with the patient in this recumbent position. Lastly, the patient is returned to the semi-recumbent position, and cardiac output is reassessed. PLR-induced increase in cardiac output of 10% ± 2% is the threshold to predict fluid responsiveness, with a sensitivity of 0.85 and specificity of 0.91 [81]. Unfortunately for most critically ill surgical patients, PLR is best suited for select patients not on vasopressors, not mechanically ventilated (i.e., normal intrathoracic pressure), and without significant abdominal pathology.

TTE is used in conjunction with PLR or independently to perform noninvasive serial examinations of fluid responsiveness and overall volume status. Stroke volume is assessed using TTE by measuring the cross-sectional area of the left ventricle outflow tract (LVOT) and the velocity time integral (VTI):

$$\text{Stroke volume} = \text{cross sectional area}\left(\text{cm}^2\right) \times \text{VTI}\left(\text{cm}\right)$$

The cross-sectional area of the LVOT is calculated by measuring the diameter of the LVOT in the apical five-chamber or parasternal long-axis views [83]. Pulsed-wave Doppler placed over the LVOT calculates the velocity time interval (VTI),

which is a Doppler parameter used to calculate blood flow across a valve. In order to calculate the cardiac output (CO), the calculated stroke volume is multiplied by the heart rate:

$$\text{Cardiac output} = \text{stroke volume} \times \text{heart rate}$$

Cardiopulmonary interactions are also responsible for pulse pressure variation (PPV), which is a surrogate for stroke volume variation (SVV) (see Fig. 9.8). In mechanically ventilated patients with controlled respiratory effort (i.e., not overbreathing the ventilator, synchronous respirations), the positive pressure delivered with each breath forces blood from the lungs to the left heart, effectively increasing preload and stroke volume. Simultaneously, the positive intrathoracic pressure decreases venous return to the right heart, lowering right heart preload and stroke volume. The pulmonary transit time of the smaller right heart stroke volume accounts for the short delay in decreased left heart stroke volume that is manifest during exhalation. PPV is monitored by examining the alterations of the arterial waveform and can only be utilized in patients who are mechanically ventilated, not spontaneously breathing, and are in sinus rhythm. Alternatively, PPV and SVV can be measured continuously with a minimally invasive lithium dilution CO (LiDCO) or pulse contour analysis CO (PiCCO) or FloTrac. PPV/SVV greater than 12% during positive pressure ventilation is predictive of hypovolemia and fluid responsiveness (see Fig. 9.8) [84]. A recent meta-analysis of PPV in septic shock has a pooled sensitivity of 0.72 (95% CI, 0.61–0.81) and a specificity of 0.91 (95% CI, 0.83–0.95) in predicting fluid responsiveness [85].

In addition to dynamic hemodynamic measurements, resuscitation can be aided by normalization of lactate. Although lactate is a surrogate marker for tissue perfusion, persistently elevated levels ≥2 mmol/L despite resuscitation have been shown to correlate linearly with increased mortality in septic shock [86]. Unlike dynamic clinical variables, lactate is an objective measure that when used to guide further resuscitation, has been associated with reduced mortality in patients with septic shock [87]. However, lactate levels are the result of production due to inadequate perfusion and hepatic and renal clearance, all of which can be depressed due to sepsis or prolonged hypoxia. Thus, similar to all surrogate markers, the lactate response to resuscitation cannot be used in isolation but considered in concert with other parameters to guide resuscitation.

9.5.3 Hemorrhagic Shock

Much of the data regarding the resuscitation of patients with hemorrhagic shock comes from the study of injured patients. While there are several important differences between hemorrhage in acute care surgical patients and the injured, many of the lessons learned may be applicable.

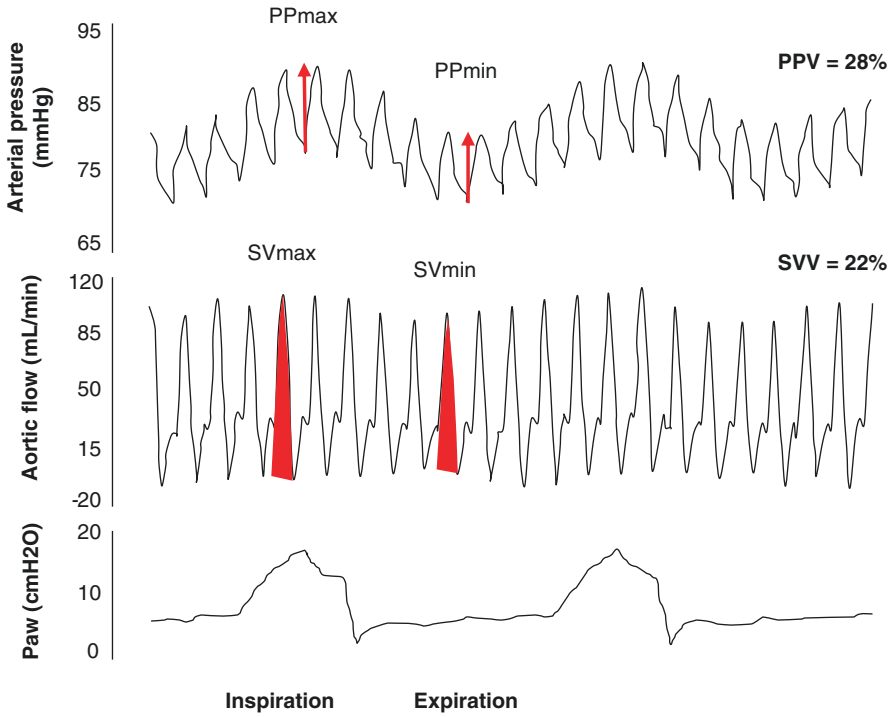

Fig. 9.8 Pulse contour analysis. *PPmax* maximum pulse pressure, *PPmin* minimum pulse pressure, *PPV* pulse pressure variation, *SVmax* maximum stroke volume, *SVmin* minimum stroke volume, *SVV* stroke volume variation, *Paw* airway pressure

Hemorrhagic shock occurs over a spectrum and is typically classified into four categories based on the estimated total blood volume lost. It is important to note that hypotension (i.e., a drop in blood pressure in a resting adult) does not manifest until there is loss of 30–40% total blood volume (class III shock) (see Table 9.3). During initial evaluation of a patient in hemorrhagic shock, rough estimation of systolic blood pressure is possible by palpation of the radial pulse (SBP ≥80 mmHg), both carotid and femoral pulses (SBP ≥70 mmHg), or only carotid (SBP ≥60 mmHg).

Other indirect but readily available measures of hypovolemic shock exist. Pulse pressure (systolic pressure minus diastolic pressure) is determined by stroke volume and vascular capacitance. Stroke volume is reduced in hypovolemic shock, which leads to a narrowed pulse pressure (normal range is 40–60 mmHg). A narrowed pulse pressure is a sensitive indicator of impending severe shock for patients with less than 30% of blood volume lost; however, pulse pressure may be unreliable in older patients with less aortic and vascular compliance. Further, a normal systolic blood pressure is markedly different in the extremes of age (e.g., lower in children and higher in the elderly), which

should be considered when attempting to evaluate a patient in shock or impending shock. For example, a systolic blood pressure of 120 mmHg in a baseline hypertensive adult may be less than adequate to maintain central nervous system perfusion.

9.5.3.1 Resuscitation Strategy in Hemorrhagic Shock

In the patient in hemorrhagic shock, identification and control of the bleeding should be the primary focus. However, the surgeon must also ensure ongoing resuscitation of the patient. Traditional resuscitation strategies for the bleeding patient have relied on the administration of large amounts of crystalloid fluid to restore circulating volume and systolic blood pressure, followed sequentially (and frequently delayed) by packed red blood cells (PRBCs), plasma, platelets, and cryoprecipitate. Major advances in the resuscitation of hemorrhagic shock have come from the experiences and research of military medicine. Most recently, damage control resuscitation (DCR) was developed by the Tactical Combat Casualty Care Committee of the US Military and utilized for combat casualties in Iraq and Afghanistan [88]. The principles of DCR include:

(1) Permissive hypotension
(2) Restriction of crystalloid resuscitation
(3) Earlier blood transfusion with balanced plasma and platelet to red blood cell transfusion ratios
(4) Goal-directed correction of coagulopathy

Permissive hypotension maintains the minimum blood pressure necessary for adequate perfusion to vital end organs, particularly prior to definitive hemorrhage control. Permissive hypotension in penetrating truncal trauma and SBP $\leq$90 mmHg was associated with lower morbidity, hospital length of stay, and overall mortality compared to comparable patients receiving immediate aggressive fluid resuscitation in the traditional manner [89]. It is presumed that permissive hypotension avoids artificial elevations in blood pressure, prevents accentuation of ongoing hemorrhage, and minimizes disruption of newly formed clots. While the optimal blood pressure target for the initial resuscitation remains unclear, permissive hypotension targeting a palpable radial pulse or systolic blood pressure >70 mmHg has been safely employed [90]. When caring for patients with non-penetrating trauma and potential traumatic brain injury, great care must be exercised to ensure adequate cerebral perfusion pressure (CPP) to avoid secondary injury to areas of threatened brain parenchyma.

Restricting crystalloid infusion resuscitation is another contrasting concept to traditional overly aggressive volume resuscitation that aimed to prevent occult hypoperfusion from splanchnic vasoconstriction and subsequent MODS. Subsequent studies have demonstrated that large-volume crystalloid-based resuscitation in the absence of physiologic targets is associated with the increased risk of ARDS, abdominal compartment syndrome, MODS, and higher mortality [55, 91–93]. In patients with hemorrhagic shock, administration of large volumes of crystalloid solutions promotes dilutional and consumptive coagulopathy, promotes hypothermia, and may

worsen metabolic acidosis with high doses of chloride; these three states have been termed the lethal triad and, when present, are associated with a marked increase in the risk of death. Therefore, modern strategies for early fluid resuscitation focus on immediate whole blood or balanced blood component transfusions in bleeding patients.

For patients in known or suspected hemorrhagic shock, universal whole blood or balanced blood product transfusion should be initiated immediately to restore tissue perfusion, frequently prior to results of coagulation testing being available in the case of severely hypotensive patients, while allowing for permissive hypotension until hemorrhage has been definitively controlled. Rapid and adequate resuscitation requires two large-bore peripheral intravenous catheters and/or central venous access with an introducer sheath. Ideally, a rapid infuser with warming capabilities is also used to administer fluids, packed red blood cells (PRBCs) units, and plasma, while platelets and cryoprecipitate are typically not given through a rapid infuser.

Patients that are likely to require a significant amount of blood product transfusion should be managed using a massive transfusion protocol (MTP). Massive transfusion (MT) has traditionally been defined as administration of ≥10 units of PRBCs within 24 h. However, this definition does not allow for prospective use or promote balanced blood product transfusion practices. A more recent definition for MT is the critical administration threshold (CAT), which is defined as the transfusion of at least three PRBC units within any one-hour period in the first 24 h of admission [94]. This new definition accounts for the intensity of ongoing resuscitation, need for early intervention to produce optimal results, avoids survivor bias implicit in the historical definition of MT, and has been prospectively validated as a sensitive predictor of mortality [95].

Higher plasma and platelet to PRBC transfusion ratios and goal-directed correction of coagulopathy are the last principles of DCR. In general, a plasma to RBC transfusion ratio of 1:1–1:2 and platelet to RBC ratio of 1:6, with one platelet pack as either a single donor apheresis or random donor platelet pool equal to 6 units of PRBCs, is preferred [96–98]. The use of conventional coagulation assays (i.e., the international normalized ratio (INR) of prothrombin time, partial thromboplastin time, platelet count, fibrinogen concentration) and newer viscoelastic assays of coagulation (i.e., thromboelastography [TEG] and rotational thromboelastometry [ROTEM]) should be used to guide correction of coagulopathy during resuscitation [99]. Transfusion, blood component therapy, and goal-directed correction of coagulopathy are covered in more detail in a subsequent chapter.

9.6 Maintenance Fluid Therapy

Maintenance fluid therapy is considered for patients not able to tolerate oral or enteral feeding. The goal of maintenance therapy is to preserve intravascular volume and electrolyte composition while avoiding complications from over resuscitation. After resuscitation, most patients will require approximately 30 mL/kg/day (i.e., 1–1.5 mL/kg/h) of fluid to compensate for gastrointestinal, renal, and insensible losses. For patients with ongoing inflammatory states, sepsis, cardiopulmonary

diseases, and/or renal insufficiency, this volume may require adjustment. Isotonic balanced salt solutions should be selected for maintenance fluid therapy and can be tailored to the electrolyte composition of ongoing fluid losses.

In general, restrictive fluid strategies are helpful in avoiding excessive resuscitation and are supported by a growing number of studies [55, 57, 58]. As able, maintenance fluid volumes should be decreased to 50–75% of estimated need and permissive oliguria accepted assuming no evidence of tissue dysoxia is identified. Restrictive strategies, along with thoughtful diuresis when appropriate, can aid in deresuscitation and avoidance of complications of prior excessive resuscitation.

In the absence of ongoing shock, dextrose can be added to maintenance fluid to stimulate basal insulin secretion and help match catabolism. For an average-sized adult, 400 kcal per day is sufficient for this purpose, which is approximately 100 g dextrose daily. However, this effect does not last beyond about 5 days, at which point catabolism will occur unless nutritional support is instituted.

In diabetic patients and patients with stress hyperglycemia, providers often remove dextrose from maintenance fluids to avoid further hyperglycemia. Although this may moderate hyperglycemia, this may result in faster onset of catabolism. A better therapy for these patients is insulin in combination with dextrose maintenance fluids. However, early use of enteral feedings has been shown to reduce the complications of the stress response; thus, as soon as possible, efforts should be made to transition maintenance fluid to enteral feeding [100, 101].

At least daily plasma chemistry profiles should be obtained in patients receiving maintenance fluids to ensure normal electrolyte composition. Additionally, serial assessment of volume status should be performed to be sure that maintenance fluid administered is needed and/or sufficient.

9.7 Summary

Understanding pathophysiology of hypovolemia and shock states allows the acute care surgeon to be systematic in the diagnosis and measured resuscitation of critically ill patients. While much remains to be learned about the most appropriate type and volume of fluid to be given to patients in shock, there is ample evidence to suggest that goal-directed fluid resuscitation is more effective than indiscriminate fluid therapy, and excessive resuscitation is counterproductive and results in worse outcomes. When part of the intensive care team, the acute care surgeon can play a vital role in the assessment of volume status, fluid deficit, and fluid needs given their understanding of underlying surgical conditions, the operative course, and resuscitation in perioperative, septic, and hemorrhagic shock states.

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Blood Therapy in the Acute Care Surgery Patient

10

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The acute care surgery patient often requires transfusion of blood and or blood products. Blood transfusion offers many benefits; however, there are potential risks. Similarly, blood component therapy must be evaluated in terms of the risk versus the benefit. Acute care surgery patients who are taking anticoagulant or antithrombotic medications often require correction of coagulopathy before surgical procedures can safely be performed. In this chapter, we will explore blood transfusion therapy including current recommendations and will review the management strategies for the anticoagulated patient.

10.1 Blood Transfusion Therapy

The first blood transfusion was reported in the mid-seventeenth century. After the development of the ABO blood group system in 1900, transfusion medicine expanded significantly. The introduction of anticoagulation of blood products in the mid-1910s allowed widespread blood storage. Transfusions became much more common after the first and second World Wars, when recognition of "wound shock" was identified as a major cause of death. Lifesaving transfusions made their way into civilian practice.

10.1.1 Risks of Blood Transfusion

From the 1970s through the mid-1990s, there was great concern about viral disease transmission associated with blood transfusions. The human immunodeficiency virus (HIV) and the hepatitis B (HBV) and C (HCV) viruses were significant risks.

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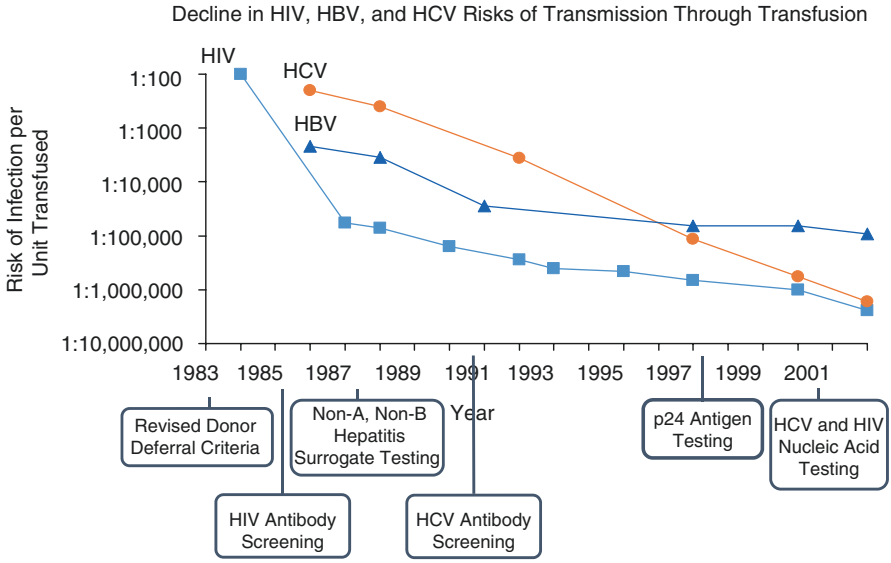

Fig. 10.1 Decline in viral disease transmission from transfusion from 1983 to 2001. Adapted from Busch et al. [1]

In the early 1980s, the risk of HIV and HCV transmission were close to 1 per 100 transfusions. Hepatitis B virus was reported in between 1 and 1000 to 1 in 10,000 transfusions. To combat this, donor deferral criteria were revised; HIV antibody screening was introduced; surrogate testing for non-A non-B hepatitis and later HCV antibody screening were implemented. By the time antigen testing and then HCV and HIV nucleic acid test were adopted, the risk of these major viral diseases being transmitted was reduced to one in millions (Fig. 10.1) [1].

By the early 2000s, the more common risks of transfusion included fever, urticaria, transfusion-related acute lung injury (TRALI), and hemolytic reactions. Transmission of bacteria was not infrequent, but bacterial sepsis was relatively rare (Table 10.1) [2]. The most common microbial disease transmitted in the world is malaria. Other transmissible agents and diseases include variant Creutzfeldt-Jakob disease, West Nile virus, cytomegalovirus, human parvovirus (B19), toxoplasmosis, and Chagas' disease from *Trypanosoma cruzi* [1, 3].

Over the past few decades, the phenomenon of transfusion-related immunomodulation (TRIM) has been recognized and characterized. In the early 1970s, it was noted that renal allograft survival improved with transfusion, leading to the common practice of blood transfusion prior to organ transplantation to improve graft survival rates [4–6]. Immunosuppressive effects of transfusion were noted to include a decrease in T-cell proliferation including CD3, CD4, and CD8 cell types; decrease in natural killer (NK) cell activity; increased suppressor T-cell activity; increased cell-mediated lympolysis; and increased serum neopterin [7].

Table 10.1 Risks of transfusion [2]

Occurrence	Risk per PRBC units
Fever	1 in 17–200 U
Urticaria	1 in 33–100 U
TRALI	1 in 1330–5000 U
Hemolytic reaction	1 in 38,000–70,000 U
Bacterial contamination	1 in 2000 U
Bacterial sepsis	1 in 500,000–786,000 U
Hepatitis B virus	1 in 205,000 U
Hepatitis A virus	1 in 1 million U
Hepatitis C virus	1 in 1–2 million U
Human immunodeficiency virus	1 in 2–3 million U

PRBC packed red blood cell, *TRALI* transfusion-related acute lung injury

Transfusion has been associated with increased postoperative infection rates in surgery of all types, including trauma surgery, colon resection, coronary artery bypass grafting, orthopedic surgery, and hysterectomy [2, 3, 8]. The link between transfusions and infections has also been demonstrated in critically ill patient populations [9]. In 1981, an association between blood transfusion and tumor recurrence was first reported [10]. Landers et al. [8] reviewed the literature in this area and reported that in most studies there was a significant difference in tumor recurrence, and the relationship between transfusions and tumor recurrence was unexplained by other variables. Even in studies failing to show a significant difference, there were still generally higher recurrence rates among transfused patients. Finally, animal studies supported the clinical relationship, and immune system downregulation was found to be consistent.

At the other end of the TRIM spectrum is hyperinflammation. Numerous proinflammatory effects of blood transfusion have been described. These include increased release of lipids, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, IL-6, and IL-8; increased neutrophil (PMN) priming for superoxide release and decreased PMN apoptosis; and increased release of IL-8 and secretory phospholipase A2 from PMNs [7, 11, 12]. Transfusion is an independent risk factor for the systemic inflammatory response syndrome, with consequent increased ICU length of stay and mortality [7]. In addition, transfusion was found to be independent risk factor for acute respiratory distress syndrome and related mortality [13, 14]. Transfusion-related acute lung injury (TRALI) is a leading cause of transfusion-related death, with a 6% mortality in the study by Toy et al. [15]. TRALI has been reported in up to 1 in 5000 units of red blood cells (RBCs), 1 in 2000 plasma-containing components, 1 in 7900 units of fresh frozen plasma (FFP), and 1 in 432 units of platelets.

Epidemiologic studies of postinjury multiple organ failure (MOF) from the Denver Health Medical Center in the 1990s found that over 60% of late deaths were due to MOF. The incidence of MOF was related to injury severity; however, blood transfusions were found to be the most robust independent risk factor for MOF [16, 17]. Studies throughout the 1990s demonstrated a relationship between the age of stored blood and the occurrence of these adverse immunomodulatory effects. In

particular, colorectal cancer recurrence, mortality rates and sepsis, pneumonia after coronary artery bypass grafting, and the occurrence of post injury MOF were all exacerbated by the administration of aged stored blood [18–20].

10.1.2 Benefits of Blood Transfusion

Blood is an effective volume expander, and its value in saving patients from exsanguination has been recognized since World War I. In less critical scenarios, the goal of blood transfusion is generally to deliver more oxygen to the tissues. Oxygen delivery is a product of the cardiac output and the oxygen content of the blood. The oxygen content is the product of the hemoglobin and the arterial saturation of hemoglobin. Cardiac output is dependent on the preload, afterload, and contractility. If all other factors stay the same, the increase in oxygen delivery based on a blood transfusion is simply calculated as the percentage increase in hemoglobin. On average, transfusion of 1 unit of RBCs will increase the hemoglobin by 1 g/dL. For example, increasing the hemoglobin from 7.0 to 8.0 g/dL would result in a 15% increase in oxygen delivery, while increasing from 10.0 to 11.0 g/dL would increase the oxygen delivery by 10%. Unfortunately, numerous clinical studies have evaluated hemodynamic and oxygen transport variables before and after transfusion in critically ill patients, and most have found no improvement in oxygen consumption following transfusion [21]. The reason for this is related to the same process that appears to influence the adverse immunomodulatory effects of blood: the blood storage lesion.

10.1.3 The Blood Storage Lesion

Blood has a shelf life of 42 days. This number was selected based on the time at which 75% of transfused RBCs would be present in the circulation for 24 h. During time in storage, there are numerous changes in the blood that impact oxygen delivery to the tissues [22]. A decrease in 2,3-diphosphoglycerate is associated with an increase in oxygen affinity and consequently a decrease in oxygen unloading in the tissues. Adenosine triphosphate decreases as well, resulting in RBC shape change, increased osmotic fragility, and decreased deformability. This adversely affects the ability of the red blood cell to navigate capillaries. Microvesiculation and loss of lipid membrane are associated with a decrease in viability of RBCs and thus the reduced number of surviving red cells in the circulation after transfusion. Lipid peroxidation in the RBC membrane results in cellular injury and death. The generation of bioactive substances such as lipids, cytokines, and histamine occurs over time and is associated with febrile nonhemolytic transfusion reactions, PMN priming, endothelial activation, cellular injury, TRALI, and MOF. Changes in the morphology of stored RBCs can be seen by electron microscopy as early as 14 days after storage.

In order to reduce the adverse immunomodulatory effects of RBC transfusion, different strategies have been suggested. These include transfusion of fresher blood

and prestorage leukoreduction. Previous studies on the clinical effects of the duration of RBC storage have reported contradictory results. A recent multicenter multinational randomized double-blind trial was performed to determine whether the duration of red cells storage affected mortality after transfusion among critically ill patients [23]. The investigators reported that the age of transfused red cells did not affect 90-day mortality or other clinically important outcomes among critically ill adults. In contrast, a single-center study examined the effects of blood transfusion on patients undergoing hepatic, pancreatic, or colorectal resection. Rather than mortality, they focused on perioperative morbidity as a primary outcome measure [24]. The investigators found that the use of older blood was an independent predictor of postoperative morbidity. When examining the mixed literature on this topic, it appears that few studies have really evaluated the oldest blood. In the TRANSFUSE trial [23], the median age of the "fresh" blood was 10.7 days, whereas the median age of the "old" blood was 21 days. In contrast, in the study of Kim et al. [24], over 75% of transfused blood was at least 21 days old, and 15% of all transfused units was stored for 35 days or longer before transfusion. This likely reflects the "real-world" experience. Moreover, mortality, while the ultimate outcome of interest, is less likely to be affected by low-volume transfusions. Importantly, it was demonstrated that a transfusion of a single unit of PRBCs aged 35 days or longer was associated with greater perioperative morbidity, even after accounting for the total number of units transfused and patient and disease characteristics [24]. It should be noted that in 2016 (prior to the publication of these two trials), the American Association of Blood Banks published a clinical practice guideline paper recommending that RBCs be transfused irrespective of their time in storage [25]. The authors of the guideline acknowledge the low quality of the evidence and the fact that it excludes patients undergoing massive transfusion. This area may continue to evolve.

Prestorage leukoreduction of RBCs has been broadly implemented in an attempt to abrogate the adverse immunomodulatory effects as well as disease transmission associated with transfusion. Currently, more than 90% of red cell and platelet transfusions in the United States are leukoreduced. The specific clinical benefit of this approach remains unclear, although the theoretical benefits have been compelling enough to lead to this near universal practice. A 2015 Cochrane review [26] concluded that there was no clear evidence for supporting or rejecting the routine use of leukoreduction in all patients requiring PRBC transfusion for preventing TRALI, death, infection, noninfectious complications, and other adverse events. They point out that the quality of evidence is very low to low and more evidence is needed before a definitive conclusion can be drawn.

10.1.4 Restrictive Blood Transfusion

In light of the risk-benefit ratio of blood transfusions, a large body of literature has emerged over the past 20 years justifying a more restrictive approach to blood transfusion. While it took many years to be adopted broadly, a restrictive blood

Table 10.2 Outcomes from the TRICC study [28]

Outcome	Restrictive	Liberal	*P* value
30-day mortality	19%	23%	0.11
ICU mortality	13%	16%	0.29
Hospital mortality	22%	28%	0.05
MOD score	10.7	11.8	0.03
Transfusion (mean PRBCs)	2.6	5.6	<0.01
Cardiac events	13%	21%	<0.01

transfusion approach and patient-focused blood management programs have been attributed for a 20% reduction in red cell transfusions per population between 2008 and 2013 in the United States [27]. The seminal paper in this area was the TRICC study [28]. In this multicenter Canadian critical care trial, 838 patients in 25 ICUs were enrolled. The patients had a hemoglobin (Hgb) <9 g/dL and were euvolemic without active blood loss. They were randomized to a restrictive transfusion strategy with a transfusion trigger of Hgb <7.0 g/dL and target Hgb 7–9 g/dL versus a liberal transfusion strategy with a transfusion trigger of Hgb <9.0 g/dL and target Hgb 10–12 g/dL. In this study, although not all statistically significant, all outcome measures favored the restrictive transfusion strategy (Table 10.2). Furthermore, subgroup analyses indicated improved survival for patients less than 55 years old as well as for patients with Apache-2 scores of 20 or less. There was no difference in survival among patients with Apache-2 score >20, age >55, a history of cardiac disease, severe infections or septic shock, or trauma. While this paper led to a change in management in many centers, there has remained concern about subpopulations of "sicker" patients and in particular among patients with cardiovascular disease.

10.1.4.1 Transfusion in Patients with Cardiovascular Disease

For many years it was recommended that patients with acute coronary syndrome (ACS) or myocardial infarction (MI) should have a Hgb >10.0 g/dL, as acute anemia was associated with increased risk of death. This recommendation was sometimes extrapolated to patients with a known cardiovascular disease, even when asymptomatic. The TRICC trial [28] excluded patients with symptomatic cardiovascular disease, but a subgroup analysis of 357 enrolled patients with known cardiovascular disease showed no difference in outcome between liberal and restrictive strategies [29]. More recently, investigators have looked at patients with symptomatic cardiovascular disease. Singla et al. [30] found that among ACS and MI patients who have a hemoglobin level >9.0 g/dL, there was a significant increase in adverse outcomes associated with transfusion. On the other hand, patients who had anemia with a hemoglobin <9.0 g/dL had similar rates of adverse events when they were transfused versus not transfused. Rao et al. [31] showed dramatic increases in the odds ratio of death associated with transfusion in patients whose nadir hematocrit was 30 or 35%. Yet another study by Aaronson et al. [32] suggested that in the setting of MI, a strategy of no transfusion was better unless the nadir Hgb was 8.0 g/dL or lower. Overall, the current evidence suggests that patients with cardiovascular disease may have higher rates of death and cardiac morbidity with a restrictive

transfusion approach. But, as reviewed by Carson et al. [27], these results should be interpreted with caution, and several trials are underway to try to clarify the outcomes. At this time, it appears that a safe Hgb range in these patients is between 8.0 and 9.0 g/dL. Of note, a meta-analysis of studies of blood transfusion strategy and anemia associated with MI concluded that a liberal blood transfusion strategy compared with no blood transfusion or a restrictive blood transfusion strategy is associated with higher all-cause mortality rates after MI. These authors suggested that a practice of routine or liberal blood transfusion in MI should not be encouraged and requires investigation in a large trial [33]. An important recent trial evaluated evaluating restrictive versus liberal transfusion strategies in patients undergoing cardiac surgery found that in patients undergoing cardiac surgery who are at moderate to high risk for death, a restrictive red cell transfusion strategy was not inferior to a liberal transfusion strategy. This was with respect to death from any cause, MI, stroke, or new-onset renal failure with dialysis [34].

10.1.4.2 Transfusion in Patients with Gastrointestinal Bleeding

A prospective randomized clinical trial of patients with severe acute upper GI bleeding compared restrictive and liberal transfusion strategies, using the same study parameters and interventions as the TRICC trial [35]. This study found that a restrictive strategy significantly improved outcomes in patients with acute upper GI hemorrhage. There were reductions in death, adverse events, and further bleeding. While these results are consistent with critical care trials and appeared generalizable, it should be cautioned that patients who are in hypovolemic shock or who have significant cardiovascular disease may benefit from more liberal transfusion therapy.

10.1.4.3 Other Subgroups of Adults

In the TRICC trial, patients with severe sepsis did not have worse outcomes with a restrictive transfusion strategy [28]. A multicenter trial of patients in septic shock reported that a restrictive transfusion strategy was safe. Specifically mortality in 90 days and rates of ischemic events and use of life support were similar between the restrictive and liberal transfusion groups [36]. There remains uncertainty about the most appropriate transfusion trigger among perioperative patients. A recent meta-analysis of randomized trials found that in surgical patients a restrictive transfusion strategy was associated with an increase in mortality [37].

10.2 Management of the Anticoagulated Patient

With development of new anticoagulation (AC) and antiplatelet (AP) pharmacological agents for various conditions such as cardiovascular and thromboembolic ailments, it has become the burden of the acute care surgeon to manage around these as well as older generation medications in the setting of urgently or emergently needed surgeries/procedures or in the setting of bleeding. This problem can be divided under two headings: anticoagulation and antiplatelet regimen. That being

said, it is common to see dual antiplatelet therapy (DAPT) and less common single antiplatelet therapy (SAPT) in combination with an AC medication, and fortunately least common is DAPT and AC medication.

To manage the bleeding patient, general hemostatic maneuvers such as good surgical techniques, correction of hypocalcemia, and maintaining normothermia and normovolemia to avoid acidosis are paramount. The lethal triad of bleeding—concomitant hypothermia, acidosis, and coagulopathy—carries a high mortality. Beyond that, attention to the patient's history and medications to assess risks of bleeding and prepare accordingly becomes also crucially important.

10.2.1 Anticoagulation Medications

They are used mostly for the prophylaxis or treatment of cardiovascular and genetic or induced pro-thrombotic conditions manifesting as thromboembolic phenomena such as atrial fibrillation and deep vein thrombosis with or without pulmonary embolism.

Warfarin, vitamin K antagonist initially developed as rat poison, was by far the most used if not the only oral AC medication until the advent of the novel or direct oral anticoagulants (NOACs or DOACs). These are either direct thrombin inhibitors such as dabigatran (generic, Pradaxa) or direct factor Xa inhibitors: apixaban (Eliquis), edoxaban (Savaysa), rivaroxaban (Xarelto), or betrixaban (Bevyxxa, only approved for venous thromboembolism prophylaxis). Comparatively to warfarin, the DOACs have shown equal if not better stroke prevention in non-valvular atrial fibrillation or outcomes in treatment/prophylaxis of thromboembolic disease while maintaining an equal if not safer profile in terms of bleeding risk. Additionally, they do not require lab monitoring or dietary modifications and thus carry a better safety profile [38, 39].

However, the advantage of warfarin remains that we are more confident in our ability to monitor the therapeutic effect or its reversal with PT/INR. The effect usually resolves in 2-5 days of holding it depending on the initial INR and the patient's metabolic and nutritional status. For more rapid reversal, oral or intramuscular/subcutaneous vitamin K (2–10 mg) requires 12–24 h to reach effect, and intravenous vitamin can be used for a faster effect (about 6 h) at the expense of the known risk of an anaphylactic-like reaction. Alternatively, fresh frozen plasma transfusion at a dose of 10–20 mL/Kg can be given for even faster effect if the patient can tolerate the volume rapidly from the cardiopulmonary standpoint; fixed dosing of starting with 2 units of FFP has not shown as consistent reversal [40, 41]. With the advent of recombinant factor VIIa (rFVIIa) and 3- or 4-factor prothrombin complex concentrates (PCC), the volume concern was abated, but these agents are more expensive. rFVIIa has been slowly losing favor with studies showing less efficacy and more thrombotic complications than PCC. Other studies, comparing 3-factor PCCs that contain factors II, IX, and X and 4-factor PCC also containing factor VII, found that the reversal of warfarin effect is faster and better with 4-factor PCC. Although 4-factor PCC is more costly per dose, it is still more cost-effective when taking

into consideration the improved efficacy with less need for additional dosing or interventions. Dosing for PCC is usually 25–50 units/Kg with repeat INR obtained in about 30 min to guide if an additional dose or other intervention (FFP, cryoprecipitate, etc.) is needed [42–44]. An INR rebound effect is noted with these agents especially if vitamin K is not concomitantly given or a dose on the lower range is used. Keep in mind that thrombotic complications such as stroke, deep vein thrombosis with or without pulmonary embolism, and acute coronary syndromes are seen with PCC with rates ranging from none to up to 15% of cases depending on the study and its population.

Not infrequently, we are called to operate or control bleeding on patients on heparin infusion, low molecular weight heparin (LMWH), or direct thrombin inhibitors (DTI, argatroban, bivalirudin, lepirudin) infusion. Heparin infusion reversal starts with stopping the infusion, and effect resolves within few hours (half-life is 90 min). If emergent reversal is needed, then protamine can be given at a dose of 1–1.5 mg for every 100 units of heparin with max dose of 50 mg and infused at a max rate of 5 mg/min; premedication with steroids and antihistamines is recommended specially in patients with fish allergy or previous exposure to protamine. LMWH (half-life 4.5–7 h) effect resolves in 12–24 h depending on the dose given (prophylaxis or therapeutic) and renal function; protamine can also be given for emergent reversal with 1 mg for every 100 units if dose is given less than 8 h prior and 0.5 mg if given 8–12 h prior; protamine is not recommended beyond that time frame. For DTI infusions, there are no known antidotes, but they have short half-lives (argatroban 40–50 min, bivalirudin 25 min, lepirudin 80 min), and just stopping them is the main stay of reversal [45–50].

DOACs are newer and as noted above have favorable pharmacology and safety while being at least as effective as warfarin. The concern however is the shorter and newer experience with these agents and the limited readily available ability to monitor their effect with laboratory testing although Factor Xa activity testing is becoming more common. In the setting of non-emergent surgery, stopping these agents 24–48 h has been sufficient to resolve the effect. Below we discuss rapid reversal options.

There are general approaches to reversal of the anticoagulant effects of these agents such as PCC or factor VIIa with animal, ex vivo, and in vivo human small studies showing variable results. These varied by the DOACs being reversed as well as the reversing agent, but overall they seem to offer a therapeutic option until specific reversal agents are available; it does seem that however they work better with the Xa inhibitors rather than dabigatran.

Activated PCC or FEIBA (factor eight inhibitor bypassing activity) contains factors II, IX, and X as well as activated VII with small amount of protein C, protein S, and tissue factor pathway inhibitor (TFPI) with trace amounts of factors V and VIII; the dose of 100 units/Kg seems to offer the best effect, but this may also bring in thrombotic complications. It does however show reversal effect with dabigatran due to the tissue factor element.

One more thing to add is that dabigatran is only 35% protein bound and can be successfully dialyzed. It is not recommended in patients with chronic renal failure,

but if the patient arrives in acute renal failure and bleeding, dialysis should be considered early in the plan of interventions.

There are now targeted reversal agents. Idarucizumab (Praxbind) is a monoclonal antibody that binds to dabigatran. It has FDA approval with ongoing Phase III trials.

It irreversibly binds the drug with 350 times more affinity than thrombin, and the dose is 5 g infusion with onset of action within minutes and near complete anticoagulation reversal in most patients (>90%). It is excreted by the kidneys with a short half-life (47 min), but the binding is irreversible, and it is retained longer in patients with renal failure that are more prone to also retaining dabigatran making this an advantage. Side effects have been minimal in studied patients so far, but some thrombotic events have been noted specially if anticoagulant treatment has not been restarted few days after the initial event.

Andexanet alpha (Andexxa) is another targeted reversal agent as it competes with Factor Xa to binding to the DOACs. It is an inactive modified Factor Xa that acts as decoy to the DOACs. At the time of completion of this chapter, June 2018, andexanet had just received FDA approval for reversal of factor Xa inhibitors in patients with life-threatening or uncontrollable bleeding and on apixaban or rivaroxaban. The production company initiated early limited market launch with wide release beginning 2019. The dose is usually an intravenous bolus followed by an infusion and can be low (400 mg bolus at a rate of 30 mg/min followed by 4 mg/min for up to 2 h) or high (800 mg bolus at a rate of 30 mg/min followed by 8 mg/min for up to 2 h) depending on the DOACs used, its dose, and the timing from the last dose. Effect is more than 90% anti-Xa activity reduction in 2–5 min, but due to its short half-life, the initial bolus is followed by an infusion. So far it has been studied with apixaban and rivaroxaban with the latter likely requiring a higher dose. It has not been shown to be effective for the other factor Xa inhibitors in clinical trials with bleeding patients (Phase 3) and is accordingly not indicated yet but has shown success in in vitro studies and animal models. It also showed anticoagulation reversal in healthy older (50–75 years old) volunteers given enoxaparin. Thrombotic events have occurred after its use in up to 18% of cases, but this rate is reduced to ~12% if anticoagulation was resumed prior to the occurrence of such an event.

Ciraparantag (aripazine) is a small water-soluble molecule shown to bind to all DOACs (factor IIa and Xa inhibitors), heparin, low molecular weight heparin, and fondaparinux and prevent these molecules from binding to their targets. It is considered the universal anticoagulation reversal agent. It is still in investigation stages with successful preclinical trials and promising phase 2 trials on the way with enoxaparin and edoxaban.

10.2.2 Antiplatelet Medications

Antiplatelet (AP) medications have become a first line of prophylaxis and treatment for coronary artery and vascular disease in general especially aspirin. It is quite common to see patients over 50 on it even without documented such history. DAPT, most commonly used aspirin and clopidogrel (Plavix, P2Y12 blocker), is

started after acute coronary syndrome whether treated medically or by stent placement; it is recommended for at least a 1 month for bare-metal stents and up to a year and no less than a year with drug-eluting stents. It is frequently continued well beyond the 6–12-month interval recommended when the patient can be changed to only aspirin or single agent with the fear of premature cessation resulting in significantly increased risk of stent thrombosis, up to 30%, and associated 45% mortality. Nonsteroidal anti-inflammatory drugs and LMWH have not shown adequate cardiac protective effect even if started early after surgery when AP therapy is stopped. Additionally, clopidogrel is a pro-drug, and depending on the patient's metabolic and genetic status, the activity can vary, so an active drug was produced for use in non-responders, and it is prasugrel (Effient). Ticagrelor (Brilinta) is also a newer P2Y12 receptor blocker. There are other less commonly used AP medications and no specific management of bleeding attributed to them, so we will focus on aspirin and P2Y12 blockers.

Tests available to assess platelet function and response to AP therapy have gained increased use, not just in the cardiovascular care lines but also in evaluation of the bleeding or pre-surgical patient. Platelet Function Assay evaluates the overall function of the platelets. Aspirin Reaction Units test assesses the amount of aspirin binding to platelets as a surrogate for effect. P2Y12 level measures the blockade of clopidogrel or prasugrel on the platelet receptor.

The problem for the acute care surgeon is the effect of these agents is irreversible, so it lasts the life of the platelet, 7–9 days. Stopping them is the main stay of effect reversal with platelet function improving after 3 days of holding aspirin and 5 days for clopidogrel. Ideally these are stopped 7 days before a surgery in collaboration with the cardiologist to make sure they are out of the time frame of absolute necessity. It should be considered in low bleeding risk situations to continue on aspirin only from DAPT to prevent stent thrombosis or coronary event. On the other hand, the biggest difficulty arises when there is high bleeding risk emergent surgery or high-risk bleeding such as intracranial or uncontrolled bleeding. Options of emergent reversal are limited and include some limited recommendations that have not all been fully supported by clinical trials. One such option is desmopressin (DDAVP) at a 0.3 mcg/Kg IV; this carries low side effects without known thrombotic risk. Tranexamic acid has been used in cardiovascular surgery and trauma to improve hemostasis with apparent platelet function improvement.

Last to discuss is the use of platelet transfusion. There have been no data to support the use of platelet transfusion prophylactically, but such transfusions have shown improved platelet function in patients on AP. This being said more recent studies showed similar outcomes with or without transfusion for patient on AP therapy and spontaneous intracranial hemorrhage. Actually the recent PATCH study showed possible worse outcome. One recent relatively small study showed no improvement in mortality after traumatic brain injury for patient on antiplatelet therapy with platelet transfusion compared to no transfusion but did improve aspirin, not clopidogrel, effect by lab; however, the transfused group had longer length of stay and more importantly significantly higher ISS and admission CT scores.

The variability of AP therapy and different patient population with different presentation are far from being well studied, and it falls on the clinician's judgment to assess the risk and benefit of platelet transfusion for the patient he or she is caring for. For the acute care and trauma surgeons, platelet transfusion seems to be an acceptable option until more literature is available [50–54].

To summarize, the AC medications are close to being all reversible, but the DOACs and their reversing agents are all new, and there will be lessons to learn. AP therapy has shown its merit in managing vascular diseases, but we are still far from finding reversing agents. The references below are only the sample of articles used to prepare this chapter but include some review articles that will guide you to more available research old and new.

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Coagulation Derangements in the ACS Patient: Understanding and Addressing Acute Coagulopathy

11

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11.1 Introduction

Coagulation abnormalities in the acute care surgery (ACS) patient may be due to a number of pre-existing factors, but the common etiology is typically acute blood loss. There is limited data to address coagulation changes that occur in emergency general surgery, but massive transfusion protocols from trauma systems have been utilized and effective for this patient population [1, 2]. There has been a worldwide interest in the pathogenesis of trauma-induced coagulopathy (TIC) and its early management [3]. While not all mechanisms of TIC are applicable to all non-trauma ACS, it is important to understand the existing rational for transfusion protocols in trauma and how they can be applied to bleeding patients during emergency general surgery.

The shortcomings of research on TIC over the past decade have been related to a heavy emphasis a single mechanism via protein C driving all forms of coagulopathy following injury [4, 5]. This same shortcoming of ascribing one mechanism causes death in sepsis with protein C demonstrating no improvement in mortality when using a recombinant form of protein C in two subsequent randomized control trials [6, 7]. Recent appreciation that pathology in clot formation and clot degradation (fibrinolysis) processes may be driven by different mechanisms after severe injury [8, 9] suggesting that trauma patients can present to the hospital with unique phenotypes of coagulation abnormalities. This same concept can be applied to emergency general surgery in which patients can be bleeding related to a sepsis-related complication or uncontrolled hemorrhage from GI or vascular rupture. This has clinical

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significance as patients are optimally cared for with personalized resuscitation strategies, rather than empirically using a "cookbook formula" to treat all patients in the same fashion, e.g., the 1:1:1 platelets/fresh frozen plasma/red blood cell protocol. The benefits of goal-driven hemostatic resuscitation have been validated in a single center institution prospective study in which a patients' coagulation status was treated with goal-directed blood products with rapidly available coagulation tests vs. standard of care, in which mortality was reduced by nearly 50% in the personalized care group [10].

11.2 Coagulopathy in Trauma

Trauma-induced coagulopathy is global term to describe coagulation changes following severe injury. There are multiple phenotypes of TIC that can be categorized by changes in (1) thrombin generation, (2) fibrinolysis, and (3) platelet function measured by coagulation protein levels [8] and functional viscoelastic assays [9, 11]. The pathophysiology of TIC is even more complex than the measured changes in the coagulation system, because metabolites [12] and catecholamines [13], which accumulate rapidly post-injury and alter their host's immune response [14], and activation of the endothelium [15] all may contribute to coagulation derangements. To ascribe one name and one mechanism to this multifactorial process appears short-sighted, and its complexity has been documented repeatedly through many failed clinical trials, including the Novo7 trial with activated factor VIIa [16] and the PROPPR trial which implemented fixed ratios of blood products for resuscitation [17]. Before delving into mechanisms which cause an "opathy" of coagulation in trauma, it is essential to describe the process of clot formation and degradation under normal conditions to appreciate where specific abnormalities can lead to excessive bleeding or thrombosis.

11.3 Cell-Based Model of Hemostasis: Thrombin Generation

Hoffman and Monroe [18] enhanced the understanding of the mechanisms of coagulation by shifting from of a simple enzymatic cascade to a cell-based paradigm with tightly regulated events. The key concept underlying the paradigm of "cell-mediated hemostasis" is that cells play active roles in regulating and localizing the coagulation reactions. Many cells can participate in hemostasis and thrombosis, but the two critical players are platelets and endothelial cells. This model consists of three overlapping phases: initiation, amplification, and propagation. A breach of the endothelium promotes clot formation via exposed collagen and tissue factor. Collagen localizes platelets via their GP-VI receptor. Circulating von Willebrand factor also binds collagen, and this complex further promotes platelet adherence through the platelet GP-Ib-V-IX receptors, particularly important under high stress flow. Tissue factor (TF) binds circulating factor VII, and the resulting TF/FVIIa complex activates factors IX and X. The initial amount of thrombin generated is insufficient to cleave fibrin but activates platelets through their PAR-1 and PAR-4 receptors and

also activates factors V and VIII. In the ensuing amplification phase, these activated factors form the tenase (VIIIa/IXa) and prothrombinase (Va/Xa) complexes on the surface of platelets. "Tenase" (VIIIa/IXa) generates sufficient amounts of factor Xa to support thrombin generation through prothrombinase (Va/Xa). These coagulation complexes require phospholipid and calcium for their activity. Prothrombinase and tenase then potentiate the "thrombin burst" in the propagation phase, which cleaves fibrinogen. The resulting fibrin polymerizes and integrates platelets by binding via their GP-IIb-IIIa receptors. This thrombin further generates Va and VIIIa for prothrombinase and tenase assembly and activates XIII which cross-links fibrin to stabilize the evolving clot. Activated platelets release adenosine diphosphate (ADP) and thromboxane A_2 (TxA_2) that further recruit platelets to form an outer shell to stabilize the clot.

11.4 Partitioning of Coagulation and the Antithrombin System

Spatial partitioning of the coagulation is of physiologic significance. VII and TF are found in high concentrations in the extravascular space around blood vessels forming a VIIa/TF complex that produces basal level of Xa activity [19]. Prevention of thrombin generation inside the vasculature space is accomplished by differential distributions of pro- and anti-thrombin generating proteases between the intravascular and extravascular space in addition to platelets. In particular, V and VIII are higher in concentration in the intravascular space, in addition to higher concentration of antithrombin (AT) and tissue factor pathway inhibitor (TFPI). AT is a serine protease inhibitor protein that has a broad range of targets (including XIa, Xa, IXa, VIIa, and IIa) which has marked increased activity in the presence of its heparin-based cofactors [20]. The endogenous source of heparin is from lining of the endothelium called the glycocalyx which is rich in heparin proteoglycans [21]. The glycocalyx also serves an antithrombotic role by forming a direct barrier between circulating platelets and underlying endothelium by preventing adhesion and activation [22]. TFPI is another antithrombotic protease inhibitor found in high concentrations in the intravascular space, which binds and inhibits IIVa and Xa, and certain isoforms can also inhibit the prothrombinase complex through binding for Va [23].

Terminal protease formation of thrombin also results in an autoregulation and suppression of future thrombin generation. There are two main pathways of prothrombin degradation to thrombin which are dependent on the cell surface which the prothrombinase complex is associated with [24]. Prothrombinase bound to activated platelet cell membranes cleaves prothrombin into an inactive prethrombin, while synthetic phospholipid membranes and endothelial membranes produce an active intermediate meizothrombin. Both of these intermediates are subsequently converted to α-thrombin, the primary protease involved in fibrinogen cleavage to fibrin. α-thrombin activation promotes inhibition of future thrombin generation via the protein C pathway (APC). APC achieves its primary anticoagulant function through proteolytic cleavage of activated factors Va and VIIIa [25–28]. APC activation is augmented by the binding of thrombin [29] or meizothrombin [30]

to the thrombomodulin receptor. Protein S also increases activated protein C complex adherence to the phospholipid membrane, further enabling the more efficient inactivation of factor Va [31]. Independent of these anticoagulant properties, APC has been shown to have multiple cytoprotective effects as well, acting as an anti-inflammatory agent and preventing endothelial barrier leakage [32, 33]. By these two mechanisms, the APC pathway serves to maintain vascular flow by preventing excessive thrombosis and also protects cells from damage associated with inflammatory insults, such as sepsis and trauma.

11.5 Fibrinogen: The End of Thrombosis and Beginning of Fibrinolysis

Fibrinogen is a complex multi-domain protein which is found in high concentration in circulating plasma. This 340 KD protein is a dimer made from two homologous proteins containing three chains (Aα, Bβ, and γ). Fibrin(ogen) has a structural core which includes a central E region that is *flanked* by two terminal D regions [34]. Thrombin preferentially binds at the γ chain [35] located in the D region and cleaves fibrinopeptide A and/or B to form fibrin [34]. Cleavage of fibrinopeptides exposes a binding surface (knob) that binds to "holes" located in the D domain. This knob-hole interaction [36] allows spontaneous polymerization of fibrin monomers in which the D and E region of adjacent monomers interact to form a growing fibrin chain. This interaction is associated with a significant conformational change in which a carboxy region of the α chain (αC domain) becomes exposed [37].

Fibrin polymers form an antiparallel two molecular linear chains called a protofibril primarily through knob-hole *a* interactions, which form lateral associations with the αC domain to create fibrin fibers [38]. Lateral branching points also occur via *b* knob-hole interactions forming complex fibrin network [39]. Branching of fibrils is dependent on the type and amount of available fibrin, which is often proportional to the amount of thrombin generated [40]. In low-thrombin conditions, fibrils branch at a higher frequency and form a tight network (nonporous), which have increased elasticity [41]. The fibrin network also becomes strengthened from cross-linking between the γ chain of adjacent D domains with XIIIa [42]. This transglutaminase enzyme (XIII) activated by α-thrombin can also cross-link additional structural proteins such as fibronectin to the fibrin network to increase clot strength [43]. These fibrin networks are also constructed with antifibrinolytic proteins, such as α_2-antiplasmin (α_2-AP) [44], which can also be cross-linked into the clot with XIIIa [43]. Profibrinolytics can also be included into the growing clot such as plasminogen which can be found bound to plasminogen in circulation [41].

Forming a fibrin network is not sufficient to form a stable clot. Clot stability is gained by additional cellular interactions to connect the fibrin mesh with the cellular components of coagulation and the underlying vascular structures to foundation the hemostatic plug. Integrins are a class of transmembrane receptors which form an adhesion with extracellular matrix proteins and, in the setting of coagulation fibrin(ogen), are important targets. Platelets connect to fibrin(ogen) through

glycoprotein IIb/IIIa [45]. This interaction not only provides structural support for fibrin network but also links platelets to each other [46]. Platelets bridging links the fibrin network to the extracellular matrix of the blood vessel through additional integrin interactions such as glycoproteins Ia/IIa to collagen [47] and Ib-IX with von Willebrand factor [48]. Recent evidence also suggests that red blood cells and neutrophils can increase fibrin stabilization, although not through a direct interaction with fibrin [49]. Integrins also exist on endothelial cells to capture fibrin(ogen) [50].

11.6 Fibrinolysis and Vasculature Patency

Fibrinolysis is the process of dissolution of fibrin polymers resulting in clot degradation. During the 1960s a number of investigators emphasized that fibrinolysis was a physiologic process to counter balance thrombosis and was continuously active [51, 52]. The activity of plasmin, the most abundant fibrin protease, is highly dependent on its local environment, and its proenzyme plasminogen binds numerous receptors/proteins indicating the process occurs on surfaces and not in circulation [53]. The conversion of plasminogen to plasmin occurs through proteolytic cleavage by one of its activators, tissue plasminogen activator (t-PA), or urine-type plasminogen activator (u-PA).

Fibrinolysis is dependent on plasminogen and t-PA binding to fibrin forming a complex [54, 55]. While t-PA levels are associated with fibrinogen degradation in some in vitro models [56], fibrin has long been known as the activator of the fibrinolytic system and increases t-PA and plasmin activity by magnitudes compared to fibrinogen [55]. Both plasminogen and t-PA can bind fibrin on the same region of the α chain, and t-PA has an exclusive binding domain on the γ chain [57]. Plasminogen effectively accomplishes this task by binding lysine residues with its multiple kringle domains, of which plasminogen binding of the αC domain of fibrin appears to be key for initiation of fibrinolysis. The organization of polymerized fibrin enables concentrated PLG and t-PA on the fibrin surface, putting these two enzymes in close proximity that result in initiation of fibrinolysis [58]. Plasmin, when bound to fibrin, is at a relatively slow rate (10–100 s) compared to in circulation, which has a half-life of 0.1 s due to rapid sequestration by α_2-AP [59]. Fibrin clot structure dictates the rate of clot degradation in addition to cross-linked inhibitors into fibrin fibers such as α_2-AP [60]. Regulation of clot degradation is also through cleavage of these lysine domains, with the carboxy peptidase TAFI, principally cleaving off of the αC domain preventing plasminogen (not t-PA) binding [61].

The regional distribution of specialized endothelial cells contributory to the fibrinolytic system is reflective of the importance of localizing this process [62]. The primary driver of intravascular fibrinolysis, t-PA, is released from precapillary arterioles and postcapillary venule endothelial cells [63]. There are only a few known cellular receptors that co-localize t-PA and plasminogen (annexin-A_2 and α enolase) and are predominantly located on the vascular endothelium [64]. However there are numerous additional receptors for plasminogen that have a diverse range in biological function [53]. u-PA utilizes plasminogen binding and conformation changes

by receptor to mediate cellular migration and tissue remodeling [65]. These two mechanistically distinct activities of t-PA and u-PA support their unique biological roles. While t-PA appears to be a primary driver or intravascular fibrinolysis, u-PA acts as a global plasmin generator for tissue remodeling, not relegated to fibrin.

11.7 Drivers of Coagulopathy

11.7.1 Activated Protein C

The most widely accepted mechanism of TIC is through the activation of protein C leading to PAI-1 depletion and loss of fibrinolysis inhibitors. This process is dependent on severe injury and systemic hypotension, which leads to high levels of circulating thrombin and upregulation of thrombomodulin [66]. Thrombomodulin increases the activity of thrombin-mediated clearance of protein C by 20,000-fold [67]. The dual effect of shock and tissue injury causing coagulopathy in mice has been reproduced and demonstrated that protein C activation and prolongation of aPTT are dependent on both tissue injury and shock and animals subjected to just one intervention (shock or tissue injury) did not demonstrate coagulation abnormalities [68]. Interestingly, APC-deficient mice used in this set of experiments could not tolerate hemorrhagic shock and died of diffuse thrombosis. Therefore APC appears to be a physiologic functioning at the microvascular level to promote hypocoagulability to prevent thrombosis [68]. This finding is consistent with previous work by Hardaway et al. who demonstrated heparinization of dogs prior to shock prevented irreversible shock by attenuating microvascular thrombosis [69]. An alternative explanation of the protective role of APC during shock is through an anti-inflammatory mechanism. This view is supported by data from a trauma cohort demonstrating that poor outcomes associated with increased levels of inflammatory histones are abrogated by simultaneous increases in endogenous APC, implying a protective effect of APC in the setting of widespread inflammation [70].

While the APC theory encourages a more scientifically based approach to understanding TIC, there is growing evidence that APC only represents a small component of trauma-induced coagulopathy. Subsequent work from San Francisco has demonstrated that the drivers of thrombin generation are discordant with the drivers of fibrinolysis regulation [8] and argue against a single mechanism driving impaired thrombin generation and hyperfibrinolysis. This disparity has also been supported using viscoelastic assays, which thrombin generation and fibrinolysis are not a fully linked [9, 11]. The most recent publication from the Brohi group has even refuted their own previous claims that APC drives hypocoagulability through factor V and VIII depletion [71]. Authors from this paper conclude that APC does not drive abnormally low activity levels of V and VIII but cause of prolonged INR through fibrinogen depletion via driving hyperfibrinolysis through PAI-1 depletion [71]. However, this group has not reported protein S activity [72], which is dependent for PAI-1 degradation. An alternative mechanism to explain increased fibrinolysis is an increase in circulating t-PA levels, which appear to saturate circulating PAI-1 rather

than depletion [73]. Even though more disparities exist in this theory as it has been demonstrated in non-trauma patients in circulatory arrest, hyperfibrinolysis is common without an associated increase in APC [74]. The physiologic function of APC in trauma remains unclear, as it may represent a biomarker of activated endothelium, but its direct role in pathologic coagulopathy remains in question, especially when thrombomodulin promotes TAFI activation, a potent antifibrinolytic.

11.7.2 Autoheparinization from Glycocalyx Degradation

Shortly after the proposed role of APC in TIC, Johansson et al. [75] from Copenhagen added evidence implicating endothelial glycocalyx degradation as a major mediator of TIC, emphasizing the "endotheliopathy" component. The vascular endothelium comprises a single layer of cells that line blood vessels and lymphatics in every organ, covering a surface area of 4–7000 m^2 with a weight of 1 kg [76]. The luminal surface of the endothelial cells is covered by a 0.2–1.0 μm thick, negatively charged, carbohydrate-rich surface layer, the endothelial glycocalyx. The glycocalyx that represents a large structural component of the vascular system comprises a fixed noncirculating volume of approximately 1 L in adults, equal to one third of the vascular plasma volume [77]. The glycocalyx is an anti-adhesive and anticoagulant structure that protects endothelial cells and maintains vascular barrier function [77, 78]. It is bound to the underlying endothelial cells through various backbone molecules of proteoglycans (the most abundant are syndecan-1 and glypican) and glycoprotein. The proteoglycans have long glycosaminoglycan side chains comprised mainly of heparan sulfate that has heparin-like functions [79]. Glycocalyx damage can range from discrete disturbances in the composition of the most luminal layer to complete degradation and loss of the entire glycocalyx. Upon shedding, the glycocalyx glycosaminoglycans retain their anticoagulant (heparin-like) activity and promote measurable hypocoagulability in the circulating blood through endogenous autoheparinization [80]. Rehm et al. [81] provided the first evidence of acute destruction of the endothelial glycocalyx in patients undergoing vascular surgery associated with ischemia/reperfusion injury. This study reported that syndecan-1 and heparan sulfate levels increased after ischemia/reperfusion injury during vascular surgery, and this increase correlated to shedding of glycocalyx as detected by electron microscopy. Despite 40- to 60-fold increases in syndecan-1 post-ischemia, the levels of the classical endothelial adhesion molecules ICAM-1 and VCAM-1 did not change, emphasizing the occurrence of selective glycocalyx disruption. Blomback et al. [40] translated these observations to trauma when his group demonstrated reversibility of prolonged clotting time by heparinase TEG in critically injured trauma patients. These patients had syndecan-1 levels fourfold higher than non-coagulopathic patients in this study in addition to a higher injury severity and transfusion requirements. However, beyond impairment of thrombin generation, glycocalyx shedding does not explain other coagulation changes acutely following injury including platelet dysfunction and fibrinolysis, which will be described in the next sections.

These shedding events have been proposed to be a marker of "endotheliopathy" of trauma, which is associated with protein C activation and cellular damage [15]. However, ascribing a single mechanism to explain the range of different coagulation abnormalities would be short sighted. This is particularly true in regard to measuring systemic blood and predicting endothelial activation. The endothelium of different organ beds is unique and responds discordantly to various stimuli [82]. There is a large gap in the trauma literature in identifying which organ beds the endothelium is activated upon and if more than glycocalyx shedding after endothelial activation contributes to acute changes in systemic coagulation.

11.7.3 DIC and Consumptive Coagulopathy

The role of disseminated intravascular coagulopathy (DIC) in depleting circulating clotting factors resulting in impaired thrombin generation is a matter of debate [41]. Theoretically the distinction is that DIC occurs within the vessel lumen; whereas, consumption occurs from disrupted endothelium exposing tissue factor bearing calls and collagen. Most investigators do not believe DIC is a dominant mechanism in TIC but acknowledge its potential contribution. The innate immune response to injury has been implicated in the genesis of DIC, particularly with the release of damage-associated molecular patterns (DAMPs) [83]. But beyond increased tissue factor expression on monocytes and microparticles, the mechanism remains unclear. Among those with procoagulant implications are $HMBG_1$, histone DNA complexes [42], and polyphosphates [43]. Additionally, neutrophils are believed to contribute to a procoagulant state via degranulation of elastase, which can act as an indiscriminate protease [44]. Neutrophil extracellular traps (NETs) are also believed to be critical in the pathogenesis of DIC in sepsis [84]. NETs are extracellular DNA fragments and nucleosomes excreted by neutrophils which have a role in killing bacteria [85]. These NETs are also procoagulant [86] and antifibrinolytic [87] and are believed to play a role in pathologic venous thrombosis during sepsis [88]. Finally, with extensive tissue disruption, there is undoubtedly some element of coagulation factor consumption to achieve hemostasis. The DIC theory has had gained more traction in sepsis, but scores have been validated to predict mortality related to organ failure and extrapolated to trauma patients [89]. Interestingly, the treatment for patients with high DIC scores has shifted to a focus on anticoagulation protease replacement [90, 91] that paradoxically improves coagulation profiles after treatment.

11.7.4 Hypothermia and Acidosis

Hypothermia and acidosis are no longer considered the primary drivers of coagulopathy, but they can become secondary events that complicate the management of bleeding. In vitro [92] and in vivo [93] data suggest that hypothermia affects hemostasis when the temperature is below 33 °C. Below this temperature, hypothermia

inhibits the initiation phase of clotting. This would be anticipated as most of the coagulation enzymes are slowed by hypothermia. Thus, while moderate hypothermia delays the onset of thrombin generation, the total amount of thrombin generation is unaffected [92, 93]. The effect of hypothermia on platelet function is contradictory due to limitation in the ability to replicated platelet function under physiologic conditions [94]. Some studies indicate enhanced platelet activation (priming) and aggregation [95, 96], while others indicate decreased adhesion and aggregation [92]. Profound hypothermia has been long recognized for promoting hepatic sequestration of platelets, but the clinical relevance outside of cardiac surgery is minimal, as a temperature below 30 °C is needed for this phenomenon to become physiologically relevant.

Metabolic acidosis has a more profound effect on TIC than hypothermia at clinically relevant levels [93, 97]. A reduction of pH from 7.4 to 7.0 has been shown in vitro to reduce FVIIa activity by 90%, FXa and FVa activity by 70%, and FVIIa-TF complex activity by 55% [98]. In vitro data have confirmed a pronounced inhibition of the propagation phase of thrombin generation at a pH of 7.1, resulting in a marked reduction in clot strength [93]. These studies also suggest this degree of acidosis increases fibrinogen degradation twofold. While impaired platelet aggregation and adhesion at a pH <7 has been appreciated for decades, more recently the mechanism has been elucidated and associated to the store-operated calcium entry (SOCE) channels. Perhaps more worrisome, the correction of pH with bicarbonate [93] or tris-hydroxymethylaminomethane (THAM) [99] does not restore platelet function. This may have implications for the optimal timing of platelet transfusion in the critically injured patient.

11.7.5 Hemodilution

Hemodilution is no longer considered the dominant mechanism for coagulopathy, but overzealous crystalloid resuscitation can exaggerate an existing coagulation changes. Reduced levels of coagulation proteins have been documented in healthy volunteers after administration of crystalloids, colloids, and stored RBCs [55] and remain a fundamental rationale for permissive hypotensive resuscitation. Interestingly, acute hemodilution to 50% in vitro does not impair clot formation [56], but this magnitude of hemodilution enhances the sensitivity to t-PA due to the dilution of endogenous antifibrinolytics [57].

11.7.6 Platelet Dysfunction

Endogenous activators of platelets have been well characterized in both the arterial and venous systems with a focus on collagen and thrombin that work in conjunction with platelet-released adenosine diphosphate (ADP) and thromboxane. However, the precise roles of these platelet activation pathways during TIC and emergency surgery are not well defined. Interestingly, the TIC patient is more likely to display

platelet dysfunction as opposed to platelet consumption [100, 101]. Platelet dysfunction occurs early after injury and has been documented with isolated traumatic brain injury [102]. One proposed mechanism is through the Toll-like 4 (TLR-4) receptors of platelets, in which TLR-4 knock out mice are protected after hemorrhage and resuscitation in a murine model [103]. The TLR family is a group of receptors that act as part of the innate immunity that monitors the body for foreign pathogens or evidence of cell death [104]. Specifically the TLR-4 receptor has been identified as the driver of sterile inflammation after trauma [105]. However, the mechanism of TLR-4 causing platelet dysfunction remains unclear. In non-trauma patients with sterile inflammation from autoimmune disease, the etiology of platelet dysfunction has been attributed to "exhausted" platelets, in which circulating platelets are activated and release significant amounts of their granules [106]. However, recent evidence suggests that platelets dysfunction following trauma is not due to exhaustion, rather it relates to an intrinsic problem with the platelet preventing effective degranulation [107]. An alternative hypotheses of platelet dysfunction following trauma include metabolic derangements from hemorrhagic shock causing platelet inhibition [108]. Therefore, circulating platelets likely experience a combination of sequential exposures of agonists to trigger modes of activation or inhibition following injury that results in their functional activity while circulating.

11.7.7 Hyperfibrinolysis

Interest in fibrinolysis as a component of TIC was stimulated by Brohi et al. [66] who suggested activated protein C degraded PAI-1. However, recognition of systemic fibrinolysis following injury did not occur until the widespread use of viscoelastic assays. Recent clinical studies indicate that systemic hyperfibrinolysis occurs in 2–5% of critically injured patient and 10–15% of those requiring massive transfusion [109]. Currently, the only established mechanistic factor for hyperfibrinolysis is inadequate tissue perfusion, suggested by a number of retrospective studies [66, 109–111] and further strengthened by the fact that the patients in the CRASH II trial who benefited from antifibrinolytics had a systolic blood pressure <75 mmHg [112]. Patients who have non-traumatic cardiac arrest have a high prevalence of hyperfibrinolysis supporting this observation [113]. Conversely, shock may also generate metabolic disturbances that enhance fibrinolysis. For example, taurocholic acid increases fibrinolysis in vitro and is markedly elevated following shock [114]. The consistent finding in trauma patients who have hyperfibrinolysis is abnormally elevated t-PA activity [73, 115]. The original TIC animal model failed to demonstrate increases in fibrinolytic activity [68], and human data suggest that tissue injury is not needed to cause this alteration in coagulation [113]. The cause of increased systemic t-PA levels following trauma remains unclear [110], and an animal model that can produce high levels of tissue plasminogen activator is needed to further our understanding of hyperfibrinolysis following trauma.

High systemic t-PA levels are likely not the only driving force of hyperfibrinolysis in trauma. t-PA levels have been reported to reach the 40 ng/mL in trauma

patients [110], but to induce an appreciable increase in fibrinolysis in healthy volunteers requires 75 ng/mL of t-PA. The inflection point of 75 ng/mL of t-PA is based on a small unpublished study evaluating the effects of clot activators and fibrinolysis sensitivity. In this study, a cohort of healthy volunteers was used to test the hypothesis that TEG performed without a coagulation activator (kaolin or tissue factor) detected the greatest degree of fibrinolysis. Three simultaneous TEG assays were performed: rapid-TEG (r-TEG; tissue factor and kaolin added), kaolin TEG (k-TEG), and citrated native TEG (n-TEG; no activator added). Fibrinolysis was induced with tissue plasminogen activator (t-PA) (0, 50, 75, 150, 300 ng/mL). The TEG parameter of fibrinolysis (LY30; percent clot breakdown) was compared among assays for each t-PA dose and tested for significance. N-TEG detected the greatest degree of t-PA-induced fibrinolysis (75 ng/mL) compared to k-TEG and r-TEG (LY30: 15.8% [9.7–23.6] vs. 4.2% [3.3–5.8], $p < 0.001$) and (15.8%[9.7–23.6] vs. 6.7%[4.6–11.6], $p = 0.002$). The threshold for detection of a change in fibrinolysis was significant for n-TEG between 50 and 75 ng/mL of t-PA ($p = 0.001$), compared to 75–150 ng/mL for the r-TEG and k-TEG assays ($p < 0.001$).

The buffer capacity of healthy volunteer blood to tolerate nearly double the concentration of t-PA measured in trauma patients is likely related to plasma and platelets. Plasma has numerous proteins [116], which have been described as regulators of the fibrinolytic system by inhibition of t-PA, plasmin, and altering clot structure to render fibrinolysis less efficient. This buffering capacity of fibrinolysis can be diminished with plasma dilution, which has been demonstrated in vitro [108] and in vivo [117]. There is also a protective role of platelets on the fibrin core [118] in which platelets can form a local environment to promote clot stability [119]. Platelets in vitro have been demonstrated to promote fibrinolysis resistance [120], and platelet dysfunction in trauma patients has been associated with increased susceptibility to t-PA-mediated fibrinolysis [12]. Therefore, it is likely that hyperfibrinolysis requires increased t-PA levels with concurrent loss of fibrinolysis regulators. However, this remains to be proven in trauma patients beyond the depletion of the t-PA direct inhibitor PAI-1 [73, 110, 115].

11.7.8 Fibrinolysis Shutdown

The mortality rate of injured patients with impaired fibrinolysis (shutdown) was originally reported by our group to be nearly four times greater than patients with a physiologic level of fibrinolysis, and death is primarily attributable to organ failure [121]. The term fibrinolysis shutdown was first used in 1969 [122] in a review describing the effects of electroplexy, myocardial infarction, and elective surgery on fibrinolysis. Animal data prior to this time suggested microemboli in visceral small vessels lead to irreversible shock that was later found to be survivable with a profibrinolytic [123, 124]. Hardaway further translated these findings to humans and implicated trauma and shock in producing microvascular occlusion [125]. Confusion arises as the nomenclature of describing impaired removal of vascular thrombi is often referred to as either the syndrome of disseminated intravascular

coagulation (DIC) or pathologic impairment of fibrinolysis (shutdown). As mentioned previously, some investigators consider DIC to have two distinct phenotypes, hyperfibrinolysis and fibrinolysis shutdown [41], which is somewhat difficult to reconcile as diffuse intravascular thrombus should not exist in the presence of systemic hyperfibrinolysis.

Trauma patients in fibrinolysis shutdown have multiple mechanisms for impaired clot breakdown. One is through high circulating levels of PAI-1 preventing t-PA binding to fibrin. The second mechanism is modification of fibrin that prevents plasminogen from binding to the lysine-binding domain. This also can be accomplished with a platelet shell in which the local microenvironment is antifibrinolytic and the clot cannot be broken down. The net results are a growing thrombus that eventually causes vascular occlusion resulting in inadequate perfusion of distal organs and venous clots that pose an embolic risk. While many have focused on hyperfibrinolysis role in TIC, but the incidence is relatively low. Conversely, impaired fibrinolysis (shutdown) is present in the majority of severely injured patients and may result in microvascular occlusion and organ dysfunction, although the timing and duration of pathologic fibrinolysis shutdown in trauma patients remain to be defined.

11.8 Measuring Trauma-Induced Coagulopathy

11.8.1 Traditional Laboratory Tests

Lack of an accurate tool to identify and track coagulopathy remains a major limitation surrounding both post-injury hemostatic derangements and empiric blood component replacement therapy. Traditional laboratory tests of coagulation function, such as PT (prothrombin time) and aPTT (activated partial thromboplastin time), were designed originally for the assessment of coagulation function with isolated clinical factor deficiencies in hemophiliacs and other patients and are based on the interaction of the coagulation factors in isolation [126, 127]. To date, the performance characteristics of these tests in the trauma patient remain unproven. Furthermore, a prohibitive amount of time (30–45 min) is required to conduct these assays. Because both the PT and aPTT are performed on platelet-poor plasma, they are sensitive only to the earliest initiation of clot formation (estimated to represent 5% of the thrombin generation during clot formation) and do not incorporate platelet function. Finally, these tests are performed in an artificial environment, irrespective of the patient's core body temperature and pH. Measurements of individual clotting factors and related proteins, such as protein C, are both costly and time-consuming. The diagnosis of fibrinolysis is also problematic with the gold standard being the euglobulin lysis time (ELT) [128]. The ELT is a complex and time-consuming procedure that can take more than 180 min, reduces some of the inhibitors, does not include platelets that may regulate fibrinolysis, and is overly sensitive for injured patients as demonstrated five decades ago [128]. Other techniques to identify hyperfibrinolysis, such as plasmin-antiplasmin complex, fibrin monomers, and D-dimers, are only reflective of the footprint of fibrinolysis, i.e., they do not represent the

patient's current systemic fibrinolytic activity. Thus, partitioning the components of a patient's blood and testing them independently in an artificial environment requires a lengthy assay time and is not clinically optimal to manage coagulopathy in the critically injured patient.

11.8.2 Viscoelastic Hemostatic Assays

In response to the shortcomings of conventional measurements of coagulopathy, point-of-care, viscoelastic hemostatic assays are emerging as the standard of care for both the diagnosis and treatment of post-injury coagulopathy in many trauma centers throughout the world [129, 130]. Viscoelastic assays quantify whole blood clot formation and degradation based on the resistance created by liquid blood solidifying and degrading after reaching maximum strength. The time and rate to achieve output of the device correlate with coagulation factor status, fibrinogen function, platelet function, and quantify fibrinolysis. Interpretation of the most clinically employed viscoelastic assays in the United States is described below.

11.8.3 Thrombelastography (TEG)

The rapid TEG (r-TEG) is designed to provide the quickest results by using both extrinsic (tissue factor) and intrinsic (kaolin) pathway activators. The drawback of maximizing clot initiation is the resulting amplification of the coagulation system, which may mask subtler changes in coagulation particularly in the hypercoagulable setting or when quantifying fibrinolysis. For example, a native TEG performed without activators after recalcification demonstrated a high rate of hypercoagulability early after injury [12] which an r-TEG would have not detected. The indices of a TEG assay represent different component of coagulation. The reaction time (*R*, minutes) is defined as the time elapsed from the initiation of the test to the point where the onset of clotting provides enough resistance to produce a 2-mm amplitude reading on the TEG tracing [131]. Of note, in the r-TEG assay (discussed below), due to the acceleration of clotting initiation, the *R* time is represented by a TEG-derived activated clotting time (TEG-ACT). The *R* time and TEG-ACT are most representative of the initiation phase of clotting due to enzymatic factors. A prolonged *R* time or TEG-ACT is diagnostic of hypocoagulability; whereas shortened times suggest hypercoagulability. The α-angle (α, degrees) is the angle formed by the slope of a tangent line traced from the *R* to the time required to reach 20 mm amplitude (k-time) measured in degrees and represents the rate at which the clot strengthens and is most representative of thrombin's cleavage of available fibrinogen into fibrin. The maximum amplitude (MA, mm) is the point at which clot strength reaches its maximum on the TEG tracing and reflects the end result of maximal platelet-fibrin interaction and is often used to guide platelet transfusions. The LY30 variable represents the percent of clot degradation 30 min after the clot reaches MA and is used to quantify fibrinolysis. The functional fibrinogen

(FF-TEG) assay is a more specific method to quantify fibrinogen levels and is performed by using a monoclonal antibody to glycoprotein IIb-IIIa to eliminate the contribution of platelets to clot strength [132]. One of the limitations of the viscoelastic assay is the generation of abundant thrombin, which masks the effects of antiplatelet therapy or potential platelet dysfunction by activating platelets via the robust protease-activated receptors (PAR)-1 and PAR-4. In order to quantify platelet dysfunction, a platelet mapping assay (PM-TEG) relies on heparin to eliminate thrombin activation and employs reptilase and FXIII to cross-link fibrin and, thus, eliminate the fibrin contribution to clot strength. The contributions of the P2Y12 or thromboxane receptors to clot formation are measured by the addition of adenosine diphosphate (ADP) or arachidonic acid (AA), respectively. There are additional TEG variables that are not routinely used clinically which also provide information on clot strength and fibrinolysis that are, at this time, mostly used in vitro.

11.8.4 Clinical Implementation of Viscoelastic Assays

A recent prospective randomized trial has shown that viscoelastic assays are superior compared to PT/INR, aPTT, platelet count, and fibrinogen level for the management of TIC [133]. Furthermore, a retrospective cohort study indicated that viscoelastic assays are better than a fixed ratio (1:1:1) strategy [134]. TEG is also capable of detecting hypercoagulability (increased MA), whereas the PT and aPTT do not [135]. Perhaps the greatest advantage of viscoelastic assays is to individualize management of patients based on their phenotype of TIC. Considering the diverse mechanisms driving TIC, severely injured patients manifest unique patterns of TIC [58, 59]. Patients with predominately impaired thrombin generation have a prolonged R and low MA. The hyperfibrinolytic phenotype has also been identified with TEG using the LY30 parameter and associated with high mortality [111, 136]. While TEG has been used predominantly to identify and direct treatment for hypocoagulability, it also can measure hypercoagulability, and there is an interest in its utility to predict adverse outcomes [137].

11.8.5 Clinical Significance of Hypercoagulability Following Injury

The incidence of proximal lower extremity deep venous thrombosis (DVT) in injured patients without preventive measures has been reported at 18–32% and the risk of significant pulmonary embolism (PE) from 0.3–2% [138]. These risks are confounded by the fact that surveillance duplex will identify a higher incidence of asymptomatic DVT, but post-injury PE occurs in the absence of DVT in the majority of patients. Furthermore, asymptomatic PE has been identified in >25% of severely injured patients on admission chest CT scanning [139], yet early, symptomatic PE has been associated with extremity trauma but not thoracic injuries [140]. Consequently, it is not surprising that the prevention of post-injury VTE remains

controversial, underscoring the critical need to understand the pathophysiology and fundamental mechanisms to design effective preventive strategies.

The prothrombotic state caused by changes in blood flow, blood vessel injury, and blood composition was described by Virchow in the 1700s [141]. Nearly 200 years later, Cannon recognized that the initial response to severe trauma is hypercoagulability, quickly followed by hypocoagulability [142], and thus, severely injured patients survive their injury transition to a hypercoagulable state as early as 24 h following injury [143]. In fact, patients presenting with advanced TIC requiring a massive transfusion are at the greatest risk for VTE [144]. The etiology of this hypercoagulability is likely multifactorial, involving endothelial injury, circulatory stasis, platelet activation, hyperfibrinogenemia, decreased levels of endogenous anticoagulants, and impaired fibrinolysis. Furie and Furie emphasize the role of the endothelium in maintaining blood flow via the generation of anticoagulants, nitric oxide, prostacyclin, and receptor expression [145]. But even intact endothelium, when activated, can provoke thrombus formation. Furthermore, circulating leukocytes and microparticles contain and release tissue factor [146]. Obesity and traumatic brain injury are independent risk factors for post-injury VTE, although the responsible mechanisms remain speculative [147, 148].

11.8.6 Diagnosis of Hypercoagulability

The diagnosis and, thus, treatment of hypercoagulability following injury has been limited by the lack of accurate laboratory testing addressing the pathogenesis. Conventional tests, such as the aPTT and PT/INR, are neither able to diagnose hypercoagulability nor delineate the relative contributions of enzymatic and platelet components. Previous trials investigating the benefit of various mechanical and chemoprophylactic regimens among injured patients have neither documented hypercoagulability nor monitored the efficacy of prophylaxis. Severely injured patients develop inflammation-driven hyperfibrinogenemia within days of injury [149], and there is a growing body of evidence that has implicated platelet activation in the development and propagation of VTE [150]. Our recent publication has identified platelet function is inversely related to fibrinolytic activity [12]. In light of these limitations, it is not surprising that most VTEs among trauma patients occur because of prophylaxis failure rather than failure to provide prophylaxis. In a recent comprehensive international analysis of medical and surgical ICUs, the current rate of DVT is 7.7% and PE 1.3% [151].

Viscoelastic hemostatic assays may provide a breakthrough in managing hypercoagulability. A TEG shortened *R* time, increased α-angle, and enhanced MA are indicative of hypercoagulability [152]. There is a strong correlation between hypercoagulability as evidenced by the aforementioned TEG parameters and subsequent VTE [68]. Despite standard chemoprophylaxis, 60% of patients displayed evidence of hypercoagulability [68]. Furthermore, TEG can distinguish platelet versus fibrinogen contribution to clot formation as well as calibrate fibrinolysis shutdown [153]. Preliminary data demonstrated that t-PA resistance (fibrinolysis shutdown) is a risk

factor for post-injury VTE, and we have developed a t-PA sensitivity assay to quantify a patient's resistance/sensitivity to fibrinolysis.

11.9 Future Direction: Redefining Coagulopathy

The trauma and acute care surgery community as a whole need to come to a global definition of TIC and its various phenotypes. Coagulopathy definitions are currently heavily weighted on INR [144, 154–157]. INR is performed in platelet-free plasma and designed to monitor prothrombin levels [126], which to some investigators chagrin, nearly 80 years after its clinical implementation, correlates well with prothrombin levels in trauma patients [158]. Emerging data from the Brohi group now supports that an elevated INR after trauma is not related to factor V and VIII depletion and now hypothesize it is related to a fibrinogen depletion [71]. The shortcomings of using a plasma-based assay include inability to detect hypercoagulability [135] and neglect the cellular component of coagulation. While an INR is a great biomarker marker for risk of mortality, it has major limitations in understanding the pathophysiology of TIC. It is important to not forget that thrombin generation and fibrinolysis changes have previously been implicated to be driven by different processes in trauma [8, 9, 11]. Therefor using a functional assay that measured all of the components of coagulation is a more logical approach to classifying and understanding TIC. Fibrinolysis shutdown represents just one of likely many TIC pathologies that would have never been appreciated with using an INR test. Other components of hypercoagulability may also be attributable to poor outcomes in trauma. This re-emphasizes the importance of targeting homeostasis during resuscitation and attempting to avoid overshooting a hemostatic resuscitation to hypercoagulability which has recently been discussed in an editorial in treating TIC [159].

The agenda of the national trauma community is to obtain zero preventable death through civilian and military collaboration [160] and should be the same for acute care surgery. Keys for implementation of zero preventable deaths have been proposed to be through research to generate evidence-based best trauma care practices, timely dissemination of trauma knowledge, and patient-centered trauma care [160]. Civilian investigators [121, 161–163] have prompted numerous clinical editorials on treating post-injury fibrinolysis [164–167] meeting the objective of a timely dissemination of trauma knowledge. The rediscovery of fibrinolysis shutdown acutely after injury has increased the questionable beneficial role of empiric antifibrinolytics after trauma [168]. Forcing a physiologic endpoint in coagulation does not have sound scientific merit. Stafford et al. in 1964 [169] began his review on fibrinolysis and hemostasis by writing "circulating blood must remain fluid; if it does not, the culminating thrombosis is a pathologic event with definable sequelae." A key in trauma resuscitation is to maintain a coagulation system that can be pro-/antithrombotic or pro-/antifibrinolytic based on its local environment but remain homeostasis and liquid in systemic circulation. Therefor successful resuscitation in all trauma patients cannot be accomplished with measuring an INR and cannot be treated with one medication. These traditionalist ways of thinking about coagulation are

a step back in advancing patient care. While the evidence of shutdown has been disseminated, the next step of best practice evidence-based medicine needs to be adopted. The current best practice care appears to be related to goal direct resuscitation based off of the individuals viscoelastic output reduced mortality by 50% [10]. While some centers have adopted TEG- and ROTEM-based resuscitation, there is a still a large room for improvement [170]. These strategies are limited to treating hypocoagulability and do not address systemic hypercoagulability and fibrinolysis resistance. Precision medicine to treat the individual has been an objective of the US healthcare system since completion of the human genome project over a decade ago [171]. This exciting time of function hemostatic assessment, paired with proteomic analysis, will help elucidate the underlying mechanisms of the multiple phenotypes of TIC and translation into therapeutic interventions. It is already possible to extrapolate numerous phenotypes of trauma-induced coagulopathies, but identifying which are pathologic and most effective treatment strategy will remain a challenge. The same is applicable to emergency general surgery where sepsis and inflammation compounded by active bleeding create a complex clinical picture. Looking for unique phenotypes in these patients will likely lead to therapeutic strategies to reduce bleeding and reduce postoperative complications. Despite over a century of work on coagulopathy on trauma and acute care surgery, we are still in our infancy of understanding the mechanisms driving these processes, and more research is needed to continue to translate clinical observations to translatable models for therapeutic strategies to reduce mortality.

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12 Nutrition and Metabolic Support of the ACS Patient: Understanding Goals and Ways to Achieve Them

Martin D. Rosenthal and Frederick A. Moore

12.1 Introduction

Over the past two decades, the treatment of intra-abdominal problems requiring emergency surgical intervention and postoperative ICU care has increasingly fallen within the domain of the acute care surgeon (ACS). A substantial portion of these patients present in life-threatening hemorrhagic shock or sepsis may require damage control interventions and are at high risk for multiple organ failure (MOF) and prolonged intensive care unit (ICU) stays. As the surgical treatment paradigm for these patient has been refined and with improved implementation of evidence-based ICU care, early hospital deaths from refractory shock and fulminant MOF have decreased substantially. Unfortunately, many of the survivors are progressing into a new predominant MOF phenotype of chronic critical illness (CCI) termed the persistent inflammation, immunosuppression, and catabolism syndrome (PICS). This begs the question of are we creating survivors or casualties? CCI-PICS patients represent an extremely vulnerable population that are discharged to nonhome destinations in severe debilitated states, fail to rehabilitate, and frequently suffer an indolent death months after their initial EGS intervention. Currently, there are no specific nutritional intervention for CCI/PICS patients. The traditional strategy has been to provide early enteral nutrition (EEN) and place the patient into a positive caloric balance in hope to attain positive nitrogen balance and thereby maintain lean body mass. While EEN does reduce secondary nosocomial infections that contribute ongoing inflammation that drives CCI-PICS, it has not been shown to decrease the profound catabolism and loss of lean body mass that results in long-term functional disability. To better understand the implications of nutritional support in EGS ICU

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patients, this chapter will review (a) the evolving epidemiology of MOF into PICS; (b) the rationale for EEN; (c) recommendations for parenteral nutrition (PN); (d) the role of protein calories over nonprotein calories to improve outcomes; (e) adjuncts to protect the gut, probiotics, prebiotics, and synbiotics; and (f) adjunct therapies to resolve inflammation, reduce immunosuppression, and improve catabolism.

12.1.1 The Evolving Epidemiology of MOF into PICS as the Current Clinical Challenge

MOF emerged in the 1970s with the advent of ICU care which allowed patients to survive single organ failure. Over the ensuing four decades, its epidemiology has evolved as a result of the tremendous ongoing advances in the care of the critically injured and ill patients. The earliest case series describing MOF were in EGS patients with uncontrolled sepsis [principally from intra-abdominal infections (IAIs)] which resulted in refractory fulminant early MOF with an inhospital mortality rate exceeding 80%. Considerable research attention was directed at better understanding IAI, and as a result, care and early mortality improved. However, by the mid-1980s, it became apparent that the primary culprit causing the collateral organ injury causing MOF was the body's own inflammatory response. It was also recognized that this same auto-destructive response frequently caused MOF after noninfectious insults (e.g., blunt trauma, pancreatitis, etc.). The term "sepsis syndrome" was popularized, and research focused on determining its driving mechanisms (e.g., bacterial translocation, the "cytokine storm," etc.). In the early 1990s, this response became known as "SIRS." Additionally, studies demonstrated that the mortality of early SIRS-induced MOF had decreased substantially, but many of the survivors developed secondary nosocomial infections that worsened existing MOF or precipitated a different form of late onset MOF. This was associated with immunosuppression that was believed to be due to a compensatory anti-inflammatory response syndrome (CARS), and the result was significant late mortality. By the late 1990s, the concept of SIRS followed by CARS became the accepted MOF paradigm to explain early versus late onset MOF. The 2000s were notable for implementing evidence-based medicine into the standard operating procedures (SOPs) starting in the emergency department through the ICU. As a result the inciting events (e.g., trauma, sepsis) were better managed with a substantially reduction in early MOF mortality. Additionally, the surviving patients were better supported in the ICU with fewer iatrogenic insults and less nosocomial infections. Although not initially recognized, studies in the 2010s documented that late MOF deaths were disappearing. MOF was still occurring, but critically ill patients were "weathering the storm" and not dying in the ICU. Unfortunately, many of the survivors were now progressing into chronic critical illness (CCI), characterized by persistent organ dysfunction requiring prolonged intensive care unit (ICU) care. These CCI sepsis survivors are often discharged to long-term acute care facilities (LTACs), where they experience dismal outcomes.

Recent studies have shown that after severe trauma and sepsis, patients develop simultaneous SIRS and CARS, but relatively few (<10%) progress into the SIRS/early

MOF death trajectory. As SIRS resolves, roughly half of the survivors exhibit rapid recovery of their organ dysfunction and achieve immune homeostasis. Unfortunately, the remainder develop CCI, characterized by prolonged ICU stays (>14 days) with (a) low-grade organ dysfunction (especially kidney injury), (b) persistent inflammation (increased inflammatory cytokines interleukin [IL]-6 and IL-8), (c) immunosuppression (lymphopenia and increased soluble programmed death-ligand 1 [sPDL-1]) requiring frequent treatment of nosocomial infections, and (d) catabolism with muscle wasting and cachexia (similar to cancer and other chronic inflammatory diseases). These patients are discharged to LTACs for expensive custodial care because there are no effective interventions and their profound disabilities preclude home care. Here they experience accelerated aging and induced frailty, sepsis recidivism (requiring rehospitalization), physical and cognitive disabilities (resulting in dismal life quality), and a high rate of ongoing indolent death (~40% at 1 year). The elderly are especially vulnerable. Germane to this chapter, this patient population despite aggressive nutritional intervention continue to lose weight and tremendous amounts of lean body mass (a cachexia-like state) portending to decreased functional status.

12.1.2 The Rationale for Early Enteral Nutrition (EEN)

In the late 1970s, PN became widely available and was increasingly utilized critically ill ICU to provide nutrients to support hypermetabolism induced by injury stress response. However, Dr. Frank Cerra note that despite this exogenous PN, the body continued to breakdown available protein stores to mobilize substrate, and this result is what he called "septic auto-cannibalism" which worsened the acute protein malnutrition that played a key role in the MOF cascade [1]. Special "stress formula" PN fortified with branched chain amino acids (BCCA) and arginine was developed and widely used to combat this "auto-cannibalism," but PN fell out of favor by the early 1990s. PN had been embraced as a panacea for surgical patient, and this spurred numerous prospective trials that unfortunately failed to document improved outcomes in surgical patients. In fact, several trials showed perioperative PN in stressed surgical patients worsened adverse outcomes, primarily by increased nosocomial infections. Additionally, a series of trials done in major torso trauma patients demonstrated that EEN when compared to early PN reduced nosocomial infection [2]. A number of subsequent studies in different types of critically ill patients have confirmed that EEN (started within 24 h) improves outcomes by reducing infectious morbidity, coinciding with the SCCM/ASPEN guidelines [2–17].

In the early 1990s, these EEN vs PN data were vigorously debated. While most agreed that inappropriate PN could cause the increased infectious morbidity (e.g., hyperglycemia, line sepsis), opponents of EEN cited a lack of a logical explanation EEN beneficial effects. This spurred tremendous research in determining the gut-specific mechanisms by which EEN worked. It was shown that for a variety of reasons, the gut becomes progressively dysfunctional after major trauma/sepsis, and as a result, it becomes the reservoir for bacteria and toxins that escape the gut and drive late sepsis-related MOF. EEN achieves its benefits by maintaining vital

gut functions. Intraluminal nutrients reverse shock-induced mucosal hypoperfusion [18, 19]. The ramifications of an under-perfused state are gut barrier disruption, microvilli sloughing, altered gastrointestinal motility, changes in bacterial virulence, potentially worsening systemic inflammation, and even the dreaded abdominal compartment syndrome [20–25]. EEN has also been shown to reduce impaired intestinal transit when given after a gut ischemic/reperfusion (I/R) insult, as well as reduce bowel edema after resuscitation. Improved transit in theory decreases ileus-induced bacterial colonization and overgrowth [26–30]. Additionally, EEN attenuates the gut permeability defect that is induced by critical illness [31]. Finally, and likely most importantly, is that the gut serves as a very important immunologic organ, and the severity of systemic immunosuppression can be lessened by feeding the gut. Dr. Kudsk and others have performed a series of laboratory studies that have nicely elucidated a mechanistic explanation of how this occurs [32–34]. Enteral nutrition supports the function of the mucosal-associated lymphoid tissue that produces 70% of the body's secretory immunoglobulin A [35]. Naive T and B cells target and enter the gut-associated lymphoid tissue, where they are sensitized to antigens sampled from intraluminal content making them more responsive to potential pathogens in the external environment. These stimulated T and B cells then migrate via mesenteric lymph nodes and the thoracic duct into systemic circulation demonstrating how GALT and MALT contribute to the immune system. Lack of enteral stimulation (i.e., the use of PN) causes a rapid and progressive decrease in T and B cells within gut-associated lymphoid tissue and simultaneous decrease in intestinal and respiratory immunoglobulin A levels [36]. Previously PN-fed laboratory animals, when challenged with pathogens via respiratory tree inoculation, succumb to overwhelming infections. These immunologic defects rendering the animal susceptible to infection are reversed within 3–5 days after initiating enteral nutrition [37–40].

As a result of these research observations, by the early 2000s, EEN had clearly become the gold standard for treating EGS patients if possible, but often times the gut cannot be utilized for various reasons: either patient is in discontinuity, prolonged ileus, lack of enteral access, high output proximal fistulas, etc. When EEN cannot be achieved, PN can be substituted to provide nutrient supplementation, but will not promote vital gut functions and thus prevent nosocomial infections. Future research should be directed at determining how adjuncts to PN could protect the gut.

12.1.3 Recommendation for Parenteral Nutrition (PN)

Achieving caloric goals with EEN can present a challenge, as often seen in postsurgical EGS patients [7, 41]. PN has shown benefit in providing supplemental calories in patients where gut dysfunction make it prohibitive to provide enteral nutrition or where caloric needs from EEN would not be met within a reasonable period of time. When to "reasonably" initiate PN has long been a controversy between the European Society of Parenteral and Enteral Nutrition (ESPEN) and North American nutritional societies (American Society for Parenteral and Enteral Nutrition (ASPEN)),

whereby ESPEN recommended early PN (after 2 days of not obtaining target nutrition) [42]. ASPEN, in contrast, recommended to wait for a week prior to initiating PN if the patient is not reaching target caloric goals [43].

Casaer et al. compared the two guidelines in the EPaNIC trial in which 2312 patients had early initiation of supplemental PN (within 48 h after ICU admission, the ESPEN approach) compared to 2328 patients with late initiation of PN (initiated day 8 after ICU admission, the ASPEN approach) to supplement insufficient EN. The overall outcomes were that the patients who received late PN were more likely to be discharged alive from the ICU and hospital, without evidence of decrease functional status, sustained lower infection morbidity, lower incidences of cholestasis, and modest cost savings [44].

Understanding the literature is paramount before prescribing early PN, but even after reviewing the EPaNIC trial, there are patients where early PN is beneficial or, at least, equivalent to EN when observing mortality risk. In a recent meta-analysis, Elke et al. suggest that in the critically ill patients population where use of "EN as compared to PN had no effect on overall mortality, but EN still remains to have less infectious morbidity and ICU length of stay" [45]. Harvey et al. go on to proclaim that if the patient is determined to be at high risk for malnutrition (based off various nutritional risk calculators: NUTRIC score), the current literature suggests that PN, and even supplemental PN, is equivalent to EN in primary outcomes of mortality and infectious morbidity [46–48]. This benefit, however, may be lost in lower risk patients but remains an interesting concept in treating our EGS patients who have contraindication to providing EN. Still, guidelines and gold standard care stipulate early enteral nutrition when possible for providing supplemental nutrition to our critically ill patients [43].

12.1.4 The Role of Protein

There are no specific recommendations for optimal protein dosing in EGS patients who are at high risk for PICS. Recent evidence suggests that protein is the most important component of nutrition support in critically ill ICU patients and that the old recommendation of providing >1.2 g/kg/day is insufficient to promote anabolism [43, 49–52]. While there are no specific data related to PICS patients, there are data in other patient populations who experience similar persistent catabolism recommend considerably higher amounts of protein.

Delano and Moldawer demonstrated that cancer cachexia patients experience remarkably similar alterations in metabolism as compared to PICS patients and suggest that what works in cancer cachexia should be applicable to PICS. Cancer guidelines recommend at least 1.2–2.0 g protein/kg/day [53, 54]. Aging sarcopenia is another example where muscle wasting is linked to a chronically inflamed, catabolic state inducing a cachexia-like phenotype. Here the evidenced-based recommendations are to provide at least 1.5 g protein/kg/day [55]. Similarly, among burn patients, "the hyper metabolic response to major burn injury is associated with increased energy expenditure, insulin resistance, immunodeficiency, and whole

body catabolism that persists for months after injury" [56]. Alexander et al. demonstrated improved survival and even less bacteremia in burn children who received early aggressive high-protein nutritional support [57]. Thus, Herndon et al. make a recommendation that protein requirements for the burn patient double to 2.0 g/kg/day to compensate for the catabolic insult these patients are challenged with. This recommendation was based on the observation that amino acid oxidation in burn patients is twice that of normal healthy controls [58]. Of note, both American Burn Association (ABA) guidelines and ESPEN recommended the provision of 1.5–2 g/kg of protein for patients with burn injury [59, 60]. The questions remains: How much protein is enough for EGS patients either in the acute or chronic phase of their critical illness?

Studies have shown clear benefit to protein calories over nonprotein supplements in the critically ill population, which likely represents most of the EGS postoperative patients. Weijs et al. showed that early high-protein delivery had survival benefit, yet energy overfeeding was linked to increased mortality [51, 61]. Allingstrup echoed Weijs findings, adding that incremental higher provision of protein (>1.46 g/kg/day vs 1.06 or 0.79 g/kg/day) was associated with a lower mortality [62]. Compher et al. showed that increased protein delivery had a significant survival benefit in nutritionally high-risk (score >5) patients based off the Nutrition Risk in the Critically Ill (NUTRIC). Compher concluded that greater nutritional and protein intake is associated with lower mortality and faster time to discharge alive in the high-risk, longer stay patients but not true for low-risk patients (NUTRIC score <3) [63]. Moreover, in 2013 Wolfe and Deutz et al. described an "anabolic response" where higher protein supplementation suppresses catabolism. The anabolic response was a measure of fractional synthetic rate (FSR) minus the protein breakdown and was even more positive with higher amounts of protein provided [64]. This has inordinate implications for our EGS patients to combat catabolism and potentially feed them with increasing doses of protein.

12.1.5 Adjuncts to Protect the Gut

12.1.5.1 Probiotics, Prebiotics, and Synbiotics

The microbiome has proven to be a very complex entity that is not yet fully understood in how it clinically impacts patients care, but it is safe to say that dysbiosis can lead to a host of complications. In fact, the gut microbiome has recently become heavily researched in various pathologic states, and the role of pro, pre, and synbiotics has increasingly shown benefits such as protecting intestinal barrier and modulation of host inflammatory response [65–67]. Alverdy et al. even demonstrated that intraluminal gut acidosis and phosphate depletion promotes ileus and renders normally symbiotic bacteria virulent in critically ill patients [26–30]. As an example, after I/R from shock, normally symbiotic organisms can turn against the host and infect them. This has broad implications for the EGS patients as the application of pre, pro, and symbiotic supplements can restore balance to an otherwise threatened microenvironment.

A probiotic is defined as a live, microorganism-fed supplement that improves the host's intestinal microbial balance. Among these bacteria are lactobacilli,

bifidobacteria, and saccharomyces. Prebiotics are defined as a nondigestible food ingredient that beneficially affects microbiota in the host by selectively stimulating the growth in the colon such as the nondigestible oligosaccharide, fructooligosaccharides (FOS). The colon will ferment FOS into short-chain fatty acids providing nutrition to colonocytes and promoting the growth of bifidobacteria, which reduces the colonization of virulent bacteria such as staphylococcus, clostridia, and fusobacteria [68–70]. Synbiotics are a combination of pro- and prebiotics, and the combination is thought to improve the survival of the probiotics by having a specific substrate readily available for fermentation, a fuel source for the probiotics once they reach the colon.

Manipulation of the colonic microbiome can also reduce the incidence of enteral nutrition and antibiotic-associated diarrhea by promoting water and electrolytes uptake, improving tight junctions, and suppressing enteropathogens [67, 71]. A report on trauma patients, who were provided symbiotic supplementation, even had decreased intestinal permeability, as well as lower combined infection rates compared to those receiving other immune-modulating formulas. The authors hypothesized that the presence of synbiotics in the GI tract reduced pathogenic flora, thereby decreasing the incidence of pneumonia [72]. Since then a subsequence blinded study confirmed the beneficial effects of prophylactic probiotics on reducing incidence of ventilator-associated pneumonia in mechanically ventilated patients [73]. Nevertheless, maintaining symbiosis and, at the very least, reducing dysbiosis have emerged as a potent therapy for the EGS patients who often times endure broad-spectrum antibiotics, multiple abdominal operations, long ICU stays, and profound physiologic derangements.

12.1.6 Adjunct Therapies

12.1.6.1 Resolve Inflammation: Specialized Pro-resolving Mediators (SPMs)

Specialized pro-resolving mediators (SPMs) are omega 3 polyunsaturated fatty acids (PUFAs) that not only decrease inflammation by cessation of leukocyte infiltration or activation, but "pro-resolve" inflammation by stimulating macrophages to clear debris, bacteria, and apoptotic cells [74, 75]. Champion of SPMs, Dr. Serhan, has shown that they attenuate efferocytosis (clearing of cellular debris) of macrophages to eliminate the source of inflammation through class shifting of M1 to M2 phenotypes of macrophages. Simplified for this discussion, SPMs are endogenous molecules derived from omega 3 PUFAs and resolve inflammations with the hosts own endogenous pathways without causing immunosuppression [75].

While the data specific for EGS, CCI, and PICS patients are yet to be determined, all these patients have one thing in common, inflammation. SPMs used to promote resolution of the irregular inflammatory cascade can hopefully restore homeostasis sooner for patients plagued with critical illness. Additionally, by resolving the persistent inflammation, SPMs will decrease the amount of energy consumed by the catabolic demand of the acute or chronic pathophysiologic state. Not only would the clinical ramifications of reducing inflammation in the EGS and CCI patients be

welcomed, but the impact of the financial burden on society would be realized, as well.

Kahn and Iwashyna et al. estimated that 5–7.6% of patients admitted to the ICU develop CCI, accounting for more than 380,000 cases, 107,000 inhospital deaths, and over $26 billion in healthcare expenses [76, 77]. Iwashyna also demonstrated that despite CCI accounting for only 5% of ICU admissions, CCI patients utilize over 30% of ICU resources [78]. Both authors report that these patients are less likely to be discharged home and have higher inpatient mortality [76, 78].

Ultimately, the dysregulated immunologic response to inflammation (polytrauma and burn) was established by the NIH-supported study: Inflammation and Host Response to Injury or the "Trauma Glue Grant." In this multicenter project, they demonstrated that an aberrant "cytokine and genomic storm" was driven by the innate immune system within the first 24 h and can be highly predictive of multiple organ failure or death by 14 days after injury [79]. The ability for these patients to resolve their cytokine storm was then classified into complicated versus uncomplicated recovery. One attempt to explain this discrepancy between the cohorts was a secondary, post hoc analysis of the Glue Grant Data. They speculated that those who had "uncomplicated recovery" produced higher levels of pro-resolving mediators and lower levels of leukotrienes based off upregulated genes responsible for the biochemical conversions of DHA and EPA to resolvins. The conclusions were "that trauma patients with complicated courses and worse clinical outcomes have higher expression ratios of leukotriene pathway (pro-inflammatory) compared to resolvin pathway (pro-resolution/anti-inflammatory)" [80]. Although this study included trauma and burn patients, ACS can extrapolate this data and apply it to the EGS patients.

More recently, understanding developed that the initial genomic response to the insult of polytrauma is very similar to the onset of sepsis [81]. For those patients who endure large inflammatory insults, it is not a far reach to hypothesize that those who do not resolve the "cytokine storm"/have complicated clinical course do not have enough resolvins? Thus, if the host response to major insult is equitable, the conclusions of the Glue Grant study above, we should be able to be apply them to sepsis is our EGS patients. Dalli et al. produced a lipid profile for 22 septic medical ICU patients, comparing 9 non-survivors to 13 survivors concluding that although SPMs were found in non-survivors, they did not have high enough concentrations to resolve their robust septic event [82]. Finally, in a very germane review, Levy et al. concluded that resolvins not only have pro-resolving inflammatory capabilities but also anti-infective protection. Patients clear bacteremia, viremia, and fungemia quicker with higher concentrations of resolvins. In a systemic response, these molecules helped decrease the dysregulated inflammation through an immunologic mechanism, as well as clear infections quicker promoting catabasis [83].

12.1.6.2 Reduce Immunosuppression: Arginine

Arginine is a semi-essential amino acid with not only immune-modulating properties but also promotes wound healing [84–86]. Immune enhancing, enteral diets fortified with arginine have convincingly been shown to be beneficial in surgical

patients undergoing major operations at high risk for MOF [87–89]. Although, ACS do not typically have the luxury of preoperative optimization, arginine can still be useful in the postoperative period. This conditional amino acid is severely deficient in septic states, but caution must be discussed as there is controversy in using arginine in septic patients [90]. This controversy stems from arginine serving as a substrate for nitric oxide (NO) production causing vasodilation. Some speculate that during a vaso-deplete state (severe sepsis/septic shock), arginine can cause unresponsive, decompensated shock. Though this has never been tested, the ramification has unfortunately raised enough concern that most intensivists do not prescribe this amino acid during sepsis. Additionally, the ASPEN/SCCM 2016 guidelines recommend against routine supplementation of arginine containing immune nutrition in septic patients; however, arginine along with fish oil has been shown to be beneficial in pre- and postsurgical patients [87, 91].

Luiking et al., however, showed in an underpowered study of critically ill septic patients that parenteral arginine did not alter mean arterial pressure, reiterating that again this controversy is unfounded. She took eight critically ill patients with a diagnosis of septic shock and infused varying doses of L-Arginine-HCl in three incremental doses (33, 66, and 99 $\mu mol \cdot kg^{-1} \cdot h^{-1}$). Her conclusions were that "septic patients demonstrated elevated protein breakdown at baseline ($P < 0.001$ compared with healthy controls), whereas protein breakdown decreased during arginine infusion ($P < 0.0001$). Mean arterial pressure, mean pulmonary pressure and regional gastric mucosal carbon dioxide ($PrCO_2$—measured by tonometry) did not change during arginine infusion ($P > 0.05$), whereas stroke volume (SV) increased ($P < 0.05$) and arterial lactate decreased ($P < 0.05$)" [92]. Thus, Luiking showed that supraphysiologic doses of arginine not only decreased endogenous protein catabolism but also reversed septic shock (as reflected by increased SV and lactate clearance) without compromising systemic hemodynamics or gut mucosal perfusion [92].

Nonetheless, arginine serves as an intracellular substrate for NO production in macrophages to improve bactericidal activity, as well as improve T-cell function, proliferation, and maturation [84–86, 93–96]. Arginine depletion renders the zeta chain of the T-cell receptor (TCR) dysfunctional and causing T cells incompetent [94, 97–103]. Arginine depletion also promotes immunosuppressed through yet another mechanism, T-lymphocyte expansion, and, more importantly, circulating CD-4 cells are stunted, which are paramount for fighting infection. Arginine depletion thus culminates in decreased T-cell expansion and TCR dysfunction resulting in multifactorial immune incompetence contributing to an increased risk of nosocomial infections in critically ill and PICS patients [94, 104, 105].

Another contributor to immunologic disturbance after critical illness and arginine deficiency is the expansion of immature, immunosuppressive leukocytes known as myeloid derived suppressor cells (MDSCs). These cells are released from the bone marrow into the circulation during times of stress and elaborate pro-inflammatory cytokines, potentiate acute cachexia, serve relatively no immunologic function, and express high levels of arginase-1 [101, 106–113]. Arginase-1 enzymatically reduces

circulating arginine levels, thus making severe stress and critical illness an arginine deficient state [90, 93, 101, 114–117]. Arginine supplementation, therefore, becomes an attractive therapeutic option in EGS and CCI/PICS patients.

12.1.6.3 Improved Catabolism: Leucine

Leucine is another amino acid with interesting potential. It is a branched chain amino acid that stimulates anabolism through the mammalian target of rapamycin (mTOR) signaling pathway in septic rat model. After sepsis, however, in humans, mTOR is downregulated and becomes relatively inactive to leucine [118, 119]. It is not well understood how long this persists and whether there would be benefit in the chronic phase of MOD seen in CCI/PICS to reduce the catabolic nature of these patients. Thus, in this setting leucine supplementation could potentially be used to help dampen, and even reverse, the catabolic state [120, 121].

Stimulating the mTOR pathway increases protein synthesis and inhibits proteosomal protein breakdown. Leucine stimulates multiple enzymes that ultimately increase either mRNA to induce anabolism (protein synthesis). These include ribosomal protein S6 kinase, S6K1, and eukaryotic initiation factor 4E-binding protein, 4E-BP1 [122, 123]. The end goal is that leucine simulates mTOR to promote hypertrophic muscle growth. It is well known that critically ill patients loose lean muscle mass at an accelerated rate [124–129]. PICS patients persist in this catabolic state indefinitely, unable to rebuild muscle mass even with adequate caloric intake. In fact, this unique patient population suffers greatly for catabolism, and it is this pathologic state that leucine supplementation would provide the most benefit. Through mTOR signaling, PICS patient would hopefully reduce catabolism and enter an anabolic state to regain muscle mass, increase the possibility of rehab, and regain baseline function/independence once discharged from the ICU.

12.2 Conclusion

The role of supplemental nutrition in EGS patients is paramount for ACS to understand. No longer is nutrition just providing calories, but as this chapter has outlined can be used to modulate the profound and persistent inflammatory, immunosuppressive, and catabolic response these patients endure. Nutrition can drastically alter clinical courses and have lasting ramifications. Through both nutritional and non-nutritional value, EN provides substantial benefit. Though the recommendations clearly are in favor for EN to be initiated early, PN has shed most of the stigma from early generations. PN formula has evolved and is no longer quite as toxic as before but still has negative effects on the immune system and microbiome. Providing PN can be beneficial if provided to the right patient population: high-risk patient that can't be fed enterally. The horizon of critical care nutrition is ever-changing, and in the near future, modulation through microbiome manipulation could prove to be a great tool in the armamentarium of improving outcomes in the critically ill, EGS patient population.

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13 Intra-Abdominal Hypertension, Abdominal Compartment Syndrome and the Open Abdomen: Looking Beyond the Obvious to New Understandings in Pathophysiology, Harm-Reduction and Systemic Therapies

Andrew W. Kirkpatrick, Derek J. Roberts, and Federicco Coccolini

13.1 Introduction

The abdominal organs are subject to marked functional changes due to alterations in both physical pressure and perfusion due to the nature of the viscera themselves, the tendency for inflammatory fluid to accumulate within this container, and even physical changes in the container and contiguous body cavities [1–4]. The normal relaxed supine pressure within the peritoneal cavity, intra-abdominal pressure (IAP), is under 10 mmHg [5], with 12 mmHg being defined as the beginning range of IAH [6]. Many processes will increase the physical contents of the abdominal cavity such as ileus or obstruction of the hollow viscera or the accumulation of intraperitoneal fluids such as inflammatory ascites, enteric leakage, and/or hematoma. Finally, the container itself can be rendered non-compliant due to inflammation and resuscitation of the abdominal wall itself [7]. Ultimately when the abdominal contents are increased and especially if the abdominal compliance is decreased, the IAP will rise sometimes markedly [4, 8].

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Table 13.1 Gradation of IAH as defined by the World Society of the Abdominal Compartment Syndrome

IAH is graded as follows:
Grade I, IAP 12–15 mmHg
Grade II, IAP 16–20 mmHg
Grade III, IAP 21–25 mmHg
Grade IV, IAP >25 mmHg

Thus, in any critical situation, IAH is common and associated with significant morbidity and mortality in critically ill and injured patients [1, 8]. IAH can be somewhat simply equated with malperfusion. The abdominal compartment syndrome (ACS) represents the end of a pathophysiologic spectrum beginning with normal intra-abdominal pressure (IAP) and proceeding through worsening grades of IAH [6]. By consensus, grades of progressive IAH are given as I–IV (Table 13.1) [6, 9]. We prefer the term "overt ACS" to describe a catastrophically ill/injured patient with severe IAH and new-onset cardiorespiratory and/or renal failure. The effects of IAH/ACS are not limited to intra-abdominal organs; they are enacted systemically through biomediator generation resulting in multiorgan dysfunction syndrome/multisystem organ failure and/or through polycompartmental pressure interactions [2, 6, 10].

13.1.1 Consensus Definitions of the World Society of the Abdominal Compartment Syndrome

Early barriers to studying and thus understanding the IAH/ACS phenomenon related to variable definitions and concepts in the world literature frequently preclude comparison of data and experience. A notable milestone in defining and subsequently studying IAH/ACS was the establishment of the World Society of the Abdominal Compartment Syndrome (wsacs.org) in 2004 to "promote research, foster education, and improve the survival of patients with IAH and ACS" [9, 11]. This group published expert consensus definitions relating to IAH/ACS in 2006 [9], clinical practice guidelines in 2007 [11], and recommendations for research methodology in 2009 [12]. In 2013, they updated their consensus definitions (Table 13.2) and clinical practice guidelines (Table 13.3) [6]. In these guidelines, a dedicated pediatric subcommittee evaluated the adult definitions for use among children [6]. The subcommittee set the value used to define IAH and ACS in children lower as physiologic IAP values in these patients are lower than in adults [6, 13, 14]. This highlights that alternate definitions and management strategies may be needed for other patient populations, including pregnant women [15], those with obesity [16] or undergoing complex abdominal wall reconstruction [17], and the elderly, which are areas requiring future research.

In an effort to maintain vigilance in preventing ACS, while emphasizing the need to better understand IAH and its relationship to abdominal wall physiology [2, 18], the group was rebranded as the "WSACS—The Abdominal Compartment Society"

Table 13.2 Final 2013 consensus definitions of the World Society of the Abdominal Compartment Syndrome

No.	Definition
Retained definitions from the original 2006 consensus statements [13]	
1.	IAP is the steady-state pressure concealed within the abdominal cavity
2.	The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline
3.	IAP should be expressed in mmHg and measured at end-expiration in the supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line
4.	IAP is approximately 5–7 mmHg in critically ill adults
5.	IAH is defined by a sustained or repeated pathological elevation in IAP ≥12 mmHg
6.	ACS is defined as a sustained IAP >20 mmHg (with or without an APP <60 mmHg) that is associated with new organ dysfunction/failure
7.	IAH is graded as follows:
	Grade I, IAP 12–15 mmHg
	Grade II, IAP 16–20 mmHg
	Grade III, IAP 21–25 mmHg
	Grade IV, IAP >25 mmHg
8.	Primary IAH or ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention
9.	Secondary IAH or ACS refers to conditions that do not originate from the abdominopelvic region
10.	Recurrent IAH or ACS refers to the condition in which IAH or ACS redevelops following previous surgical or medical treatment of primary or secondary IAH or ACS
11.	APP = MAP − IAP
New definitions accepted by the 2013 consensus panel	
12.	A polycompartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures
13.	Abdominal compliance is a measure of the ease of abdominal expansion, which is determined by the elasticity of the abdominal wall and diaphragm. It should be expressed as the change in intra-abdominal volume per change in IAP
14.	The open abdomen is one that requires a temporary abdominal closure due to the skin and fascia not being closed after laparotomy
15.	Lateralization of the abdominal wall is the phenomenon where the musculature and fascia of the abdominal wall, most exemplified by the rectus abdominis muscles and their enveloping fascia, move laterally away from the midline with time

ACS abdominal compartment syndrome, *APP* abdominal perfusion pressure, *IAH* intra-abdominal hypertension, *IAP* intra-abdominal pressure, *MAP* mean arterial pressure
Reproduced from Kirkpatrick et al. [6]

in 2015 [19]. The mission of the Society was broadened to maintain the need to understand the optimal treatment of overt ACS but even more importantly to study IAH in all manner of its acute and chronic forms as an independent and a multifactorial condition in human disease and injury. Further in 2016, the WSACS collaborated closely with the World Society of Emergency Surgery to review contemporary data and to produce consensus guidance statements for OA management that are congruent and follow upon the WSACS/ACS guidelines for IAH/ACS management [20, 21] (Table 13.4).

Table 13.3 Summarized consensus statement of the World Society of the Abdominal Compartment Syndrome

Recommendations
1. We recommend measuring IAP when any known risk factor for IAH/ACS is present in a critically ill or injured patient [GRADE 1C]
2. Studies should adopt the trans-bladder technique as the standard IAP measurement technique [not GRADED]
3. We recommend the use of protocolized monitoring and management of IAP versus not [GRADE 1C]
4. We recommend efforts and/or protocols to avoid sustained IAH as compared to inattention to IAP among critically ill or injured patients [GRADE 1C]
5. We recommend decompressive laparotomy in cases of overt ACS compared to strategies that do not use decompressive laparotomy in critically ill adults with ACS [GRADE 1D]
6. We recommend that among ICU patients with open abdominal wounds, conscious and/or protocolized efforts be made to obtain an early or at least same-hospital-stay abdominal fascial closure [GRADE 1D]
7. We recommend that among critically ill/injured patients with open abdominal wounds, strategies utilizing negative pressure wound therapy should be used versus not [GRADE 1C]
Suggestions
1. We suggest that clinicians ensure that critically ill or injured patients receive optimal pain and anxiety relief [GRADE 2D]
2. We suggest brief trials of neuromuscular blockade as a temporizing measure in the treatment of IAH/ACS [GRADE 2D]
3. We suggest that the potential contribution of body position to elevated IAP be considered among patients with, or at risk of, IAH or ACS [GRADE 2D]
4. We suggest the liberal use of enteral decompression with nasogastric or rectal tubes when the stomach and colon are dilated in the presence of IAH/ACS [GRADE 1D]
5. We suggest that neostigmine be used for the treatment of established colonic ileus not responding to other simple measures and associated with IAH [GRADE 2D]
6. We suggest using a protocol to try and avoid a positive cumulative fluid balance in the critically ill or injured patient with, or at risk of, IAH/ACS after the acute resuscitation has been completed and the inciting issues have been addressed [GRADE 2C]
7. We suggest the use of an enhanced ratio of plasma/packed red blood cells for resuscitation of massive hemorrhage versus low or no attention to plasma/packed red blood cell ratios [GRADE 2D]
8. We suggest the use of PCD to remove fluid (in the setting of obvious intraperitoneal fluid) in those with IAH/ACS when this is technically possible compared to doing nothing [GRADE 2C]. We also suggest using PCD to remove fluid (in the setting of obvious intraperitoneal fluid) in those with IAH/ACS when this is technically possible compared to immediate decompressive laparotomy as this may alleviate the need for decompressive laparotomy [GRADE 2D]
9. We suggest that patients undergoing laparotomy for trauma suffering from physiologic exhaustion be treated with the prophylactic use of the open abdomen versus intraoperative abdominal fascial closure and expectant IAP management [GRADE 2D]
10. We suggest not to routinely utilize the open abdomen for patients with severe intraperitoneal contamination undergoing emergency laparotomy for intra-abdominal sepsis unless IAH is a specific concern [GRADE 2B]
11. We suggest that bioprosthetic meshes should not be routinely used in the early closure of the open abdomen compared to alternative strategies [GRADE 2D]
No recommendations
1. We could make no recommendation regarding the use of abdominal perfusion pressure in the resuscitation or management of the critically ill or injured

Table 13.3 (continued)

2. We could make no recommendation regarding the use of diuretics to mobilize fluids in hemodynamically stable patients with IAH after the acute resuscitation has been completed and the inciting issues have been addressed
3. We could make no recommendation regarding the use of renal replacement therapies to mobilize fluid in hemodynamically stable patients with IAH after the acute resuscitation has been completed and the inciting issues have been addressed
4. We could make no recommendation regarding the administration of albumin versus not to mobilize fluid in hemodynamically stable patients with IAH after acute resuscitation has been completed and the inciting issues have been addressed
5. We could make no recommendation regarding the prophylactic use of the open abdomen in non-trauma acute care surgery patients with physiologic exhaustion versus intraoperative abdominal fascial closure and expectant IAP management
6. We could make no recommendation regarding the use of an acute component separation technique versus not to facilitate earlier abdominal fascial closure, *ACS* abdominal compartment syndrome, *IAP* intra-abdominal pressure, *IAH* intra-abdominal hypertension, *PCD* percutaneous catheter drainage

Reproduced from Kirkpatrick et al. [6]

Table 13.4 Summary of management statements from the World Society of Emergency Surgery on Open Abdomen Management

	Statements
Indications	
Trauma patients	Persistent hypotension, acidosis (pH <7.2), hypothermia (temperature <34 °C), and coagulopathy are strong predictors of the need for abbreviated laparotomy and open abdomen in trauma patients (Grade 2A)
	Risk factors for abdominal compartment syndrome such as damage control surgery, injuries requiring packing and planned reoperation, extreme visceral or retroperitoneal swelling, obesity, elevated bladder pressure when abdominal closure is attempted, abdominal wall tissue loss, and aggressive resuscitation are predictors of the necessity for open abdomen in trauma patients (Grade 2B)
	Decompressive laparotomy is indicated in abdominal compartment syndrome if medical treatment has failed after repeated and reliable IAP measurements (Grade 2B)
	The inability to definitively control the source of contamination or the necessity to evaluate the bowel perfusion may be an indicator to leave the abdomen open in post-traumatic bowel injuries (Grade 2B)
Non-trauma patients	Decompressive laparotomy is indicated in abdominal compartment syndrome if medical treatment has failed after repeated and reliable IAP measurements (Grade 2B)
Peritonitis	The open abdomen is an option for emergency surgery patients with severe peritonitis and severe sepsis/septic shock under the following circumstances: abbreviated laparotomy due to the severe physiological derangement, the need for a deferred intestinal anastomosis, a planned second look for intestinal ischemia, persistent source of peritonitis (failure of source control), or extensive visceral edema with the concern for development of abdominal compartment syndrome (Grade 2C)

(continued)

Table 13.4 (continued)

	Statements
Vascular emergencies	The open abdomen should be considered following management of hemorrhagic vascular catastrophes such as ruptured abdominal aortic aneurysm (Grade 1C)
	The open abdomen should be considered following surgical management of acute mesenteric ischemic insults (Grade 2C)
Pancreatitis	In patients with severe acute pancreatitis unresponsive to step-up conservative management surgical decompression and open abdomen are effective in treating abdominal compartment syndrome (Grade 2C)
	Leaving the abdomen open after surgical necrosectomy for infected pancreatic necrosis is not recommended except in those situations with high risk factors to develop abdominal compartment syndrome (Grade 1C)
Management	
Trauma and non-trauma patients	The role of damage control resuscitation in OA management is fundamental and may influence outcome (Grade 2A)
ICU management	A multidisciplinary approach is encouraged, especially during the patient's ICU admission (Grade 2A)
	Intra-abdominal pressure measurement is essential in critically ill patients at risk for IAH/ACS (Grade 1B)
	Physiologic optimization is one of the determinants of early abdominal closure (Grade 2A)
	Inotropes and vasopressors administration should be tailored according to patient condition and performed surgical interventions (Grade 1A)
	Fluid balance should be carefully scrutinized (Grade 2A)
	High attention to body temperature should be given, avoiding hypothermia (Grade 2A)
	In the presence of coagulopathy or high risk of bleeding, the negative pressure should be downregulated balancing the therapeutic necessity of negative pressure and the hemorrhage risk (Grade 2B)
Technique for temporary abdominal closure	Negative pressure wound therapy with continuous fascial traction should be suggested as the preferred technique for temporary abdominal closure (Grade 2B)
	Temporary abdominal closure without negative pressure (e.g., Bogota bag) can be applied in low-resource settings accepting a lower delayed fascial closure rate and higher intestinal fistula rate (Grade 2A)
	No definitive recommendations can be given about temporary abdominal closure with NPWT in combination with fluid instillation even if it seems to improve results in trauma patients (not graded)
Re-exploration before definitive closure	Open abdomen re-exploration should be conducted no later than 24–48 h after the index and any subsequent operation, with the duration from the previous operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (Grade 1C)
	The abdomen should be maintained open if requirements for ongoing resuscitation and/or the source of contamination persists, if a deferred intestinal anastomosis is needed, if there is the necessity for a planned second look for ischemic intestine, and lastly if there are concerns about abdominal compartment syndrome development (Grade 2B)

Table 13.4 (continued)

	Statements
Nutritional support	Open abdomen patients are in a hypermetabolic condition; immediate and adequate nutritional support is mandatory (Grade 1C)
	Open abdomen techniques result in a significant nitrogen loss that must be replaced with a balanced nutrition regimen (Grade 1C)
	Early enteral nutrition should be started as soon as possible in the presence of viable and functional gastrointestinal tract (Grade 1C)
	Enteral nutrition should be delayed in patients with an intestinal tract in discontinuity (temporarily stapled stumps) or in situations of a high-output fistula with no possibility to obtain feeding access distal to the fistula or with signs of intestinal obstruction (Grade 2C)
	Oral feeding is not contraindicated and should be used where possible (Grade 2C)
Patient mobilization	To date, no recommendations can be made about early mobilization of patients with open abdomen (not graded)
Definitive closure	
Trauma and non-trauma patients	Fascia and/or abdomen should be definitively closed as soon as possible (Grade 1C)
Open abdomen definitive closure	Early fascial and/or abdominal definitive closure should be the strategy for management of the open abdomen once any requirements for ongoing resuscitation have ceased, the source control has been definitively reached, no concern regarding intestinal viability persists, no further surgical re-exploration is needed, and there are no concerns for abdominal compartment syndrome (Grade 1B)
Non-mesh-mediated techniques	Primary fascia closure is the ideal solution to restore the abdominal closure (2A)
	Component separation is an effective technique; however it should not be used for fascial temporary closure. It should be considered only for definitive closure (Grade 2C)
	Planned ventral hernia (skin graft or skin closure only) remains an option for the complicated open abdomen (i.e., in the presence of entero-atmospheric fistula or in cases with a protracted open abdomen due to underlying diseases) or in those settings where no other alternatives are viable (Grade 2C)
Mesh-mediated techniques	The use of synthetic mesh (polypropylene, polytetrafluoroethylene (PTFE), and polyester products) as a fascial bridge should not be recommended in definitive closure interventions after open abdomen and should be placed only in patients without other alternatives (Grade 1B)
	Biologic meshes are reliable for definitive abdominal wall reconstruction in the presence of a large wall defect, bacterial contamination, comorbidities, and difficult wound healing (Grade 2B)
	Non-cross-linked biologic meshes seem to be preferred in sublay position when the linea alba can be reconstructed (Grade 2B)
	Cross-linked biologic meshes in fascial-bridge position (no linea alba closure) maybe associated with less ventral hernia recurrence (Grade 2B)
	NPWT can be used in combination with biologic mesh to facilitate granulation and skin closure (Grade 2B)

(continued)

Table 13.4 (continued)

	Statements
Complications management	
Trauma and non-trauma patients	Preemptive measures to prevent entero-atmospheric fistula and frozen abdomen are imperative (i.e., early abdominal wall closure, bowel coverage with plastic sheets, the omentum or skin, no direct application of synthetic prosthesis over bowel loops, no direct application of NPWT on the viscera, and deep burying of intestinal anastomoses under bowel loops) (Grade 1C)
	Entero-atmospheric fistula management should be tailored according to patient conditions, fistula output, and position and anatomical features (Grade 1C)
	In the presence of entero-atmospheric fistula the caloric intake and protein demands are increased; the nitrogen balance should be evaluated and corrected and protein supplemented (Grade 1C)
	Nutrition should be reviewed and optimized upon recognition of entero-atmospheric fistula (Grade 1C)
	Entero-atmospheric fistula effluent isolation is essential for proper wound healing. Separating the wound into different compartments to facilitate the collection of fistula output is of paramount importance (Grade 2A)
	In the presence of entero-atmospheric fistula in open abdomen, negative pressure wound therapy makes effluent isolation feasible and wound healing achievable (Grade 2A)
	Definitive management of entero-atmospheric fistula should be delayed after the patient has recovered and the wound completely healed (Grade 1C)

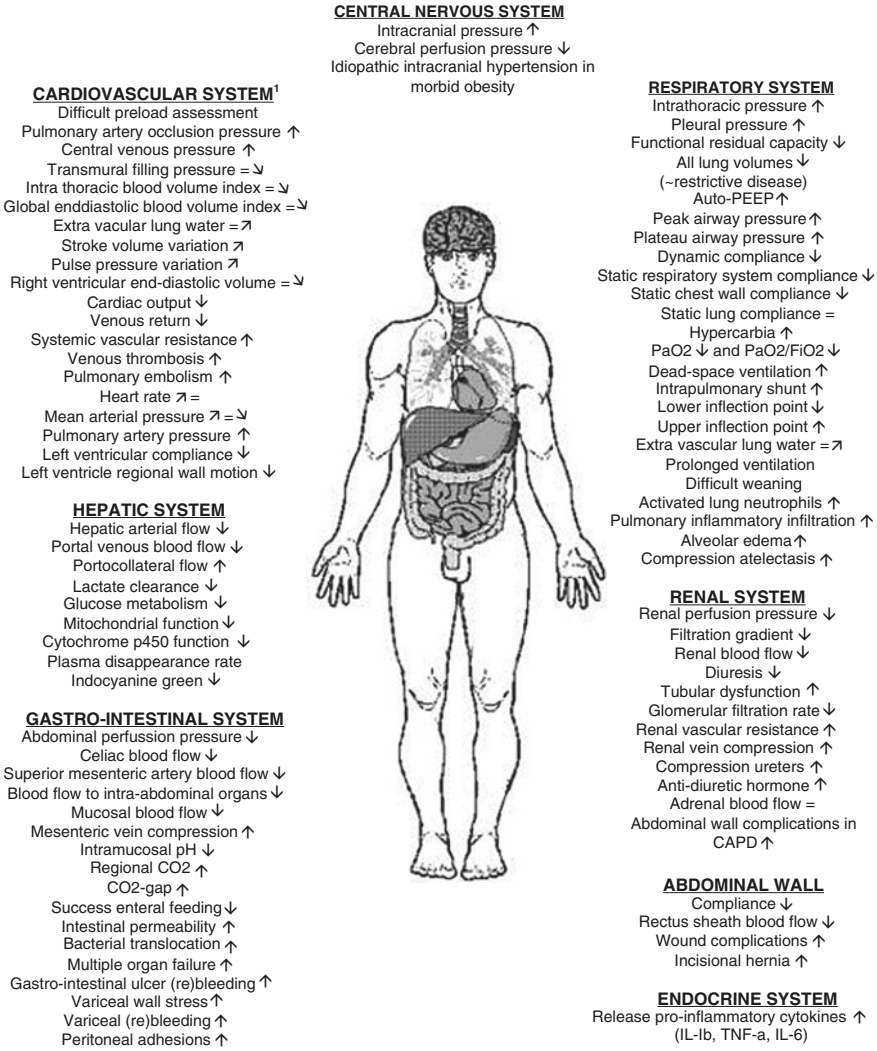
Reproduced from Coccolini et al. [20]

13.1.2 The Abdominal Compartment and Abdominal Compliance

The concept of abdominal compliance (AC) is critical to appreciate for emergency surgeons. Intra-abdominal pressure is the direct result of both the abdominal volume and the abdominal compliance [2, 4, 22]. The volume of the abdominal contents varies greatly with both physiological and pathophysiological conditions. The second paradigm-changing concept is the related appreciation that abdominal compliance is not fixed. Abdominal compliance is a dynamic property reflecting the underlying tissue properties and health of the abdominal wall, which also reflects the therapies administered to any patient in the inter- and perioperative periods [2, 4, 23].

13.1.3 Pathophysiology

Although centered upon the abdominal cavity, the pathophysiology of IAH/ACS affects the entire body physically and biochemically (Fig. 13.1). Cardiac output is reduced owing to decreased preload and right heart volumes. Although increased systemic vascular resistance initially maintains apparent blood pressure, decreases in preload from the pooling of blood in splanchnic and lower extremity vascular beds eventually lead to reduced central venous return [24–28]. Cardiac



[1] Cardiovascular effects are exacerbated in case of hypovolemia, hemorrhage, ischemia and high PEEP ventilation

Fig. 13.1 Whole body effects of increased intra-abdominal pressure. Reproduced from Malbrain ML [41]

underfilling also occurs despite apparently increased central hemodynamic measurements (central venous pressure and pulmonary artery occlusion pressure).

A distended tight abdomen with IAH physically compresses the lungs especially at the bases created a restrictive lung disease model. As respiratory compliance decreases, mechanical ventilation with increased ventilatory pressures and decreased

volumes becomes difficult [25, 29, 30]. The partial pressures of oxygen will decrease, and carbon dioxide will increase [30, 31]. Even modest IAH appears to exacerbate acute lung injury and the acute respiratory distress syndrome (ARDS). When IAP levels greater than 20 mmHg are applied to critically ill animals, a dramatic exacerbation of ARDS-associated pulmonary edema is evident [30, 32]. Furthermore, elevated IAP results in a stiffer chest wall with much lower transpulmonary pressures and therefore less susceptibility to ventilator-induced lung injury [33, 34].

Oliguria is a common manifestation of the ACS, noting that the degree of renal failure has a dose-dependant relationship with IAH [35–37]. Further, these effects are exaggerated by hypovolemia and positive end-expiratory pressure [31, 38], and renal failure is often multifactorial in critical care settings. Blood flow to the kidney operates in series, with a high-pressure capillary bed in the glomerulus having a mean pressure of about 60 mmHg, although mean capillary pressure of the peritubular capillary system operates at a mean pressure of approximately 13 mmHg [39]. Such pressure and flow relationships make the kidney's very susceptible to IAH, and the renal recovery after decompression may be dramatic [40].

Beyond the heart, lungs, and kidneys, almost every other organ system is altered by IAH, even if the effects are not clinically overt. IAH appears to contribute to increased intracerebral pressure (ICP) via transmitted intrathoracic pressure [41, 42] to the extent that laparotomies have been reported to reduce ICP in patients with secondary ACS [43, 44]. Patients in shock are at a particularly high risk for splanchnic malperfusion because even modest elevations in IAP greatly reduce hepatic and splanchnic perfusion [45]. This effect is exacerbated by prior hemorrhage [46] and is observed at much lower IAPs than required to induce other clinical features of ACS.

13.1.4 Pathobiology of IAH/ACS

Owing to intra-compartment physiology, there is a marked reduction to all the viscera inducing relative or actual organ ischemia. This ischemia initiates the inflammatory cascade of vasoactive biomediators common to sepsis. The effects of IAH on the gut are similar to those of prolonged hypoperfusion, and therefore these two issues are compounding. In the face of IAH, the damaged gut seems to act as a continued source of inflammation propagating SIRS and potentiating MODS [47–49]. Even after resuscitation and normalization of hemodynamics, gut vasoconstriction persists and is further exacerbated by IAH. Even relatively mild IAH (e.g., an IAP of 15 mmHg) has been reported to decrease intestinal microcirculatory blood flow, increase bowel wall permeability, and induce irreversible gut histopathological changes, bacterial translocation, and multiorgan dysfunction syndrome [50–52]. Prolonged gut hypoperfusion can precipitate a severe inflammatory response due to mobilization of damage-associated molecular patterns (e.g., high mobility group box 1, heat shock proteins, s100 proteins, nucleic acids, and hyaluronan), proinflammatory cytokines, and other mediators [53]. Thus, IAH may help transition severe injury/infection to subsequent MODS.

This process itself may be exacerbated by series of physiologic stresses associated with prior priming of the immune system elements, such that IAH/ACS

will be potentiated due to sequential physiological "hits," which produce a self-perpetuating process termed the "acute intestinal distress syndrome" [54, 55]. In the first hit, resuscitation of patients in shock induces injury especially of the splanchnic circulation [50, 55, 56]. This "acute bowel injury" results in release of pro-inflammatory mediators into the peritoneum and systemic circulation, leading to neutrophil priming, increased intestinal wall permeability, extravasation of fluid into the bowel wall and mesentery, translocation of intestinal bacteria, and absorption of bacterial endotoxin [51, 57–60]. In any subsequent hit such as a severe infection or delayed bleeding requiring further resuscitation, the resultant abdominal visceral edema leads to further IAH, compressing intra-abdominal lymphatics and resulting in a progressive visceral malperfusion, mucosa-to-serosa intestinal necrosis, a further increase in bowel wall permeability, and heightened bacterial translocation/endotoxin absorption and release of pro-inflammatory mediators [51, 57]. Such a two-hit theory may explain why patients without a primary inciting cause of shock (e.g., during elective abdominal wall reconstruction) may sometimes tolerate IAH/ACS better than predicted [17, 61], if they do not suffer a secondary insult in the postoperative period.

13.1.5 Epidemiology of IAH/ACS in a Changing Playing Field

Although the incidence of IAH may have not changed substantially, that of overt postinjury ACS has markedly decreased presumably because of increased awareness and the use of prevention strategies [62–64]. These include damage control resuscitation and increasingly well-tolerated and effective methods of open abdominal management [62, 64]. Damage control resuscitation is a strategy characterized by rapid hemorrhage control, permissive hypotension, administration of blood products in a ratio approximating whole blood (i.e., 1:1:1 packed red blood cells/plasma/platelets), and minimization of crystalloid fluids [65]. Such balanced resuscitation practices appear to be one the most profound evolutions in critical care/trauma in the last several decades [66].

13.1.6 Diagnosis

A critical pitfall is assuming that IAH/ACS can be excluded clinically without measuring IAP. Clinical examination, however, is unfortunately insufficient for detecting raised IAP [67, 68]. The current gold standard technique for diagnosis uses the urinary bladder for pressure transduction [6]. It is recommended that patients be supine with relaxed abdominal musculature in the end-expiratory phase of respiration and the transducer zeroed at the iliac crest in the midaxillary line [6]. The requirement for supine positioning is often a logistical barrier to frequent measurements in the critically ill/injured and a potential liability regarding supine positioning. Thus, corrections that allow inference of the effective IAP without recumbency or understanding the implications of IAP measurement at the phlebostatic axis are attractive, but not yet widely implemented [69–71].

13.2 Management of IAH/ACS

The updated 2013 consensus management statements and management algorithm of the WSACS are outlined in Table 13.3 and Fig. 13.2, respectively [9]. These recommendations represent the best efforts of an International Collaboration led by the WSACS to update the previous definitions [9] and recommendations [11] based on scientific progress over a decade in studying IAH/ACS [72]. It is hoped that these guidelines will require frequent updating as new scientific evidence emerges from well-performed studies.

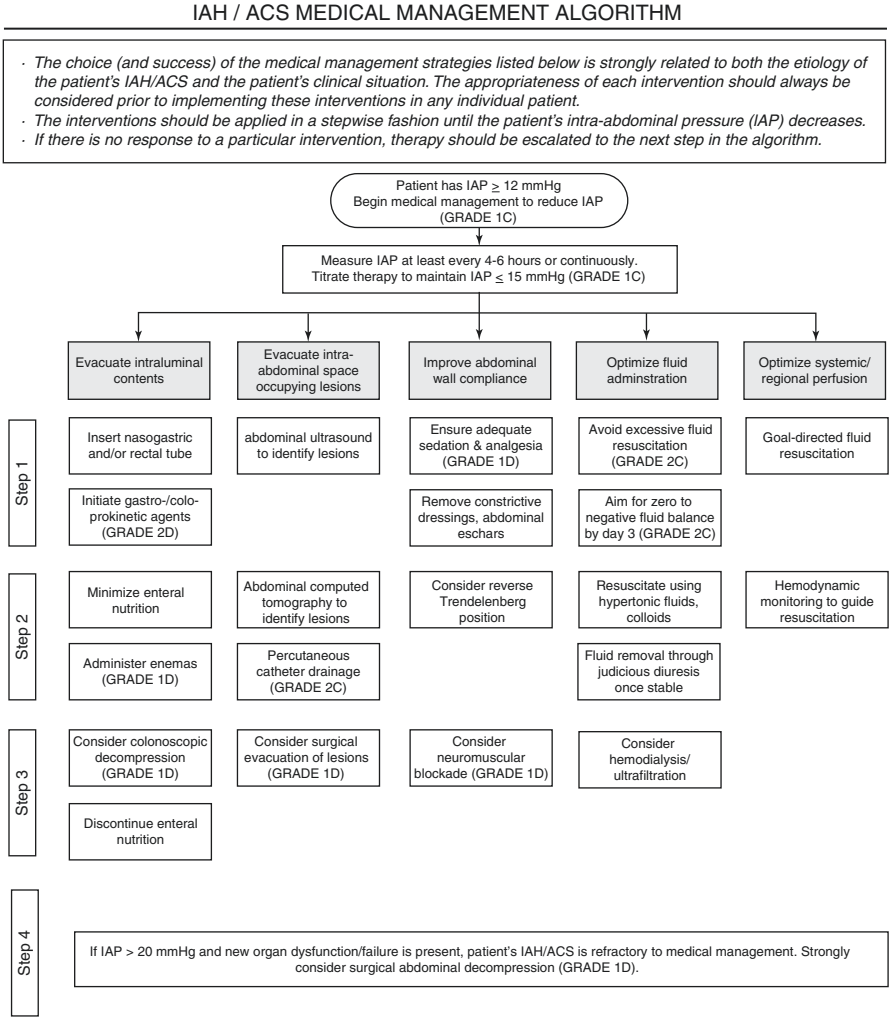


Fig. 13.2 Abdominal Compartment Society Intra-Abdominal Hypertension/Abdominal Compartment Syndrome Management Algorithm. Reproduced from Kirkpatrick et al. [6]

13.2.1 Medical and Percutaneous Management

Several medical and minimally invasive management options for IAH and ACS exist. Although many have not been well studied, these should be instituted prior to surgical intervention where safe and feasible. The WSACS medical management algorithm is outlined in Fig. 13.3 [3].

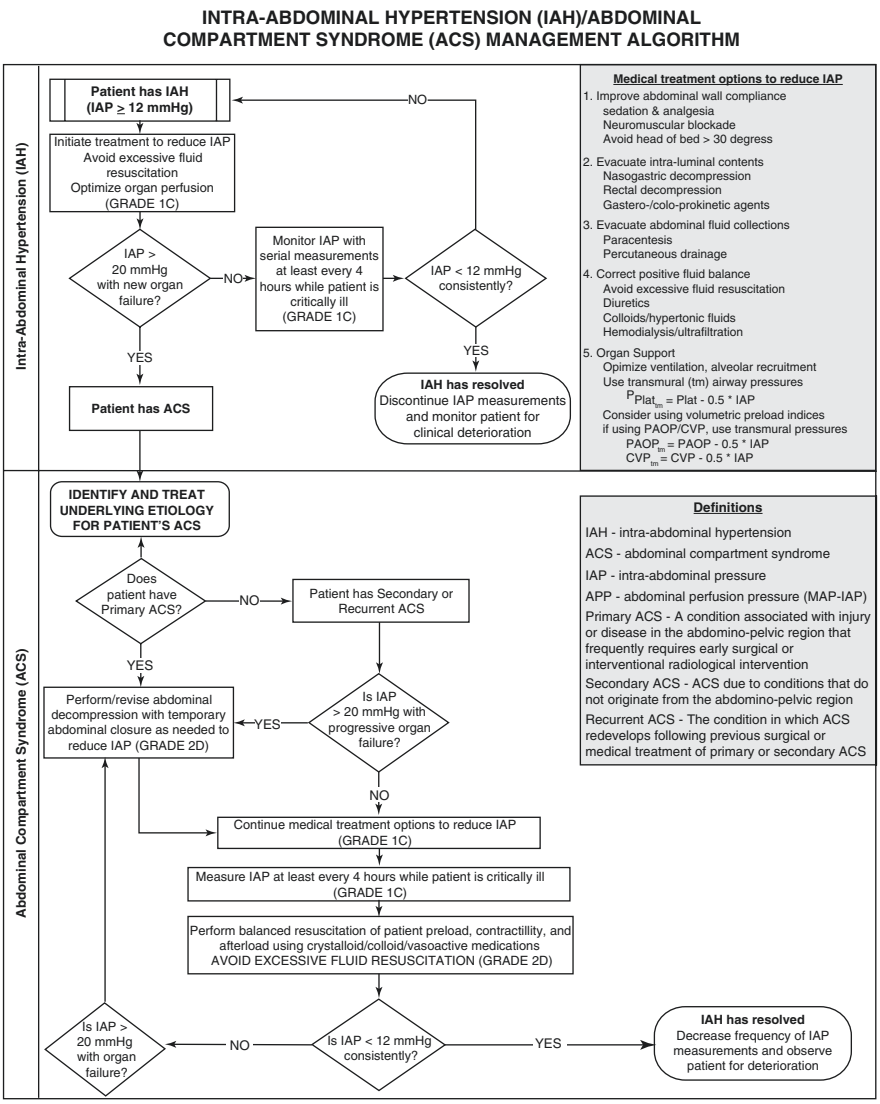


Fig. 13.3 Abdominal Compartment Society Intra-Abdominal Hypertension/Abdominal Compartment Syndrome Medical Management Algorithm. Reproduced from Kirkpatrick et al. [6]

Medical management strategies may be broadly divided into those that may increase abdominal wall compliance (sedation/analgesia and neuromuscular-blocking agents), evacuate gastrointestinal contents (nasogastric/rectal tubes and prokinetic agents), and decrease fluid balance [6]. As ileus and a positive fluid balance are significant and potentially modifiable risk factors for IAH in critically ill adults [73], decompressing enteral tubes should be used in patients with gastrointestinal tract distention, and a positive patient fluid balance should be avoided after the acute resuscitation phase has been completed [6]. Damage control resuscitation should be adopted in managing trauma patients with significant hemorrhage as it has been reported to be associated with a lower incidence of ACS and higher primary fascial closure (i.e., same-hospital-stay abdominal fascia-to-fascia closure) rates after damage control laparotomy when compared to traditional, crystalloid-focused resuscitation [74, 75]. Finally, although no studies have examined whether sedative or analgesic agents decrease IAP, neuromuscular-blocking agents are associated with a decrease in IAP and may be used in patients with ACS as a rescue treatment until another more definitive therapy can be performed [6, 76].

Percutaneous catheter drainage is a minimally invasive option suggested to decrease IAP in those with IAH/ACS [6, 77]. This intervention has been reported to effectively reduce IAP among patients with burns/acute pancreatitis and drainable closure rates after damage control laparotomy when compared to traditional, crystalloid-focused resuscitation [56, 57]. Percutaneous catheter drainage is a minimally invasive option suggested to decrease IAP in those with IAH/ACS [77, 78]. This intervention has been reported to effectively reduce IAP among patients with burns/acute pancreatitis and drainable intraperitoneal fluid collections. A case-control study of 62 patients with IAH/ACS and free intraperitoneal fluid or blood also reported that percutaneous catheter drainage was as effective as decompressive laparotomy at decreasing IAP and may avoid need for abdominal decompression in up to 81% of patients [79]. In this study, risk factors for percutaneous catheter drainage treatment failure included drainage of less than 1000 mL of fluid or a decrease in IAP of less than 9 mmHg in the first 4 h after catheter insertion [79, 80].

13.2.2 Surgical Management of IAH/ACS

Case reports/series have recently examined whether one of a number of different minimally invasive fasciotomy methods may be used instead of decompressive laparotomy in patients with largely secondary causes of ACS [77, 81, 82]. These studies have reported improvements in IAP and urine output [77]. Methods evaluated have included subcutaneous anterior rectus sheath fasciotomies, midline subcutaneous fasciotomy, bilateral subcutaneous anterior rectus abdominis muscle fasciotomy, subcutaneous or open linea alba fasciotomy, and midline subcutaneous fasciotomy [77].

If medical and less invasive strategies for treating IAH/ACS have failed, however, then decompressive laparotomy is lifesaving and should be expediently performed. From a realistic viewpoint, the surgical management of IAH/ACS can be

functionally equated to managing the resultant OA with an overall goal of formally closing it as soon as it is safe. The entire potential spectrum of this management can be conceptualized as potentially occurring in up to six stages. These include surgical prevention of IAH/ACS; abdominal decompression (via laparotomy or a minimally invasive fasciotomy); temporary abdominal closure with a temporary abdominal closure (TAC) device; initial management of the open abdominal wound in the ICU; avoidance of wound complications, including deep soft tissue infections, abdominal abscesses, entero-atmospheric fistulae, and complex ventral herniae; and staged abdominal reconstruction (reducing and closing the abdominal defect over time) or, as a last resort, the use of a planned ventral hernia (an open abdominal wound that is allowed to granulate and covered with skin flaps or a split-thickness skin graft) with plans for delayed abdominal wall reconstruction.

It should be emphasized that the contemporary surgeons' obvious goal should be to avoid all these stages if possible, or to minimize them, yet ensuring that the patient survives. In this current era of aggressive non-operative management, it is not a success if the patients succumb due to lack of an intervention. If prophylaxis or medical therapy can avoid or mitigate IAH, then no other interventions may be required. After decompressive laparotomy therefore, primary fascial closure is the goal. IAH/ACS may potentially be completely prevented after laparotomy by leaving the abdomen open where appropriate. However, for surgeons to recognize "when it's appropriate" however is a challenging target within a rapidly moving playing field. While a decade ago surgeons would accept that almost any seriously injured patient requiring a laparotomy would subsequently require postoperative OA to prevent postinjury ACS [83], this dictum is no longer assured related to rationalized resuscitation strategies. As there is a vacuum of scientific data, opinion is the highest level of guidance. A recent expert appropriateness rating study concluded that appropriate indications for OA use remain the development of a coagulopathy (especially when combined with hypothermia and acidosis), administration of large volumes of crystalloids or packed red blood cells, inability to close the abdominal fascia without tension, development of signs of ACS during attempted abdominal wall closure, and need for a planned relaparotomy to remove intra-abdominal packs or reassess extent of bowel viability [84–86].

To assist clinicians the World Society of Emergency Surgery in conjunction with the Abdominal Compartment Society recently published consensus guidelines on managing the open abdomen [20, 21, 87]. The summarized recommendations regarding management are presented in Table 13.4.

13.2.3 Temporary Abdominal Closure (TAC) Devices

It is implicit in now accepting an OA that an acceptable and safe temporary abdominal closure (TAC) device be utilized to protect the viscera and manage the peritoneal cavity. Current WSACS/ACS and WSES guidelines recommend the use of negative pressure peritoneal therapy (NPPT) with either noncommercial (i.e., the Barker's vacuum pack) or commercial active negative pressure wound therapy devices be

used for temporary abdominal closure [6, 20]. Other contemporary reviews have also suggested the use of fascial traction methods in addition to NPPT, in a technique known as vacuum-assisted wound closure and mesh-mediated fascial traction (VAWCM) [88–90], is the preferred therapy [91], although there is minimal controlled evidence to base decision-making upon.

While open abdomen therapy was described as far back as 1940 using light canvas covered in Vaseline [92], there has been a rapid evolution in TAC devices. Using plastic bags that did not adhere to the viscera was an advantage of the so-called Bogota bag. Subsequently a number of important principles regarding TAC devices have been recognized. The TAC should be placed well within the peritoneal cavity to maintain as much lateral separation of the viscera from the abdominal wall. It should prevent lateralization of the abdominal musculature which is an important function of VAWCM. It should preferably control peritoneal fluids, which may be one of its most unappreciated benefits.

Preclinical studies have reported that application of negative pressure to the open abdominal wound (i.e., "negative pressure peritoneal therapy") [93] may remove ascites and peritoneal pro-inflammatory mediators, reduce the systemic inflammatory response, and improve the structure and potentially function of the pulmonary, cardiac, and renal systems [94, 95]. A prospective cohort study of 280 patients published in 2013 reported that the use of the ABThera negative pressure wound therapy device (Kinetic Concepts Inc., San Antonio, Texas, USA) was associated with improved primary fascial closure rates and survival when compared with a device that provides potentially less efficient peritoneal negative pressure, the Barker's vacuum pack [96]. To date, only one RCT published in 2015 has been designed to determine if the ABThera is more efficacious than the Barker's vacuum pack at reducing the extent of the systemic inflammatory response after damage control laparotomy for intra-abdominal injury or sepsis [97]. This trial reported an improved survival with the ABThera that did not appear to be mediated by an improvement in peritoneal fluid drainage, markers of the systemic inflammatory response, or primary fascial closure rates [97].

After decompressive laparotomy, if the abdominal fascia is unable to be closed when the patient is first returned to the operating room, a staged abdominal reconstruction method may be used. These methods have been proposed to include negative pressure peritoneal therapy, the Wittmann Patch (Starsurgical, Burlington, Wisconsin, USA), progressive closure of a synthetic patch sutured between the fascial edges, dynamic retention using sutures or the Abdominal Reapproximation Anchor device (Canica Design Inc., Almonte, Ontario, Canada), and vacuum-assisted wound closure (VAC) and mesh-mediated fascial traction. Although no comparative trials have been completed, VAC and mesh-mediated fascial traction has likely received the greatest enthusiasm as it is associated with fascial closure rates of at least 77% [88, 91, 98]. In this method, patients are fitted with a VAC device at the initial laparotomy [88, 99]. At relaparotomy, a perforated polyurethane sheet is placed over the visceral block and a divided polypropylene mesh sheet sutured between the fascial edges. This sheet is subsequently sutured together

before a VAC dressing is placed atop and negative suction applied. The VAC dressing is then changed and mesh progressively tightened every 24–72 h until the fascial edges can be reapproximated.

13.2.4 Direct Peritoneal Resuscitation

DPR involves infusion of hypertonic fluid into the abdomen in addition to IV resuscitation. This causes rapid and sustained dilation of the arterioles, especially those in the intestine, which reduces organ ischemia and cellular hypoxia [100, 101]. Data from single-center RCTs shows that NPWT and fluid instillation seem to improve outcomes in trauma patients in terms of early and primary closure [102, 103]. There is a good deal of animal work supporting the conclusion that DPR prevents intestinal ischemia and helps preserve intestinal blood flow and structural integrity and reduces inflammatory cytokines even in inflammatory states such as brain death [101, 104]. With replication of these experiences in other centers, this therapy may become part of the standard OA management.

13.2.5 Current Utilization of the Open Abdomen (OA)

13.2.5.1 The OA for Trauma Surgery

The use of the OA in trauma surgery is decreasing every year. With a dramatic evolution in resuscitation practices involving balanced resuscitation practices, more and more trauma patients who previously become so edematous required OA therapy, are no longer being crystalloid over-resuscitated, and can thus be primarily closed [64, 66, 105]. This dramatic change in the trauma care paradigm has justified questions regarding the whole premise of damage control surgery for trauma [63] and justifies the randomized control trial of the practice in trauma patients [106].

13.2.5.2 The OA for Intra-abdominal Sepsis

The use of the OA for non-trauma general surgery is however increasingly being reported in uncontrolled series as a potentially beneficial option for patients with SCIAS [107–112]. The use of the OA in severe sepsis may allow early identification and increased drainage of any residual infection, control any persistent source of infection, more effectively remove biomediator-rich peritoneal fluid, provide prophylaxis against development of the abdominal compartment syndrome, and allow for the safe deferral of gastrointestinal anastomoses in settings where the risk of anastomotic leak is initially high [111]. Although the WSACS/ACS guidelines recommended NOT to use the open abdomen for intra-abdominal sepsis [6], largely based on economic reasons [113], more contemporary WSES guidelines differ. The 2018 WSES guidelines on OA management state that the open abdomen is an option for emergency surgery patients with severe peritonitis and severe sepsis/septic shock under the following circumstances: abbreviated laparotomy due to severe physiological derangement, the need for a deferred intestinal anastomosis, a

planned second look for intestinal ischemia, persistent source of peritonitis (failure of source control), or extensive visceral edema with the concern for development of abdominal compartment syndrome, albeit with the lowest confidence due to the level of evidence (Grade 2C) [20].

Compared to trauma patients, however, patients undergoing OA management for intra-abdominal sepsis have a greater risk of OA complications, including enteroatmospheric fistula (EAF) and intra-abdominal abscess formation, and a lower rate of primary fascial closure (i.e., fascia-to-fascia closure within the index hospitalization) [87, 91, 111, 114, 115]. Risk factors for frozen abdomen and EAF in OA are delayed abdominal closure, non-protection of bowel loops during OA, the presence of bowel injury and repairs or anastomosis, colon resection during DCS, the large fluid resuscitation volume (>5 L/24 h), the presence of intra-abdominal sepsis/abscess, and the use of polypropylene mesh directly over the bowel [116–120]. Although RCT data comparing techniques is needed, meta-analyses conducted by our group [121] and the Amsterdam group [91] have concluded that negative pressure wound therapy (NPWT) treatment appears to potentially be the safest and most effective OA management technique currently available. Newer commercial active negative pressure peritoneal therapy (ANPPT) systems now available for OA may reduce the risk of enterocutaneous fistula and facilitate enhanced delivery of negative peritoneal pressure to the peritoneal cavity [1, 6, 121].

Animal studies [94] and in silico modeling of these animal studies [95] have shown that ANNPT provides a greater degree of negative pressure throughout the peritoneum, which may reduce plasma biomediator levels when compared to a more passive peritoneal drainage. Systemic inflammation (TNF-α, IL-1β, IL-6) in one study was significantly reduced in the ANPPT group and was associated with significant improvement in intestine, lung, kidney, and liver histopathology [94]. Although the mortality rate in the NPPT was 17% versus 50% in the control group, this difference was not statistically significant ($p = 0.19$), likely due to the smaller numbers.

As over-resuscitation becomes rare and de-resuscitation becomes a focus [122], it is intuitive that there will be more abdomens in non-trauma intra-abdominal sepsis patients who may be technically closed without inducing intra-abdominal hypertension (IAH). However, although these abdomens *may* be closed, *should* they be closed? As has been recently emphasized, there are profound differences in the basic science of sepsis and traumatic injury [123], with the previously unifying concepts of noninfectious systemic inflammatory response syndrome (SIRS) being effectively discarded as a clinically helpful construct [124–126]. The one nebulous, poorly defined "holy grail" of the optimal management of SCIAS is adequate "source control." It is suggested that even if an abdomen can be physically closed that there may be an advantage to leaving it open to allow better drainage of intraperitoneal contamination, a concept that is supported by remarkable animal lab data suggests the ability of ANPPT to mitigate the elaboration of the inflammatory biomediator cascade [94, 95, 127]. Coupled with technical advances in ANPPT dressings that are safer to utilize and that increasingly protect the viscera, this appears an attractive option for the sickest IAS patients.

13.3 Conclusion

The use of the OA after source control laparotomies for intraperitoneal sepsis is increasingly being adopted without strong controlled evidence to its effectiveness. This has been partially supported by developments in TAC devices that offer greater safety and potentially even a therapeutic modality to mitigate the biomediator propagation leading to systemic inflammation in IAS. Thus, controlled studies to determine optimal therapies are urgently required. The surgical and critical care communities must therefore design RCTs to re-examine whether negative pressure wound therapy improves outcomes over alternate temporary abdominal closure methods in critically ill adults (and determine how this occurs), to determine the optimal method of staged abdominal reconstruction in patients with open abdominal wounds, and to study the role of IAH in critical care both as an independent and how it interacts in a multifactorial way with other physiological stressors in critical illness and injury. Thus, the next decade of study related to IAH/ACS will therefore be one aimed at understanding which treatments may effectively lower IAP and whether these treatments ultimately influence patient important outcomes.

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14 Infectious Complications: Understanding Appropriate Antibiotic Choice and Utilization

Massimo Sartelli

14.1 Appropriate Antibiotics in Patients Staying in Surgical Intensive Care Units

Despite decades of sepsis research, no specific therapies for sepsis have emerged. Without specific therapies, management is based on control of the infection and organ support.

Early antibiotics, source control, and hemodynamic support of vital organ function are the cornerstones for the treatment of patients with sepsis [1].

The choice of the antibiotic regimen poses serious problems for the management of critically ill patients. In patients with sepsis or septic shock, an early and appropriate empirical antimicrobial therapy has a significant impact on the outcome, independently by the site of infection. An inadequate antimicrobial regimen is one of the variables more strongly associated with unfavorable outcomes in critical ill patients [2].

Recent international Surviving Sepsis Campaign guidelines for the management of sepsis and septic shock recommend intravenous antibiotics within the first hour after sepsis and septic shock are recognized, the use of broad-spectrum agents with good penetration into the presumed site of infection, and reassessment of the antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs [3].

Empiric antimicrobial therapy should be started as soon as possible in patients with organ dysfunction and septic shock [4]. Similar to the general ICU population, also in surgical ICU population, the empirical antibiotic scheme should cover the probable pathogen(s) [5].

The principles of empiric antibiotic treatment should be defined according to the most frequently isolated bacteria, always taking into consideration the local

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healthcare setting trend of antibiotic resistance. In this era of prevalent drug-resistant microorganisms, the threat of resistance is a source of major concern that cannot be ignored. In the past 20 years, the incidence of nosocomial infections caused by drug-resistant microorganisms has risen dramatically, probably in correlation with escalating levels of antibiotic exposure and increasing frequency of patients with one or more predisposing conditions, including elevated severity of illness, advanced age, degree of organ dysfunction, low albumin levels, poor nutritional status, immunosuppression, the presence of malignancy, and other comorbidities. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a global threat over the past decade and is now endemic in many countries, largely due to the dissemination of carbapenem-hydrolyzing beta-lactamases such as the *K. pneumoniae* carbapenemase (KPC) [6]. Penicillins, cephalosporins, and carbapenems do not demonstrate in vitro activity against these bacteria. Therefore, very few treatment options remain for carbapenem-resistant *K. pneumoniae* bloodstream infections, and combination therapy instead of monotherapy in CRKP-infected patients is needed.

Optimizing dosing strategies based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock is a crucial aspect of the antimicrobial treatment.

In recent years the changes in the pharmacokinetics in critically ill patients have received increased interest [5]. Antibiotic pharmacokinetics describes the fundamental processes of absorption, distribution, metabolism, and elimination and the resulting concentration-versus-time profile of an agent administered in vivo. The achievement of appropriate target site concentrations of antibiotics is essential to eradicate the relevant pathogen [5]. The “dilution effect” is very important for starting appropriately empirical antibiotic therapy with hydrophilic agents such as beta-lactam agents. Higher than standard loading doses (LD) of hydrophilic agents such as beta-lactams should be always administered to ensure optimal exposure at the infection site, maintaining a therapeutic threshold that considers the effects of renal function. In patients with sepsis and septic shock, missing of LD results in an underexposure to hydrophilic antibiotics that may be critical for patients. Conversely, for lipophilic antibiotics the “dilution effect” in the extracellular fluids of patients with sepsis and septic shock may be mitigated by the rapid redistribution of the drug to the interstitium from the intracellular compartment, which acts as a reservoir.

Once an appropriate initial loading dose is achieved, the antimicrobial regimen should be reassessed, at least daily, because pathophysiological changes may significantly affect drug availability in the critically ill patients [7]. Lower than standard dosages of renally excreted drugs must be administered in the presence of impaired renal function, while higher than standard dosages of renally excreted drugs may be needed for optimal activity in patients with glomerular hyperfiltration [5].

Knowledge of the pharmacokinetic and pharmacodynamic antimicrobial properties of each drug (including inhibition of growth, rate and extent of bactericidal action, and post-antibiotic effect) may provide a more rational determination of optimal dosing regimens in terms of the dose and the dosing interval. Some antibiotics, including beta-lactam antibiotics, exhibit time-dependent activity and exert

optimal bactericidal activity when drug concentrations are maintained above the minimum inhibitory concentration (MIC), whereas high peak concentrations are not beneficial. As a consequence, the more prolonged the time during which the drug levels are above the MIC value, the greater is the chance of clinical cure. In fact, prolonged or continuous infusions of beta-lactams have been proposed in order to maximize the time that the drug concentration exceeds the MIC.

The traditional intermittent dosing of each agent may be replaced with prolonged infusions of certain beta-lactam antibiotics to optimize *pharmacokinetic/pharmacodynamic principles*, especially in critically ill patients with infections caused by Gram-negative bacilli and overall for those patients with infections caused by Gram-negative bacilli that have elevated but susceptible MICs to the chosen agent.

Conversely, for antibiotics with concentration-dependent activity, such as aminoglycosides, the use of a higher dose at extended interval (i.e., once daily) is strongly recommended.

The use of therapeutic drug monitoring (TDM) has been associated with higher clinical success and lower rate of toxicity. It is recommended mainly, but not only, for drugs with a narrow ratio between efficacy and toxicity, such as glycopeptides and aminoglycosides [8].

Unnecessarily prolonged administration of antimicrobials is detrimental to society and to the individual patient. For society, excessive antimicrobial use drives antimicrobial resistance dissemination. For individual patients, prolonged antibiotic therapy is associated with specific illnesses such as *Clostridium difficile* colitis and individual risk for multidrug-resistant organisms.

An antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock.

Surviving Sepsis Campaign guidelines suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S aureus, and some fungal or immunologic deficiencies, including neutropenia. Conversely Surviving Sepsis Campaign guidelines suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis [3].

The poor specificity of clinical signs to distinguish true bacterial infections from non-bacterial systemic inflammatory disorders is one of the major reasons for prolonged therapy in intensive care units.

During the past decades, it was hypothesized that biomarkers could help to optimize critically ill patients' antibiotic therapy shortening antibiotic duration for patients evolving favorably.

Most recently, procalcitonin (PCT) has been suggested as a novel biomarker that may be useful in guiding therapeutic decision-making in the management of sepsis. It may be a helpful tool to determining the timing and appropriateness of escalation of antimicrobial therapy in sepsis [9].

Currently, procalcitonin (PCT) has emerged as a laboratory variable that allows early differentiation between SIRS and sepsis, and it has recently been used to guide antibiotic treatment in critically ill patients and predict treatment response [9].

Hochreiter et al. published in 2009 [10] a prospective trial to value the role of procalcitonin for guiding antibiotic therapy in surgical intensive care patients. Monitoring of PCT resulted a helpful tool for guiding antibiotic treatment in surgical intensive care patients.

14.2 Conclusion

The choice of the antibiotic regimen poses serious problems for the management of critically ill patients. In patients with sepsis or septic shock, an early and appropriate empirical antimicrobial therapy has a significant impact on the outcome, independently by the site of infection. The use of broad-spectrum agents with good penetration into the presumed site of infection is crucial to treat critically ill patients in surgical intensive care units. In these patients reassessment of the antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs is mandatory.

An antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock.

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15 Ongoing Intraabdominal Infection Requiring ICU Care: Prioritizing Treatment Decisions

Dieter G. Weber

15.1 Introduction

Abdominal sepsis is associated with marked morbidity and remains an acute threat to life across the globe [1]. Septic sources within the peritoneal cavity are second only to pulmonary causes among overall sepsis admissions in modern intensive care [2]. The early identification and appropriate management of both the sepsis and its underlying pathology are central in achieving the best clinical outcome [1]. However, despite optimal diagnosis and treatment, a proportion of patients develop a persistent or recurrent intraabdominal infection [3, 4].

In this chapter, the key concepts and considerations, including technical aspects that may facilitate and optimize the timely prioritization and ongoing surgical therapy in patients with intraabdominal infections are reviewed.

15.2 Intraabdominal Infection, Peritonitis, and Sepsis

Intraabdominal infections are usually uncomplicated: the sepsis is localized to a single organ and does not impact adjacent tissues. By definition, in uncomplicated intraabdominal infections, the inflammation does not extend to the peritoneum [5]. In this case, the host rarely exhibits a major inflammatory response, and direct treatment is both feasible and most likely successful. Indeed, postoperative antibiotics are rarely necessary [6, 7]. However, in complicated intraabdominal infections, the

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pathological processes and purulence involve the peritoneal cavity. The inflammatory host response is more common, and sepsis ensues. Uncontained spread of infection results in diffuse peritonitis. At present there is no single, complete classification that includes the source of the infection, the primary inciting pathological event, the anatomical extent, and the clinical condition of the patient [8].

Peritonitis can be classified anatomically by the pathological cause, as well as the extent of the physical area of suppuration and macroscopic inflammatory change. Dependent on the cause and clinical course, peritonitis is divided into concepts of primary, secondary, and tertiary peritonitis [5, 9, 10]. Primary peritonitis, also referred to as spontaneous peritonitis, is defined as an infection that occurs in the peritoneal cavity, in the absence of other intraabdominal infective pathology or an identifiable source. Secondary peritonitis is defined by the direct association of the cause of peritonitis to a pathological event in an abdominal visceral source. This is most commonly the result of organ ischemia, perforation, or traumatic injury. The resultant peritonitis (localized or generalized) is the direct result of the primary pathological event. At this clinical stage, therapeutic intervention usually halts further progress. However, where this is unsuccessful and intraabdominal infection is ongoing, tertiary peritonitis may develop.

As a clinical entity, tertiary peritonitis remains incompletely understood, and its pathophysiology continues to be the topic of current research [8, 9]. It occurs in a small proportion of patients who initially present with acute peritonitis (either due to a primary or secondary cause). The clinical picture remains varied and is affected by numerous factors, including individual patient variation in the inflammatory host response and end-organ responsiveness, as well as the underlying pathology and clinical management undertaken. This clinical picture is further modified by patient age and pre-existing comorbidities, among other points. Tertiary peritonitis is associated with excess clinical morbidity and mortality in association with challenging ongoing surgical decisions.

Sepsis is currently defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection." Organ dysfunction is further defined as an acute change in the Sequential Organ Failure Assessment (SOFA) score ≥ 2, because of the infection [11]. This recent definition replaces previous classifications and focuses the clinical concept directly on the dysregulation of the host response due to the infection. The term septic shock is now applied to the subset of patients experiencing clinically relevant situations of circulatory and cellular or metabolic abnormalities, as indicated by the need for cardiovascular support to maintain a mean arterial pressure $\geq$ 65 mmHg and having a serum lactate >2 mmol/L, despite adequate volume resuscitation [8, 11].

Several large and multi-institutional studies are available to define the epidemiology of sepsis, though they predate the current sepsis definition. An early multi-institutional study from Washington State, USA, reported that 11% of patients with peritonitis develop severe sepsis (74% of these patients exhibited single organ failure, while 20% were diagnosed with multiple organ failure) [12]. A clear trend linking mortality to the severity of sepsis was observed: overall mortality was 6%, while severe sepsis was associated with 34% mortality. A more recent European

collaborative observational study, the CIAO study (complicated intraabdominal infection observational study), reported a similar overall mortality rate of 7.5% [13]. This study identified several independent predictive variables for mortality, including advanced age, delay in initial treatment >24-h, and the presence of either sepsis or septic shock. A subsequent worldwide collaboration from the same lead author, looking at complicated intraabdominal infections, demonstrated mortality rates of 1.2% in patients with no sepsis, 4.4% in patients with sepsis, 27.8% with severe sepsis, and 67.8% in patients with septic shock [14, 15]. In all these investigations, the trend to marked, increased mortality with sepsis severity is repeatedly established. Appendicitis is the most common source of intraabdominal infection, followed by cholecystitis. Next most frequent are postoperative pathologies, including anastomotic leak or abscess, and then less common events, including colonic and diverticular pathology, small bowel perforations, complications of gastroduodenal ulcer disease, and trauma-related pathology [13, 14].

15.3 Surgical Decision-Making

In difficult clinical situations such as complicated intraabdominal sepsis with secondary and tertiary peritonitis, surgical decision-making is complex and based on the interaction of multiple individual factors [16, 17]. In practice, clinical judgment and collaboration remain central in this decision-making. To assist the clinical gestalt, computerized assistance in these decisions is reported [18–20], though such models have not yet been universally applied and have not generally superseded clinical judgment in most centers. Current clinical decisions continue to rely largely on the personal judgment of the treating clinician(s) and their associated team of health-care professionals [16, 17].

There is no current consensus on the clinical use of laboratory parameters or other investigations for the diagnosis or intraabdominal sepsis or injury [21]. However, guidelines have been published by several organizations and collaborations, for both the initial diagnostic endeavors and the subsequent treatment aims surrounding sepsis. The Surviving Sepsis Campaign [22, 23] and recommended treatments assist the timely delivery of appropriate clinical care. The most recent updates aim to deliver the diagnostic components (including the quantification of serum lactate and blood cultures) and the initial therapeutic interventions (including broad-spectrum antibiotics, fluid resuscitation, and vasopressors where appropriate) within 1 h of presentation [24].

15.3.1 Prognostic Scoring Systems

Several prognostic scoring systems for patients with abdominal sepsis are available. These are used to quantify organ failure severity, surgical findings, and predicted outcomes [8]. Established scoring systems to assess the general organ failure status include the Acute Physiology and Chronic Health Evaluation (APACHE II) as well

as the Simplified Acute Physiology Score [25]. Established scoring systems for aspects of peritonitis specific data include the Physiological and Operative Severity Score (P-POSSUM), the Mannheim Peritonitis Index, and the World Society of Emergency Surgery Sepsis Severity Score (WSESSSS) [8, 14, 26]. However, like the lack of a single, complete classification system encompassing all the aspects of peritonitis mentioned above, no single classification system currently combines all clinical aspects or provides a complete picture of clinical outcome [27].

The available scoring systems have been largely designed for research activities and are problematic in their application to the individual patient. For example, the P-POSSUM and the WSESSSS [14] predict the risk of morbidity and mortality. Unfortunately, the translation of this "on average" information to the individual circumstance is challenging. Tailored surgical strategies, incorporating the individual patient, pathological and environmental factors, have been advocated extensively in numerous recent publications [16, 17, 28], acknowledging that no one size fits all. For example, the increased risk of morbidity and mortality associated with age is increasingly reported in abdominal emergency surgery [29–31]. It is appropriate to tailor and modify the surgical therapy to these known risks [32]. At present, prognostic scoring systems will continue to serve a vital function in clinical audit and in research [8]. However, for complete clinical application, the ideal scoring system remains outstanding.

15.4 Basic Principles in the Management of Ongoing Intraabdominal Infections

Early diagnosis remains central for the timely and optimal management of sepsis [24, 33, 34]. Numerous investigators have demonstrated the critical importance in early diagnosis and its relationship with outcome. Furthermore, the experience and seniority of medical personnel also improve the overall outcome [17]. However, beyond the early and accurate recognition of the clinical problem, the basic principles of managing the intraabdominal sepsis remain largely unchanged [9, 35]. These steps may be summarized in four steps:

1. Source control
2. Restoration of gastrointestinal function
3. Antimicrobial therapy
4. Organ support

Source control aims to eradicate the focus of infection and arrest and prevent further contamination by controlling the inciting pathology [36, 37]. The surgical strategy can be summarized by the principles of drainage, decompression, and debridement, aiming to eliminate the septic focus and remove necrotic or non-salvageable tissues. Thereafter, surgical attention can focus on the restoration of gastrointestinal continuity and function [9, 35].

In an ideal clinical circumstance, a patient is sufficiently well to undergo a single-stage procedure that can address all these components of source control and restoration of gastrointestinal function in one operative setting. However, as discussed in more detail below, patient, disease, physiological, and treatment factors all affect whether this is practical, feasible, or safe. Patients who are in states of physiological exhaustion require an alternate approach to survive. The principles and maneuvers relating to damage control, relaparotomy, the role of the open abdomen, and the potential use of minimally invasive techniques are discussed below.

15.5 Advanced Principles and Maneuvers in the Management of Ongoing Intraabdominal Infections

15.5.1 Resuscitation and Timing of Source Control

Critically ill patients with intraabdominal sepsis benefit from intensive care during the initial resuscitation [9, 35]. However, depending on hospital and medical service organization, this care may be delivered in different geographic areas. The care may begin prehospital (some prehospital paramedic services have commenced screening for these patients in the prehospital environment and are delivering initial fluid resuscitation and broad-spectrum antibiotics in this environment [38, 39]). In house, the resuscitation may be delivered or is continued, in an emergency and in a preoperative environment. Depending on the service, the patient may also be formally admitted to an intensive care unit before source control. Regardless of location, the fundamental components of diagnosis and resuscitation remain unchanged. Beyond fluid therapy and antimicrobial administration, patients should be able to receive vasopressors to maintain a mean arterial pressure ≥65 mmHg, once volume has been restored [24]. Further efforts should focus on optimization of oxygenation, correction of coagulopathies and electrolyte disturbances, optimization of glucose control, and correction of acidosis [9]. The intensive care adjuncts to support organ dysfunction are beyond the scope of this chapter.

A universal or standard applicable timing for source control of intraabdominal infections is not appropriate due to the variable nature of pathologies and specific patient and environmental factors. However, in most patients, physiological well-being will improve with an initial period of resuscitation. We have proposed elsewhere that in situations of damage control (discussed further below), a resuscitation phase is appropriate for patients presenting in septic shock [16].

Regarding the timing of source control, three categories of patients have been proposed [37]:

1. Patients in need of immediate surgery (e.g., necrotizing infections and patients in physiological extremis where resuscitation is not improving physiology),
2. Patients that benefit from a period of resuscitation for physiological optimization (most patients with intraabdominal infections),

3. Patients who tolerate the current inflammatory process and whose pathology may better demarcate with time (e.g., the situation of infected pancreatic necrosis).

While every effort is made to resuscitate and "stabilize" patients presenting in septic shock, this goal may not be achieved. Practically, an optimum is often reached, where further resuscitative efforts achieve diminishing returns. At this stage there is a window of opportunity for source control or further diagnostic efforts if required.

15.5.2 Damage Control Surgery

Surgical strategy has traditionally focused on a mode of primary definitive repair at a single operation. Only a few authors published observations outside this historic standard. Pringle [40] and Halstead [41] had reported some success with staged procedures involving perihepatic packing for liver trauma, in 1908 and 1913, respectively. During the same period, Lockhart-Mummery [42] and Hartmann [43] established a role for staged surgeries for the complications of perforated sigmoid diverticulitis, though these surgeries were separated by different hospital admission episodes. These experiences were largely forgotten during the subsequent half-century, until trauma and acute care surgeons' excited renewed interest in the staging of procedures. In 1983, Stone and his colleagues reported a series of patients affected by major coagulopathy at the time of laparotomy [44]. Their clinical series challenged the mode of primary definitive repair and reintroduced the concept of staged surgeries, separated by a period for physiological restoration. Most patients in this series underwent surgery for traumatic injuries, though a handful were operated on for secondary peritonitis. In both cases, a significant survival benefit was reported in the patients undergoing staged surgeries. Following this publication, further clinical series reporting similar survival benefits were published by Ivatury in 1986 [45] and by Burch in 1992 [46]. Rotondo and Schwab subsequently coined the term "damage control" in their 1993 series [47].

The concept of a damage control treatment strategy (compared with the historical primary definitive surgery treatment strategy) has become the standard of care for surgery in severely injured trauma patients that exhibit significant physiological compromise [48]. An abbreviated initial surgical intervention for the control of bleeding and contamination is supplemented with a definitive surgical intervention at a later stage, after restoration of the physiology in the intensive care environment [49]. This approach has been extended by emergency general surgeons to non-traumatic abdominal emergencies, though minimal primary data is available to support this intuitive extension beyond trauma pathology [16, 50]. A recent consensus guideline emphasized the paucity of data in the non-traumatic abdominal emergency application of the damage control strategy [8].

Despite the limited primary data for the application of a damage control strategy to non-traumatic abdominal emergency surgery, the damage control approach offers

an alternative to a single-stage, definitive, surgical strategy. The level III and IV evidence supporting this approach establish the feasibility of the surgical mode but incompletely addresses patient selection [16]. It is likely that similar to trauma patients, the majority of patients requiring surgery for an intraabdominal infection are unlikely to benefit from the damage control strategy. The benefit will be limited to the patients with significant physiological derangement, where the additional stress of surgery will irreparably dysregulate the host inflammatory response. The appropriate selection of patients for either a primary definitive or a staged damage control strategy is central for the realization of clinical benefit. Overapplication of the damage control strategy in trauma patients has been linked with measurable harm [51].

Correct patient selection for a damage control strategy should be continually reassessed during the patient's clinical course. The damage control mode should be interchanged with a primary definitive operative mode as appropriate depending on changes in the patient's condition [16].

Factors affecting patient selection for a damage control strategy can be grouped into patient factors, injury- (for trauma)/disease-related factors, physiological factors, and issues surrounding the patient's treatment (Table 15.1). While the individual factors do not necessarily represent absolute criteria in isolation, the various factors warrant consideration in concert together. Patient factors include the medical and surgical history, including the age and comorbidities. Injury/disease factors include the nature, severity, and expected natural history or the disease. Physiological factors include the patient's hemodynamic stability, magnitude of the associated inflammatory response and possible dysregulation, coagulopathy, hypothermia, and organ dysfunction. Finally, treatment factors include the quality of the resuscitation, as well as the duration and magnitude of the predicted treatment and surgery, among other considerations [16]. Specific factors that should individually trigger a damage control surgical strategy for trauma patients have been published but individually

Table 15.1 Factors influencing the decision for a damage control strategy

Patient factors	Age
	Past medical history
	Comorbidities
	Medications
Disease factors	Nature of the pathology
	Severity of the pathology
	Expected clinical course
	Treatment options
Physiological factors	Coagulopathy
	Hypothermia
	Acidosis
	Hemodynamic stability
	Inflammation severity
Treatment/environmental factors	Quality of the resuscitation
	Physiological impact of treatment(s)
	Magnitude of treatment(s)
	Availability of treatment resources

remain incompletely validated (e.g., temperature <35 °C, pH <7.2, base excess <−8.0 mEq/L, etc.) [16]. These specific factors have been extrapolated to the setting of abdominal sepsis [50, 52], but again, no validation currently exists.

15.5.3 Relaparotomy

In septic pathologies, a single operative intervention may be insufficient to adequately achieve source control. Despite thorough operative intervention, a percentage of patients require reoperation for further debridement or for the management of complications that are a direct result from the inciting pathology or its management (e.g., abscess formation in the peritoneal cavity, an anastomotic leak, etc.). Patients requiring a reoperation have considerable associated mortality (48% in a recent case series of 114 relaparotomies) [53].

To further investigate a planned relaparotomy, the Dutch peritonitis group recently randomized patients between a planned reoperation and on-demand relaparotomy strategy [17]. Comparing these two treatment strategies, the on-demand group had a significantly shorter ICU stay (7 vs. 11 days), had a significantly shorter hospital stay (27 vs. 35 days), and had reduced medical costs. Furthermore, no increased adverse outcomes were noted in the on-demand group. An earlier meta-analysis [54] on the topic had been inconclusive, though a retrospective clinical series subsequently indicated the on-demand strategy was an independent predictor of survival [55]. In a separate investigation, patients undergoing mandatory relaparotomy were noted to exhibit aggravated inflammatory responses [56].

An operative strategy of a planned relaparotomy is currently not recommended, and, instead, an on-demand relaparotomy strategy is supported as a standard practice [8, 9]. The decision to reoperate is dependent on the clinical course of the patient. In the randomized investigation by the Dutch peritonitis group, relaparotomy "was only performed in patients with clinical deterioration or lack of clinical improvement with a likely intraabdominal cause." In this trial, "deterioration" was defined by an increase of more than four points in the Multiple Organ Dysfunction Score or prespecified surgical emergencies (including the development of an abdominal compartment syndrome, intraabdominal hemorrhage, visceral organ ischemia or necrosis, or the inability to manage intraabdominal abscesses percutaneously, among others). "Lack of clinical improvement" was considered where the Multiple Organ Dysfunction Score was unchanged (± 2 points). The decision-making around performing an on-demand relaparotomy was guided by a multidisciplinary medical team [17].

15.5.4 The Open Abdomen/Laparostomy

The feasibility of non-closure of the abdominal wall has been described at various timepoints during the last century in several abdominal surgical applications. During the late 1970s and early 1980s, the open abdomen became experimentally

incorporated into the management of patients with secondary peritonitis [57–59], with several case series reporting survival and practical benefit from this approach.

The decision to leave the peritoneal cavity open is often closely associated with the decision regarding a damage control strategy. However, the two decisions do not necessarily always agree. There are several potential benefits beyond its application in the damage control setting [9, 60, 61]. In the setting of intraabdominal sepsis, there are potential benefits in leaving the abdomen open, including the enabling of:

1. A relook/relaparotomy (usually for the reassessment of potentially ischemic tissues or in the setting of failed source control),
2. A second procedure for restoration of gastrointestinal continuity (in an effort of stoma formation avoidance),
3. Broad-based peritoneal drainage,
4. A second stage in a damage control surgery mode,
5. Prevention of an abdominal compartment syndrome.

The precise role of the open abdomen in the management of peritonitis continues to be debated and remains incompletely understood [9, 62]. This debate is confused by the partial interrelationship of the abovementioned potential benefits of the procedure and by the difficulty in conducting research in the critically ill. Debate will likely continue until well-designed studies are available to define the varied, precise indications. Of note, the study protocol for the Closed Or Open after Source Control Laparotomy for Severe complicated Intraabdominal Sepsis (the COOL trial) has been recently published [63]. Meanwhile, several consensus papers and, most recently, a guideline exist to summarize current thoughts [60, 61].

During staged laparotomies, the restoration of gastrointestinal continuity may be deferred to a subsequent procedure. At that time, the patient's physiology may be more favorable to allow the healing of a primary anastomosis [16]. Several authors have suggested that this sequencing may reduce the need for stoma formation [9, 64, 65]. While this strategy appears feasible, more detailed research is needed to clearly define the optimal patient selection and operative timings in this area.

The incidence of intraabdominal hypertension and acute compartment syndrome is incompletely described for patients with intraabdominal infections. Investigation of its occurrence is complicated by the unclear onset of pathological processes (unlike trauma) [66]. However, in a recent clinical series, 41% of postoperative patients had elevated intraabdominal pressures [67]. A higher mortality was observed in the group of patients with increased intraabdominal pressures. Further epidemiological and pathophysiological understanding of intraabdominal hypertension is required, though from a practical clinical standpoint the situation can be avoided by leaving the abdomen open. This seems prudent in cases of marked tissue swelling and difficulties with primary closure or in patients at high risk [9]. In trauma, a marked increase in mortality is seen in association with the development of an abdominal compartment syndrome [68]. Clinicians should have a low threshold to measure the intraabdominal pressures in patients with

significant intraabdominal infections allowing early intervention where an abdominal compartment syndrome is developing.

Current clinical guidelines emphasize the importance of the tailored application of the open abdomen technique, taking into consideration the unique complexities and factors affecting an individual case [8, 60, 61]. The clinical judgment is guided by factors analogous to those mentioned in the guidance of the damage control strategy (see Table 15.1). The open abdomen is not necessary in the majority of patient with intraabdominal sepsis.

Initial experiences with the management of the open abdomen were troubled by high rates of wound problems, high rates of failed primary fascial closure (and the need for delayed procedures), and frequent bleeding and fistula-related complications [9]. However, since these initial experiences, a multitude of investigators have sought to explore the optimal management of the open abdomen, the ideal prosthesis/dressing, and ongoing management of the laparostomy. Advances in prosthesis, mesh, and surgical techniques (e.g., component separation) have all contributed to reduce the morbidity associated with the open abdomen [8, 60, 61].

Temporary abdominal closure is best achieved with negative pressure therapy [61]. While prolonged negative pressure may increase the risk of fistula formation, this is mitigated by the higher rates of primary fascial closure achieved in association with the use of negative pressure therapy. In addition to the negative pressure therapy, additional benefit may be realized using dynamic retention sutures [69]. Together these strategies minimize the risk of failed primary fascial closure and associated problems with delayed surgeries, fistula formation, and the loss of domain.

15.5.5 Role of Minimally Invasive Surgery

Minimally invasive techniques potentially offer the patient and clinical team less traumatic means by which to achieve their therapeutic strategy, compared with open surgical strategies [8, 9]. For example, the readily available excellent axial imaging and interventional radiological techniques may facilitate a percutaneous drainage of an intraabdominal abscess achieving source control without the need for an open operation.

Laparoscopic approaches offer a similar, minimally invasive option for various pathologies. Robust data, demonstrating lower morbidity and mortality, supports the laparoscopic approach for cholecystectomy (compared with an open procedure) [8, 70]. Similarly, laparoscopic intervention for the complications of sigmoid diverticulitis, both lavage and resection, appears feasible and safe in appropriately selected patients [8, 28]. However, further research is required to better understand the role of these minimally invasive techniques and optimal patient selection.

15.5.6 Antimicrobial Therapy

Antimicrobial therapy should be instituted early during resuscitation—this critical component remains a cornerstone of the Surviving Sepsis Campaign [9, 23, 24]. Delayed antimicrobial administration, or the selection of ineffective drugs or regimens, is associated with increased morbidity and mortality [71, 72]. For intraabdominal infections initial broad-spectrum antibiotics should be selected. The chosen regimen should include cover for enterococci and be guided by local resistance patterns. Dose adjustments for patient comorbidities may be necessary. Antifungal cover is likely only needed in high-risk situations such as septic shock or in patients with postoperative infections. The presence of *Candida* in peritoneal culture specimens is associated with a poor prognosis [8, 9].

At the time of surgery for source control of intraabdominal infections, microbiological samples should be taken to guide and narrow the spectrum of therapy. In situations of relaparotomy, new samples can be obtained for further tailored therapy. De-escalation of antimicrobial therapy, as guided by the culture results and clinical progress, should be incorporated into the ongoing clinical review of the intensive care patient with intraabdominal infection [73]. Various authors have reported the importance of tailored antimicrobial therapy, including methods of real-time review of these decisions. Among other strategies, this ongoing review is facilitated by the antimicrobial stewardship rounds now commonplace in modern intensive care [72, 74].

15.5.7 Nutrition

Nutrition is a vital component of the complete surgical treatment of critically ill patients [60]. To minimize muscle breakdown and a catabolic state, the hypermetabolic demands of a patient with sepsis suggest that prompt and adequate nutritional support is required [61]. While malnutrition has clearly been associated with poor outcomes, the route of administration for nutrition in patients with intraabdominal sepsis is frequently complicated by gastrointestinal dysfunction.

Enteral nutrition (compared with parenteral administration) is associated with decreased septic complications. Early commencement of enteral nutrition has been associated with numerous markers of reduced morbidity, including reduced catabolism, reduced septic complications (including pneumonia and intestinal fistula formation in the open abdomen), improved immune function, improved wound healing, improved primary fascial closure rates in the open abdomen, reduced intensive care and hospital length of stay, and reduced hospital costs. It is important to note that enteral nutrition is not contraindicated by the open abdomen, per se. Enteral nutrition is withheld where patients with enteric discontinuity or non-absorption are present. It remains unclear if enteral nutrition may harm the situation in patients on significant doses of vasopressors and/or with significant intestinal hypoperfusion [9].

Supplemental parenteral nutrition has recently been shown to increase infectious complications in intensive care patients [75]. However, a subsequent randomized controlled trial found benefit in a more select group of patients guided by indirect calorimetry [76]. Further high-quality trials are required to define the timing of parenteral nutrition and the subset(s) of patients likely to benefit from parenteral nutrition.

15.6 Conclusion

Abdominal sepsis continues to be a challenging clinical problem. Recent improvements in modern surgical and intensive care medicine techniques offer patients improved outcomes and survival. Early and accurate diagnosis facilitates the timely institution of resuscitation. Source control is then tailored to optimal physiological resuscitation and in consideration with the pathology. Modern, damage control surgical strategies and minimally invasive techniques offer patients options to optimize outcomes. Many aspects of the clinical care discussed in this chapter continue to be investigated by current research. The findings of these studies will continue to evolve and modify diagnosis and treatment of intraabdominal sepsis.

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Ultrasound in the ICU: Nuts and Bolts for Managing the ACS Patient

16

Jay Doucet and Raul Coimbra

16.1 Introduction

Bedside ultrasonography by the non-sonographer clinician, also called point-of-care ultrasonography (POCUS), has become an essential part of the practice of acute care surgery. Ultrasound can facilitate and speed diagnosis and enhance the safety of procedures. Medical students in the USA are now being taught ultrasonography skills in their junior years of medical school. Residencies and fellowships are increasingly adopting ultrasound curricula. The quality of ultrasound equipment and images is improving, ease of use is better, and cost of equipment has decreased. In this chapter, we will discuss a "nuts and bolts" or basic approach to understanding and using ultrasound in the most common ICU applications for acute care surgeons.

16.2 Ultrasound Physics and Equipment

Sound is a mechanical longitudinal pressure wave that propagates through a medium, interacting with the substance it passes through. Human hearing allows sounds with frequencies 20–20,000 Hz (20 kHz or 0.02 MHz) to be heard. Ultrasound is defined as sound above the range of human hearing, above 20 kHz (0.02 MHz). Most diagnostic ultrasound is performed at frequencies of 2.5–10 MHz. The frequency

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used is a function of the transducer in the ultrasound probe and is a major factor in determining the depth of beam penetration. As frequency increases, penetration decreases. Frequency is also a determinant of image resolution—as frequency increases, resolution increases.

Sound waves travelling through media encounter interfaces with differing acoustic impedances resulting in reflection or attenuation. Reflection sends sound back to the transducer, giving us the image on the screen. Attenuation is anything that prevents return of sound to the transducer, such as scatter, where sound goes in multiple directions; absorption, where sound is turned into heat; or refraction, where interfaces with differing propagation speeds bend sound waves away from the transducer.

The target tissue under the ultrasound probe may be echogenic, which appears bright in the image—there is a large reflection component, and many waves are returning to the transducer. Anechoic or hypoechoic areas have little reflection and appear dark, there is large attenuation component, and waves are not returning to the transducer. Mixed echogenicity can also occur with intermediate brightness.

An acoustic window is an area that allows sound waves to penetrate into the body, usually with densities close to water. Good acoustic windows are the liver, the spleen, and the urine-filled bladder. Poor acoustic windows are gas such as the intestines or lung or strong reflectors such as bone. Finding good windows to image structures is a key learning task in ultrasonography.

The ultrasound transducer exploits the piezoelectric effect to receive sound—as sound waves strike the transducer elements, induced crystal deformation leads to electrical charge generation that is transformed by the electronics in the machine into an image. The reverse piezoelectric effect generates the sound waves by electrically induced crystal deformation which leads to sound wave generation. Ultrasound transducers are usually in pulsed echo mode—the crystal is receiving about 99% of the time and generating impulses 1% of the time.

Important controls on the machine include:

- Power – which powers the machine on and off, sometimes hard to find.
- Probe select – selects the various probes.
- Depth – how deep the image will go, usually in centimeters.
- Gain – higher settings increase electrical amplification of the received image and generate a brighter image. There are usually two kinds of gain:
  - Total gain – amplifies returning echo and allows lower power (patient intensity exposure) use and brighter image.
  - Time gain compensation (TGC), which amplifies returning echoes by the factor of time required for echo return, allowing homogenous tissue to be isoechoic regardless of depth. Deeper or shallower tissue can be made comparatively brighter or darker as needed. This is usually a series of sliding controls corresponding to different depths.
  - Gain and TGC must be actively used to keep like tissue looking alike (i.e., the liver) and cystic structures and vessels anechoic (black).

- Frequency – this is primarily set by the probe selected but can be adjusted by a menu selection:
  - S, standard, or G, general
  - R, resolution (higher frequency)
  - P, penetration (lower frequency)
- Mode – this is the imaging mode, such as:
  - 2D – two dimensional, sometimes called B-brightness mode
  - M – M-mode (motion on a line over time)
  - CF – color flow Doppler
  - PW – pulse wave Doppler or spectral Doppler and others
- Freeze – freezes the image, usually also allows the previous 256 or more frames to be scrolled through, and allows measurements.
- Print – prints the image on a connected printer.
- Save/clip – saves a still image file or saves a video clip file of 256 or more image frames.

Examples of typical ultrasound transducer probes are shown at Fig. 16.1. An important detail is the location of the index mark on the ultrasound probe, usually a bump or ridge molded onto the probe. This corresponds to a marker on the image screen. Care must be taken to keep the probe orientated such that index mark and the marker on the screen correspond; otherwise the image will be reversed, and confusion usually results. The convention in abdominal ultrasonography is for the marker on the screen to be on the top left of the screen, but in echocardiography the convention is reversed, and the marker is on the top right of the screen.

POCUS is not a spectator sport; to gain skill you must put the ultrasound probe onto your patients. Hands-on training is required to learn how to fan, rock, rotate, slide,

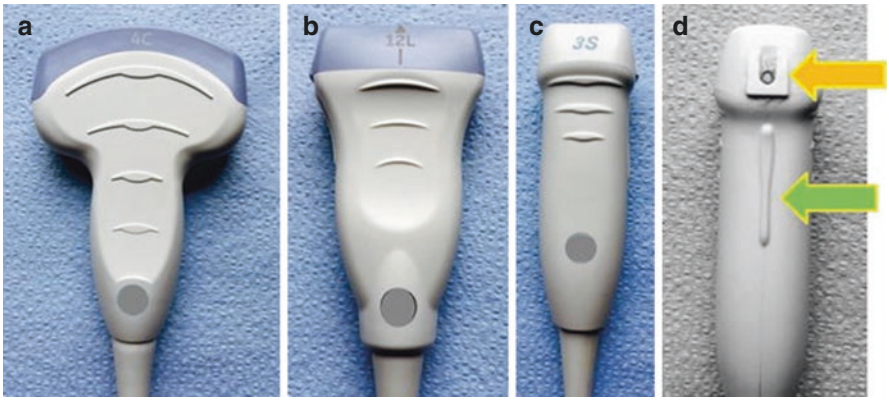

Fig. 16.1 Typical ultrasound probes. (**a**) Convex low-frequency transducer, used in abdominal exams; (**b**) linear high-frequency transducer, used in vascular and pleural exams; (**c**) phased array low-frequency transducer specifically designed for cardiac imaging/echocardiography; (**d**) showing the transducer orientation index marker. Note the ridge on the probe housing and the LED. Source: https://media.springernature.com/original/springer-static/image/chp%3A10.1007%2F978-3-319-22638-5_5/MediaObjects/323038_1_En_5_Fig26_HTML.jpg

and translate the probe to see structures. If a patient has a known abnormality, ask the patient if you may take a look with ultrasound. Patients with known ascites, hemoperitoneum, known AAA, DVT, pleural effusions, congestive heart failure, and gallstones serve as a quality check on your skills. Log your studies for future credentialing needs. Keep track of confirmatory studies after your POCUS exams so that you can perform good quality assurance on your skills. Befriend a mentor with more sonography experience to help evaluate your skills periodically and help you learn new ones.

16.3 Abdominal Ultrasound

16.3.1 Fast

In 1996, "Focused *Abdominal* Sonography for Trauma" or FAST was described by Rozycki et al. The exam was "focused"—looking for free fluid only—to simplify the test and to make it faster [1]. However, within a year the name of the exam had already changed to the "focused a*ssessment* with sonography for trauma" due to the realization that thoracic structures such as the heart, pericardium, and pleura could also be evaluated [2]. FAST is useful not just in trauma patients but can be adapted for the assessment of other acute surgical patients as well.

The purpose of the FAST examination is to determine the presence of pathologic intra-abdominal, intrapleural, or intraperitoneal free fluid, which has a distinctive hypoechoic or anechoic (that is, black) appearance on the screen [3]. About the only absolute contraindication to doing the FAST exam is when it delays performing a definitive operative procedure.

Ultrasound offers several advantages in the evaluation of the acute surgical patient. It is rapid and can be done at the bedside. It is noninvasive and does not require the use of radiation. It can be performed quickly, including in the middle of a trauma or shock resuscitation or even during CPR. The test can be repeated as often as desired. This makes it very suitable for the acute patient in shock, where the ATLS Primary Survey Adjuncts of FAST, chest X-ray, and pelvis X-ray can quickly locate the site of a large intracavitary hemorrhage and hematoma [4].

FAST ultrasound of the abdomen does have some significant limitations; the most significant is its lack of sensitivity (Table 16.1). There are other tests that are more sensitive such as the CT scan of the abdomen, which is very sensitive and specific, or the diagnostic peritoneal lavage, which is exquisitely sensitive and not very specific. Sensitivities as low as 42% have been reported with FAST. However, that may matter less when FAST is employed by surgeons using an appropriate trauma or ICU algorithm. The low sensitivity of FAST is complemented by a good selectivity which means that a positive test is likely true and the negative test simply means more evaluation is necessary.

The FAST exam has been tinkered with and continually improved since the original four quadrant exam. The eFAST (enhanced FAST) means the addition of pleural views, which can detect a pneumothorax more rapidly and with greater sensitivity than a chest X-ray [5, 6]. The thoracic views improve the utility of eFAST, even

Table 16.1 Sensitivity and negative predictive value (NPV) of FAST [7]

Study	*n*	Sensitivity (%)	Specificity (%)	NPV (%)
Ballard et al. [8]	102	28	99	85
Boulanger et al. [9]	400	81	97	96
Chiu et al. [10]	772	71	100	98
Coley et al. [11]	107	38	97	78
Hoffmann et al. [12]	291	89	97	93
Ingeman et al. [13]	97	75	96	92
Kern et al. [14]	518	73	98	98
Liu et al. [15]	55	92	95	84
McElveen and Collin [16]	82	88	98	96
McKenney et al. [17]	996	88	99	98
Rozycki et al. [3]	470	79	96	95
Rozycki et al. [1]	365	90	100	98
Rozycki et al. [18]	1227	78	100	99
Shackford et al. [19]	234	69	98	92
Thomas et al. [20]	300	81	99	98
Tso et al. [21]	163	69	99	96
Wherret et al. [22]	69	85	90	93
Yeo et al. [23]	38	67	97	93
Total	6324	75	98	94

though it shares the relative lack of sensitivity of the traditional FAST abdominal exam compared to the CT scanner.

In patients in whom there is a doubt regarding the presence of pericardial effusion or tamponade, the FAST exam of the pericardium is invaluable and can be lifesaving.

Some centers have improved the sensitivity of trauma ultrasonography by actually doing extra views and examining the organs, instead of just looking for fluid as done in FAST. We have previously demonstrated, at our Level I Trauma Center, that a combination of a comprehensive negative screening ultrasonography (US) and negative clinical observation for 12–24 h, in the setting of blunt abdominal trauma, virtually excludes missed abdominal injury [24]. We call this complete examination CUST – complete ultrasonography of trauma. Other advantages of CUST are the significant reduction in hospital charges as well as a large reduction in radiation exposure in trauma patients. Surgeon-selected blunt abdominal trauma screening with the CUST protocol appears to have similar outcomes as CTAP. While the initial CUST sensitivity was 76% in 19,128 patients, when combined with serial examination and selective CT scanning, the false-negative rate was 0.29% with a NPV of 99% [25].

There are conditions in which a negative FAST cannot be accepted as definitive, and a CT scan should be performed.

Do not accept as definitive a negative FAST examination that is:

- Of poor quality
- In cases of seat belt mark injury
- In cases of penetrating torso trauma
- If the patient is very obese

- If there is hematuria
- If the patient has significant abdominal pain without other operative indications
- If spinal and/or pelvic fractures are suspected

In such cases, the patient should undergo CT scanning.

Relative indications for CT scanning include patients who are unable or uncooperative with serial abdominal examinations or who will be unavailable for serial abdominal examinations such as those undergoing neurosurgical or orthopedic procedures.

Operating without a FAST exam might be considered in penetrating trauma or in blunt trauma with conditions such as peritonitis or evisceration. However, this means that there is no evaluation of the pleura or pericardium prior to the procedure. The exact trajectory of penetrating trauma might not be immediately known at laparotomy. The presence of an occult pneumothorax might be missed and manifest only after intubation and anesthesia. Missed tamponade can be a lethal error and can occur in both penetrating and blunt trauma.

Serial abdominal examination without FAST means that the opportunity to conduct repeat FAST exams is lost. Repeat FAST examinations increase the test's sensitivity and can indicate the need for CT or operation before peritonitis or abdominal pain manifests [26].

CT scanning as the only imaging modality in trauma ("PanScan") will mean the number of unnecessary scans will increase. We saw this at our facility when CUST is not available during evening hours 2300–0700. The number of negative abdominal/pelvis CTs at our center without CUST was 51%. When CUST was being used, the negative CT rate was 37% [25]. Adopting CUST 24/7 resulted in a $591,656 annual reduction in charges with a reduction of 188,003 mSV of radiation exposure. The latest Cochrane analysis of FAST algorithms could not show a difference in CT versus FAST algorithms' mortality but did find a substantial reduction in radiation [27].

Some providers are uncomfortable in watching the asymptomatic trauma patient with FAST and serial examinations. They may also be the same providers who are uncomfortable making a decision to operate without whole-body CT imaging, the so-called PanScan—complete head, neck, and torso CT of every major trauma patient. We believe this is wasteful of resources and leads to excess radiation doses to trauma patients. An appropriate physical examination and FAST can reduce dependency on the routine PanScan. The CT scanner may hold a siren call for the unwary provider with a metastable acute surgical patient who may subsequently suffer clinical deterioration and death in a poorly observable and accessible area of the hospital. This can be avoided by appropriate training, including the use of FAST.

A limitation of FAST is that results are operator-dependent. Less experienced operators are less sensitive to detecting fluid—in one study about 10% of residents and attendings could detect 400 mL of intraperitoneal fluid, 85% could detect 850 mL, and 97% could detect 1000 mL (Fig. 16.2) [28].

The operator-dependent nature of the FAST exam has led to a recognition that ultrasound must become part of the curriculum in medical school, residencies, and fellowships. In 2017, guidelines, including didactic education and number of

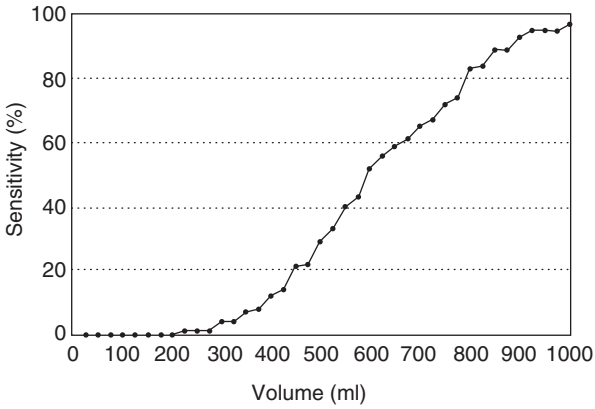

Fig. 16.2 Sensitivity of FAST to intraperitoneal fluid volume—EM attendings and residents. Source: Figure 2 in Branney et al. [28]

Fig. 16.3 Hand held, multimode, semiconductor chip ultrasound transducer connects to iOS mobile phone, uses cloud storage, and costs less than US$2000. Source: Jay Doucet (Author)

proctored examinations, were provided in the USA by the Surgical Critical Care Program Directors Society (SCCPDS) [29].

The current technologic revolution has also affected the FAST exams. It is now possible to purchase a FDA-approved ultrasound machine that performs most imaging modes, uses a semiconductor chip sound emitter, has digital image processing, connects to the cloud via mobile phone, and costs less than US$2000 (Fig. 16.3). Ultrasound machines are rapidly approaching the cost and availability of a high-quality stethoscope and will be carried by increasing numbers of providers. Ignoring the capabilities of this imaging modality will soon be impossible for acute care surgeons.

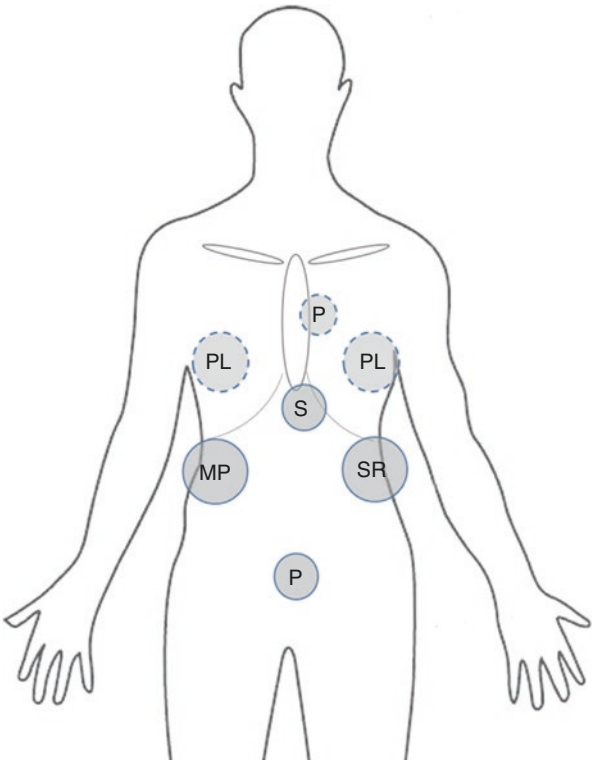

Fig. 16.4 Solid ovals are probe locations for FAST abdominal ultrasound – the Morrison's pouch (hepatorenal fossa), the splenorenal fossa (SR), the subcostal area (S), and the pelvis (P). Dashed circles are typical additional windows for eFAST—pleura (PL) and parasternal (P). Drawing: Jay Doucet—Author

The principal probe positions for the FAST examination are shown at Fig. 16.4 along with typical appearances of hemoperitoneum and pericardial fluid (Fig. 16.5). eFAST adds pleural and parasternal windows as well.

16.3.2 Specific Abdominal Organs

The acute care surgeon, after mastering the FAST examination, can expand their skills into an ultrasound repertoire that could include abdominal aortic aneurysm (AAA), gallbladder/hepatobiliary, spleen, and appendix/intestinal examinations. Each new area requires additional training and a sufficient caseload to maintain proficiency. Most of these exams are not extremely time critical, with the possible exception of the AAA examination in a hypotensive patient. In most medical centers, a skilled sonographic technician routinely performs these examinations. However these are also within the ability of an interested acute surgeon-sonographer, and in the USA, national credentialing is available in each area under the Alliance for Physician Certification & Advancement (APCA) or the American Registry for Diagnostic Medical Sonography (ARDMS).

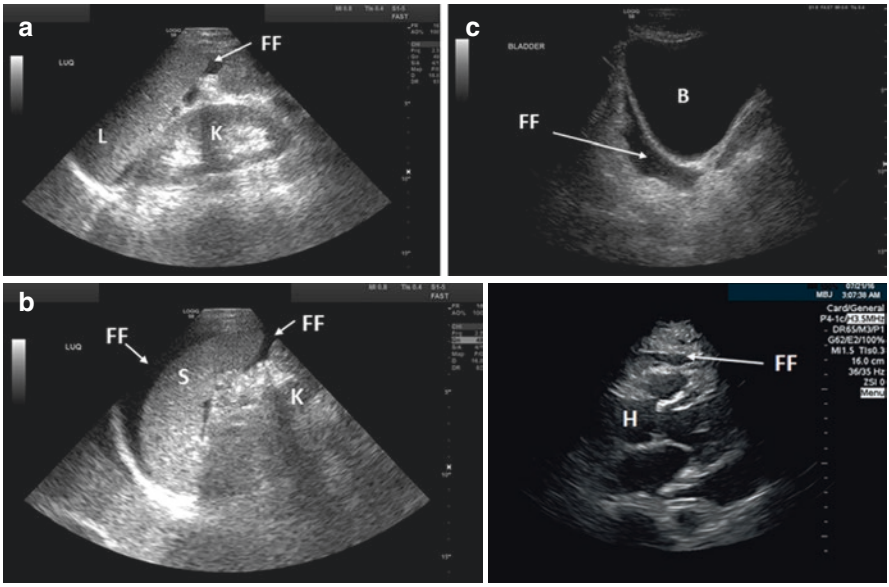

Fig. 16.5 (**a**–**c**) Example FAST images with hemoperitoneum—(**a**) Morrison's pouch (hepatorenal fossa), (**b**) splenorenal fossa, (**c**) pelvis with bladder, (**d**) FAST subcostal SLAX view with large pericardial effusion. FF marks areas of free fluid. *L* liver, *S* spleen, *K* kidney, *B* bladder, *H* heart. Source-Author—J. Doucet

16.4 Cardiac Ultrasound

The differential diagnosis and management of shock states in the ICU are frequent challenges to the acute surgeon. Clinical examination is notoriously unreliable. Invasive monitoring techniques such as central venous pressure and pulmonary artery pressure catheters have fallen out of favor in many cases due to concerns for increased complications and difficulty of interpretation. The latest addition to the FAST examination is the use of ultrasound to guide resuscitation of the acute surgical patient with shock. The intravascular volume status of the trauma patient has been estimated by the inferior vena cava (IVC) diameter and collapsibility as well as by ventricular filling [30]. More than 20 studies have been published describing the use of cardiac ultrasonography for resuscitation [31].

Bedside limited echocardiography has the advantages of being noninvasive and rapid and being performed by the acute surgeons who will make decisions on definitive management. Right and left ventricular function, intravascular volume, and tamponade physiology can be rapidly identified. The focus assessed transthoracic echocardiography (FATE) examination was first described in 1989 in Denmark as a rapid way to assess shock states in critical care patients [32]. Similarly, the focused cardiac ultrasonography (FoCUS) examination was recommended by the American Society of Echocardiography (ASE) in 2014 for non-cardiologist clinicians to obtain rapid cardiac assessments [33]. The purpose of these exams is not to replace formal echocardiography, which can detect subtle and sophisticated findings such in as chronic valvular disease, but instead to make a shortened echocardiographic

assessment of the current physiologic state, rule in or out critical diagnoses, and guide resuscitative efforts.

Limited echocardiography is a step-up in training complexity from the FAST examination. The target is moving, the useable sonographic windows are smaller, and there is a greater demand on psychomotor skills to place the probe in the exact position to obtain the desired view. In trauma patients, typically less than 50% of the cardiac echocardiographic windows are useable due to subcutaneous air, pneumothoraces, edema, wounds, dressings, spinal precautions, and difficulty in positioning the patient [34]. Another training issue is that ultrasound machines switching from abdominal to cardiac modes by convention usually reverse the image, causing the index mark on the screen to shift from top left to top right. However, acute surgeons and trainees have routinely mastered these skills and are rewarded by the ability to make rapid assessments of cardiac physiology and intravascular volume status in the shock state.

There are three typical probe locations on the thorax for limited cardiac echo—the subcostal area (S), the left parasternal area (P), and the apical area (A) (Fig. 16.6).

The subcostal location is included in the FAST examination and has two probe positions—subcostal long axis (SLAX) and subcostal short axis (SSAX)—which give long axis and short axis views of the ventricles (Fig. 16.6). A view of the inferior vena cava can also be obtained here (SIVC). The SLAX view requires placing probe below the xiphisternum, pointing the probe at the left acromion and rotating

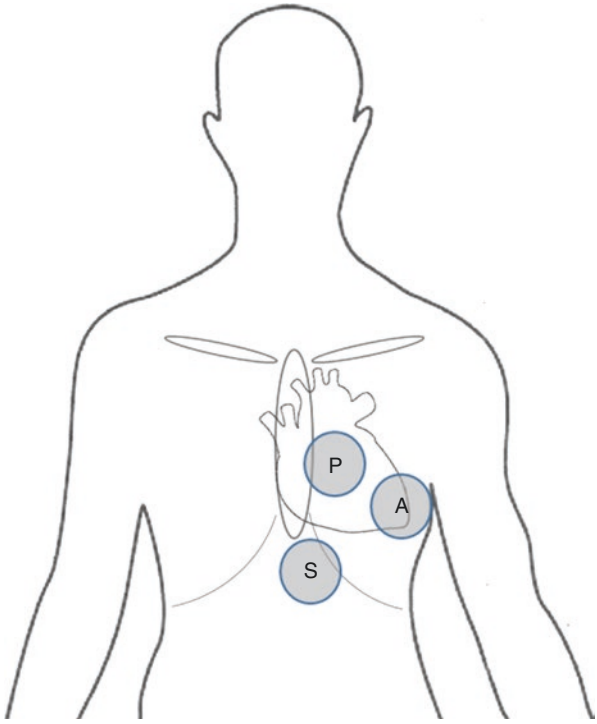

Fig. 16.6 Probe locations for point-of-care echocardiography—the subcostal area (S), the left parasternal area (P), and the apical area (A). Drawing: Jay Doucet

the probe on its long axis so that the index mark points away from the right shoulder, giving a long view of the ventricles (Fig. 16.7). The SLAX allows assessment of the left ventricle's performance. The SSAX view can then be obtained by continuing to point the probe at the left acromion while rotating the probe so that the index mark points toward the patient's feet, giving a view across the ventricles (Fig. 16.8). This allows assessment of the relative size of the left and right ventricle and comparison of performance of various areas of the left ventricle, as well as qualitative assessment of ejection fraction. The SIVC view is then obtained by pointing the probe in the subcostal area more medially to see the entry of the IVC into the inferior right atrium (Fig. 16.9). The SIVC allows assessment of intravascular volume status by IVC diameter.

If the IVC view cannot be obtained via the SIVC view due to interference from abdominal gas, incisions, dressings, or subcutaneous air, it can also be assessed by placing the probe posteriorly at the right posterior costal margin in the posterior axillary line. This has the advantage of looking through the posterior liver anteriorly without the intestinal gas being interposed. Once the hepatorenal fossa (Morrison's pouch) is identified, the probe is tilted so that the IVC, near the center of the torso, can be identified. In any view, the IVC diameter is typically assessed about 2–2–3 cm below the right atrial—IVC junction—in both transverse and longitudinal views [35].

The parasternal window offers the shortest distance to the heart but is frequently affected by chest injury, dressings, and pneumothoraces. The parasternal long axis (PLAX) view is obtained by placing the probe in about the fifth interspace just to the left of the sternum (Fig. 16.10). The probe is aligned so that the long axis of the probe head is aligned along a line from the right acromion to

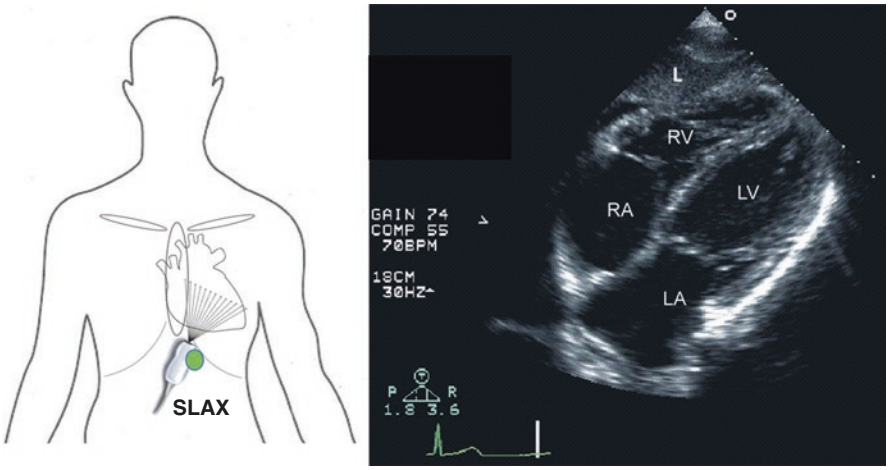

Fig. 16.7 The subcostal long axis (SLAX) view—the index mark is to the patients left. *RV* right ventricle, *LV* left ventricle, *L* liver. (From Adams D, Forsberg E. Conducting a cardiac ultrasound examination. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography. London: Springer; 2009). Drawing: Jay Doucet. Photo: https://link.springer.com/article/10.1186/s13054-014-0681-z

the left upper quadrant of the abdomen, with the index mark pointing away from the right shoulder, giving a long view of the ventricles, allowing assessment of left ventricle performance. The parasternal short axis (PSAX) view is obtained by rotating the probe 90° so that the long axis of the probe head is aligned along a line from the left acromion to the right upper quadrant of the abdomen, with

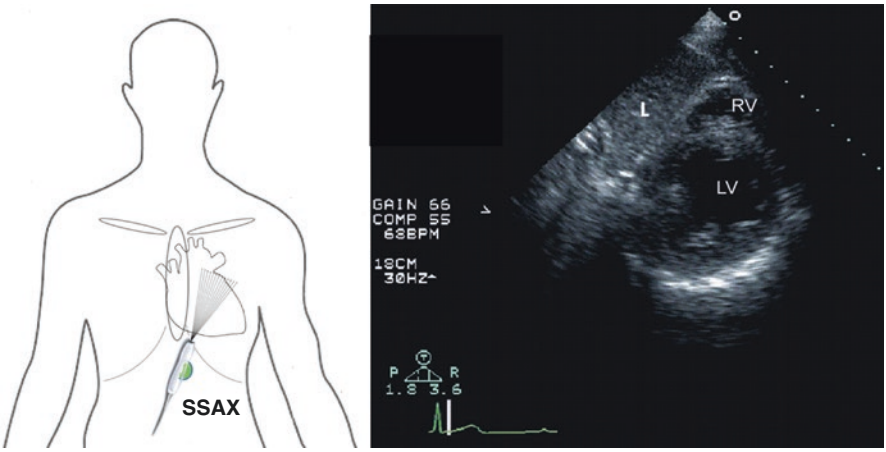

Fig. 16.8 The subcostal short axis (SSAX) view—the index mark is to the patients feet. *RV* right ventricle, *LV* left ventricle, *L* liver. (From Adams D, Forsberg E. Conducting a cardiac ultrasound examination. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography. London: Springer; 2009). Drawing: Jay Doucet. Photo: https://link.springer.com/chapter/10.1007/978-1-84882-293-1_2 (Figure 2.10)

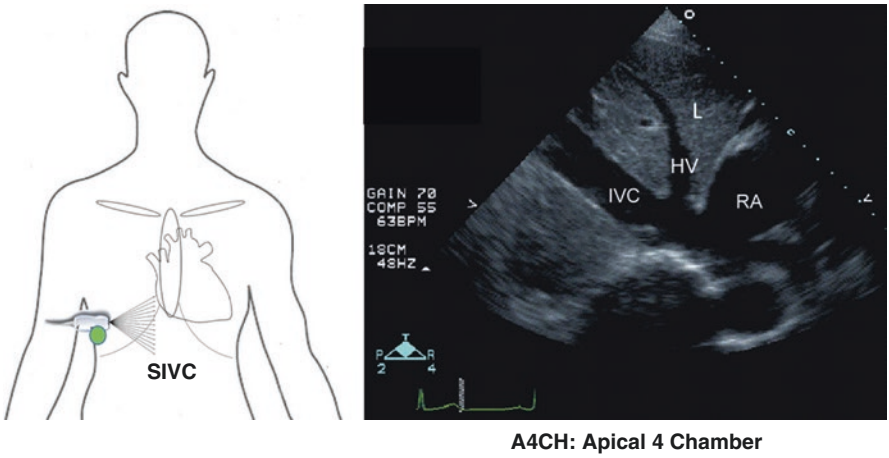

Fig. 16.9 The subcostal IVC (SIVC) view—the index mark is toward the patients feet. *HV* hepatic vein, *IVC* inferior vena cava, *RA* right atrium, *L* liver. (From Adams D, Forsberg E. Conducting a cardiac ultrasound examination. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography. London: Springer; 2009). Drawing: Jay Doucet. Photo: https://media.springernature.com/original/springer-static/image/chp%3A10.1007%2F978-1-84882-293-1_2/MediaObjects/978-1-84882-293-1_2_Fig11_HTML.gif (Figure 2.11)

the index mark pointing away from the left shoulder, giving a short view across the ventricles (Fig. 16.11). The probe can be tilted with a "fanning" motion to examine the ventricles from the tricuspid or mitral annulus to the chordae and to the apex of the heart.

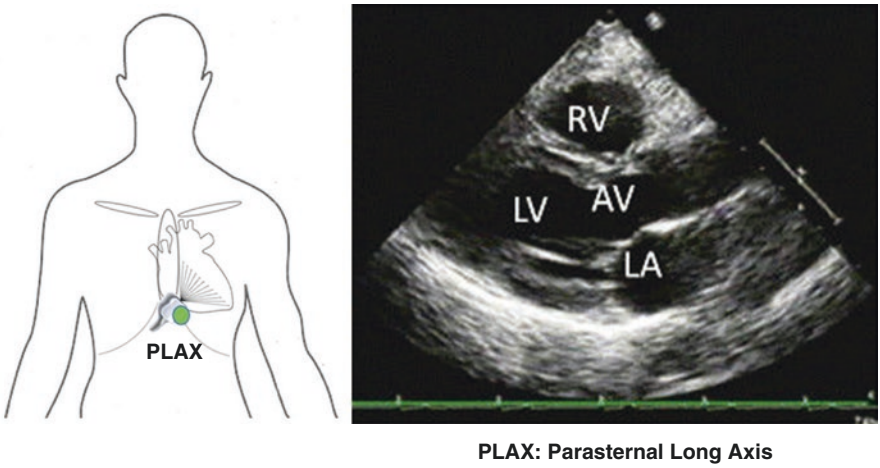

Fig. 16.10 The parasternal long axis (PLAX) view—the index mark is to the patients left upper quadrant. *RV* right ventricle, *LV* left ventricle, *LA* left atrium, *AV* aortic valve. (From Walley PE, Walley KR, Goodgame B, et al. A practical approach to goal-directed echocardiography in the critical care setting. Crit Care. 2014;18:681. https://doi.org/10.1186/s13054-014-0681-z.) Drawing: Jay Doucet. Photo: https://link.springer.com/article/10.1186/s13054-014-0681-z

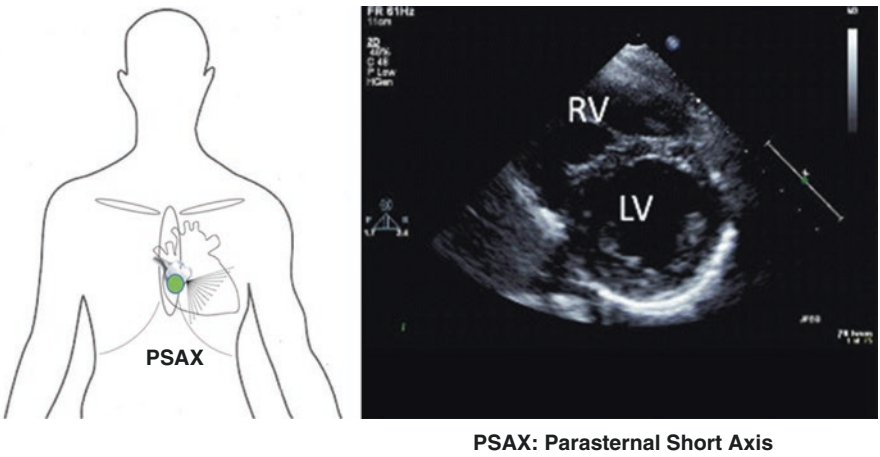

Fig. 16.11 The parasternal short axis (PSAX) view—the index mark is to the patients right upper quadrant. *RV* right ventricle, *LV* left ventricle. (From Walley PE, Walley KR, Goodgame B, et al. A practical approach to goal-directed echocardiography in the critical care setting. Crit Care. 2014;18:681. https://doi.org/10.1186/s13054-014-0681-z.) Drawing: Jay Doucet. Photo: https://link.springer.com/article/10.1186/s13054-014-0681-z

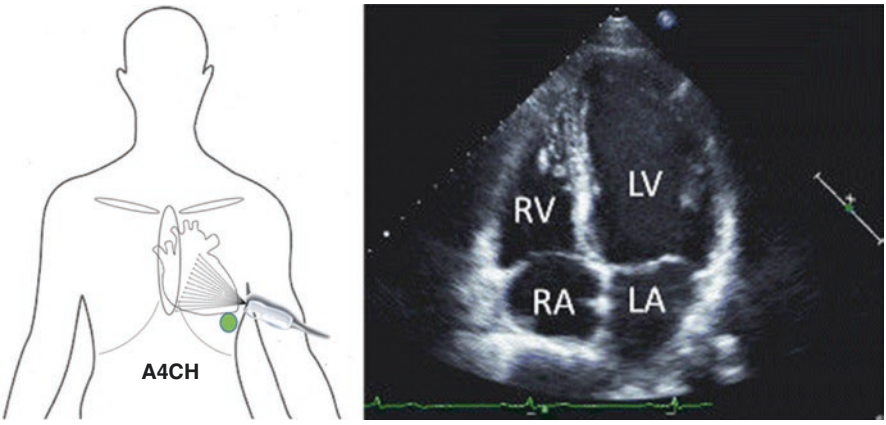

Fig. 16.12 The apical four chamber (A4CH) view—the index mark is to the patients right acromion. *RV* right ventricle, *LV* left ventricle, *RA* right atrium, *LA* left atrium. (From Walley PE, Walley KR, Goodgame B, et al. A practical approach to goal-directed echocardiography in the critical care setting. Crit Care. 2014;18:681. https://doi.org/10.1186/s13054-014-0681-z.) Drawing: Jay Doucet. Photo: https://link.springer.com/article/10.1186/s13054-014-0681-z

The apical location is often unusable in the ICU as many patients must be positioned so that they are rolled onto their left side, allowing the apex of the heart to be more proximal to the chest wall. The apical four chamber view (A4CH) is obtained by placing the probe in about the fifth intercostal space in the midclavicular line pointing at the right acromion (Fig. 16.12). The index mark is pointed somewhat posteriorly. This will achieve a view of all four chambers of the heart as well as the intraventricular septum. Comparison of left and right ventricular size and function can be made as well as views of the tricuspid and mitral valves obtained. Septal motion can also be assessed. Allowing the probe position to slide slightly more anteriorly on the chest achieves the "five chamber" view where the aortic valve is also seen as well as four ventricles.

16.4.1 Left Ventricle

A rapid qualitative assessment of left ventricular (LV) performance can be obtained from the above views. A stepwise assessment of the heart can be performed by first looking for obvious pathology such as tamponade, dilation, or hypokinesis; next looking at ventricular size, wall thickness and filling, and in systole and diastole; and then looking at contractility in both left and right ventricles. The pleura should also be imaged bilaterally to identify pleural effusions or pneumothorax.

With a reasonable amount of practice, the acute surgeon can readily identify when LV ejection fraction is below 40–45% without need of formal measurements or calculations. A baseline bedside echocardiographic study in the acute ICU admission makes subsequent identification of acute versus chronic LV dysfunction easier.

Global LV dysfunction can be seen in sepsis and septic shock, post-arrest states, stress cardiomyopathy, dilated cardiomyopathy, myocarditis, and in chronic congestive heart failure. Generally the acute surgeon is looking for gross changes that will help explain a shock state. Subtle dysfunction such as diastolic heart failure is beyond the scope of the limited echocardiogram by the acute surgeon.

A special form of LV stress dysfunction can have a specific appearance—Takotsubo cardiomyopathy or "broken heart syndrome" [36]. This can be triggered by physiologic or psychologic stress, usually in critically ill patients 50–80 years old. Women comprise 90% of cases. Classically, the base of LV is seen to have normal size and contractility, while the apical segment is seen to balloon outwards in systole, giving the heart the shape of the Japanese octopus trap that provides the name of this condition.

Areas of localized LV hypokinesis may be caused by localized ischemia such as seen in acute coronary syndromes. The echocardiogram is more sensitive than EKG in detection of myocardial infarction in the postoperative patient and can add sensitivity to troponin levels, which are already abnormal in 15–30% of non-cardiac surgery ICU patients. Although specific areas of the LV can be associated with particular coronary artery occlusions, this is beyond the scope of the usual acute surgeon echocardiographic examination—in suspected acute coronary syndromes, cardiology consultation is warranted.

16.4.2 Right Ventricle and IVC

The right ventricle (RV) views should not be ignored as they can be significant in the shock state. The RV is harder to visualize due to its thinner wall. The normal RV wraps around a portion of the thick-walled circular LV as seen in the short axis PSAX or SSAX views. The interventricular septum normally bulges in a convex manner from the LV into the RV in both systole and diastole. In the healthy heart, the stroke volume and ejection fraction are similar in the LV and RV, so the ventricular volumes should be equivalent, although each is shaped differently. As RV pressures increase such as in right heart failure, pulmonary embolism, or pulmonary hypertension, the RV can be seen to enlarge, and the septum increasingly flattens the side of the normally circular LV in the short axis views. As RV pressures increase further, the septum may begin to paradoxically bulge into the LV for a greater portion of the cardiac cycle.

Significant PE associated with shock is classically associated with a distended RV, flattened septum, under filled LV, and distended IVC. Echocardiography has a specificity of 81 and 94% and a positive predictive value of 71 and 86% for pulmonary emboli; however other sources of RV failure should be considered within the clinical context [37].

The IVC views should also be part of the cardiac ultrasound of the acute patient with a suspected shock state. Under normal conditions in healthy, spontaneously breathing, supine patients, the IVC will nearly or completely collapse with inspiration and expand with expiration. Ultrasonographic assessment of the diameter of

the inferior vena cava in expiration (IVCe) and in inspiration (IVCi) allows assessment of the collapsibility of the inferior vena cava (IVCe-IVCi) [38]. Another measurement of intravascular volume status is the IVC collapsibility index (IVC-CI). The IVC-CI is calculated using a standard formula IVC-CI = (IVCe) − (IVCi)/(IVCe) × 100%, where IVCe is the maximum IVC diameter at expiration and IVCi is the minimum IVC diameter at inspiration [39]. Respiratory variation in IVC diameter has been found to be more pronounced in hypovolemia with abnormally low CVP being increasingly likely as IVC-CI approaches 100%. However there is not yet an exact cutoff value determined for IVC-CI for hypovolemia, although 75% has been suggested as the cutoff.

Similarly to central venous pressure measurements, techniques of IVC measurement have many of the same inaccuracies of CVP measurements. Positive pressure ventilation can invert the normal inspiratory-expiratory minimal and maximum size relationship, and high PEEP levels may reduce venous inflow to the chest and distend the IVC. Increased right atrial pressures are seen in right heart failure, valvular disease, and pulmonary hypertension and may cause increased IVC diameter that is not reflective of an increased volume status. However, these conditions would not be expected in most trauma or acute surgery admissions. Another issue with IVC diameter may be the effect of increased abdominal pressure such as seen in abdominal compartment syndrome causing narrowing of the IVC [40]. However, abdominal compartment syndrome is rarely present at admission in acute surgery patients and, when it is present at admission, is usually accompanied by overt clinical signs that indicate immediate surgical intervention.

Following IVC diameters after initial therapeutic fluid challenge of the blunt trauma patient with hypotension may improve the utility of FAST in trauma patients. Yanagawa et al., in a study of 30 trauma patients presenting with shock (systolic BP < 90 mmHg), followed patients into two groups: a transient responder group ($n = 17$) in which shock recurred after an initial 2 L intravenous crystalloid fluid bolus in the emergency room and a responder group ($n = 13$) in which blood pressure remained stable [41]. IVC diameter predicted patients who would become hypotensive later despite equivalent fluid resuscitation. It also predicted those likely to need emergent hemostatic inventions such as laparotomy or angiography – the transient responder group contained a greater proportion of patients who underwent such procedures than the responder group (47.0% vs. 7.6%, $p < 0.05$).

In our own institutional experience, 127 trauma patients with persistent IVC collapsibility on a second IVC measurement 60 min after admission had significantly higher intravenous fluid requirements during the first 24 h of hospitalization, needing 1018 mL ± 484 more crystalloid.

16.4.3 PEA and CPR

There is evidence that performance of limited echocardiography during PEA and CPR can be useful [42]. Four immediately significant conditions can be identified from the SLAX view, even while CPR is in progress. Cardiac standstill, with no

visible cardiac motion, is associated with no meaningful survival in blunt trauma patients undergoing CPR for cardiac arrest and is considered justification for suspension of resuscitative efforts, precluding resuscitative thoracotomy [43]. Cardiac tamponade, identified as a pericardial effusion with RV or right atrial collapse with tamponade physiology, requires pericardiotomy for surgical causes with pericardial clot and pericardiocentesis for medically caused non-clotting effusions. An empty heart points to severe hypovolemia. Massive pulmonary embolism is associated with RV distension, septal flattening, and small LV size.

16.5 Pulmonary Ultrasound

16.5.1 Pneumothorax

Ultrasound can detect non-loculated pneumothorax more rapidly and more accurately than chest X-ray, although sensitivity can be affected by recent surgery, the presence of a chest tube, or subcutaneous air [5]. Specificity of a positive examination is excellent, and the size of the pneumothorax can be estimated in the supine patient, as the lung usually falls away from the anterior chest wall before the lateral chest wall. In this way, ultrasound can detect the presence of an "occult" pneumothorax that would not be visible on a supine chest X-ray. Either the phased array or high-frequency linear probe can be used, although we prefer the higher resolution of the linear probe.

There are four ways ultrasound can be used to identify a pneumothorax:

1. Pleural sliding—the lung slides within the pleura during respirations, and this sliding is evident by the sliding motion, especially of sonographic "B-lines," which appear as bright spots on the pleural surface with "ringdown" artifact, producing an appearance called "comet tails" (Fig. 16.13). There is no pleural sliding and no comet tails in locations where a pneumothorax is present.
2. M-mode—using M-mode provides a time-based graphical output of a single line over time. This can make pleural sliding more evident, with the normal exam with sliding producing a granular appearance below the ribs called the "sandy beach" (Fig. 16.14) and where a pneumothorax without sliding generates an undifferentiated multilayered appearance called the "stratosphere" sign (Fig. 16.15).
3. Lung point—this is a highly sensitive and specific sign of pneumothorax. As the probe is slid from the anterior portion of the chest where the pneumothorax is present to a more posterior and lateral position, the edge of the lung posterior to the pneumothorax that is just touching the chest wall may be seen. As the lung slides back and forth with respirations, periods of pleural sliding are interspersed with periods of no sliding. The edge of the lung is typically triangular in cross section, and so the name of lung point arises. Lung point may not be seen in large or tension pneumothoraces, as no part of the lung may be found in contact with the chest wall.

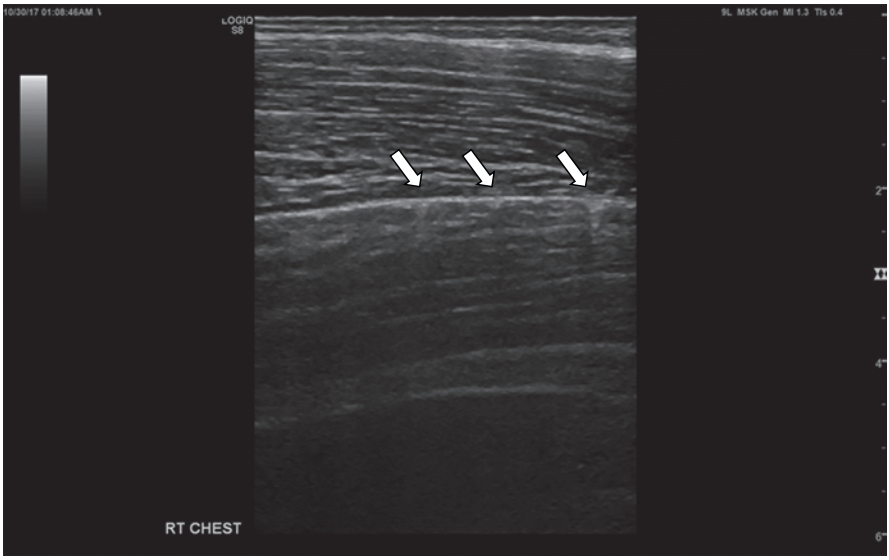

Fig. 16.13 Comet tails on pleural ultrasonography—normal—arrows indicate comet tails. Source: Jay Doucet—Author

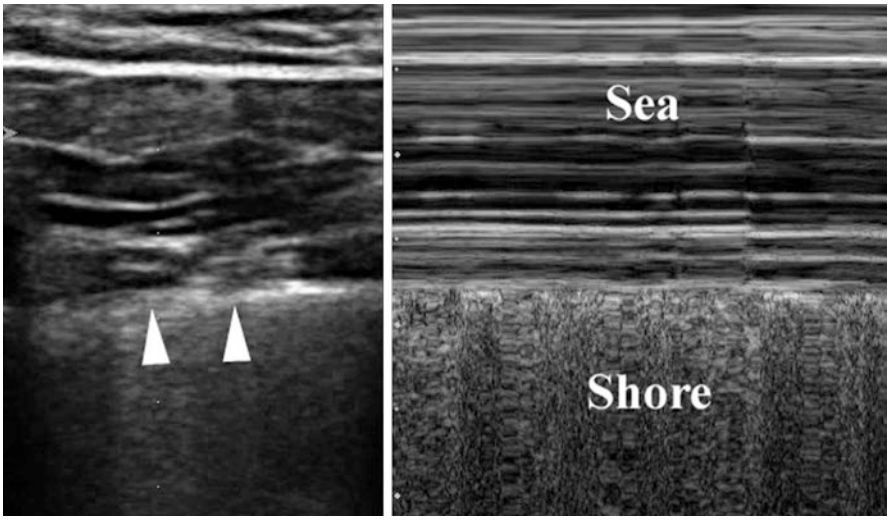

Fig. 16.14 Pleural ultrasonography—this is a split image with the left showing the 2D view of the pleural interface and the right side showing a normal M-mode image showing the "seashore" sign which is evidence of pleural sliding. (From Gillman LM, Ball CG, Panebianco N, Al-Kadi A, Kirkpatrick AW. Clinician performed resuscitative ultrasonography for the initial evaluation and resuscitation of trauma. Scand J Trauma Resusc Emerg Med. 2009;17:34. https://doi.org/10.1186/1757-7241-17-34.) Source: Gillman LM et al. Scand J Trauma Resusc Emerg Med. 2009;17(1):34

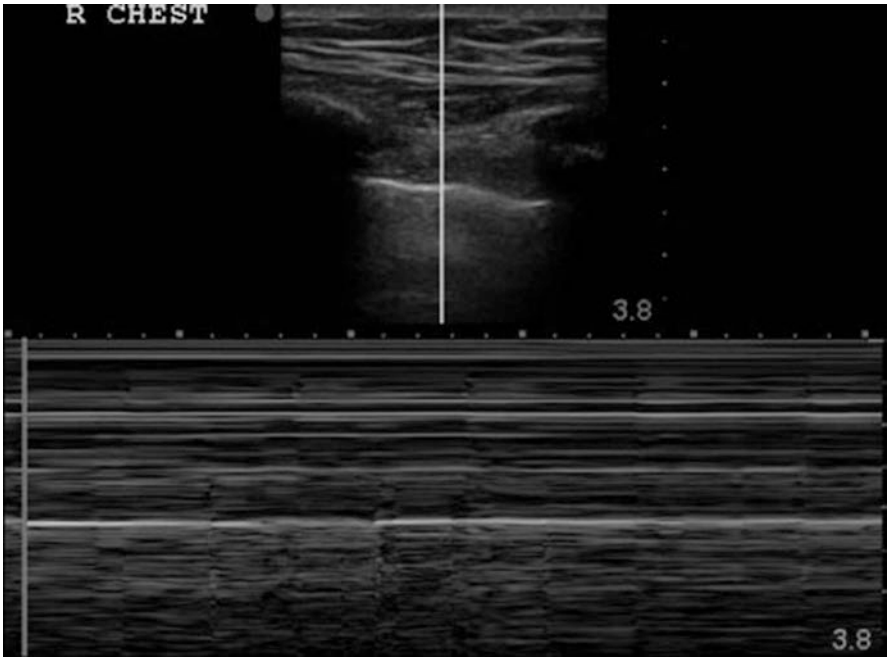

Fig. 16.15 Pleural ultrasonography—this is a split image with the top showing the 2D view of the pleural interface and the bottom showing an abnormal M-mode image showing the "stratosphere sign" due to pneumothorax and no pleural sliding. (From Gillman LM, Ball CG, Panebianco N, Al-Kadi A, Kirkpatrick AW. Clinician performed resuscitative ultrasonography for the initial evaluation and resuscitation of trauma. Scand J Trauma Resusc Emerg Med. 2009;17:34. https://doi.org/10.1186/1757-7241-17-34.) Source: Gillman LM et al. Scand J Trauma Resusc Emerg Med. 2009;17(1):34

4. Lung pulse—in some cases, there is little pleural sliding as respiratory movement may not be occurring in the portion of the lung under examination. This may occur during bronchial obstruction, apnea, contralateral main stem intubation, or near the heart. However, lung sliding can still be seen, only in small movements that correspond with the heart rate as the lung enlarges with every systole.

16.5.2 Pleural Effusion, Atelectasis, and Pneumonia

In the same way the intraabdominal fluid has a characteristic anechoic or black appearance on FAST examination, pleural effusions show as anechoic areas in the chest. These are usually best seen just above the diaphragm and posteriorly in the semi-recumbent patients. Ultrasound can differentiate between effusion and atelectasis or consolidation where the chest X-ray shows only basilar opacification of the lung field. Ultrasound can be superior to CT scanning in providing clues about the

nature of the pleural fluid – featureless anechoic fluid is typically of a transudate, whereas exudates may have fibrinous strands that move with patient movement. Retained hemothorax will layer out into serous and cellular layers producing the "hematocrit sign." An empyema will often show areas of loculation. Assessment of pleural effusions over time in the ICU can help determine their progression, nature, and potential for infection, indicating which should undergo drainage by thoracentesis.

Pneumonia with consolidation turns the normally air-filled lung into a solid mass, and the lung takes on the ultrasonographic appearance of the liver. Lobar pneumonias can have quite sharp borders on ultrasound with the bright, consolidated lung adjacent to featureless normal lung lobes. Pulmonary edema increases the amount of interstitial lung water, making the "B-lines" of the lung more prominent and increasing the number of comet tails that are visible.

16.6 Procedural Ultrasound

16.6.1 Vascular Access

Surgical residents usually get their first experience with image-guided procedures with the use of ultrasound in placing central venous catheters. For the internal jugular vein (IJV), Cochrane analysis indicates that ultrasound compared to anatomic landmark techniques increases the placement success rate, with a 57% first-pass success rate. Ultrasound for IJV also decreases time to insertion and decreases the rate complications by 71% and the rate of inadvertent arterial puncture by 72% [44]. There are fewer studies at the subclavian vein (SV) location. Cochrane indicates the use of ultrasound camped to landmark techniques at the SV reduces the relative risk of inadvertent arterial puncture (RR 0.21, 0.06–0.82), but there was no significant difference in overall complications, success rates, or time for placement. In the Cochrane analysis for the femoral location, ultrasound compared to landmark techniques increased the first-pass success rate (RR 1.73, 1.34–2.22), but there was only a small increase in overall success (RR 1.11, 1–1.23). There was no significant difference in complications [45].

The use of an ultrasound needle guide, which can be snapped onto the ultrasound probe or can be integrated into the probe itself, is associated with increased success rates (Fig. 16.16) [46].

Arterial access for arterial blood pressure monitoring and blood sampling can be difficult in many acute surgery patients due to obesity, shock, hypothermia, and vasculopathy. Here too, ultrasound decreases first-attempt failures, mean attempts to success, mean time to success, and the occurrence of hematomas [47].

Central venous catheter complications including central line-associated bloodstream infections (CLABSI) are quality measures in US hospitals, and a CLABSI is now considered a "never event" that will not be paid by insurers. The use of

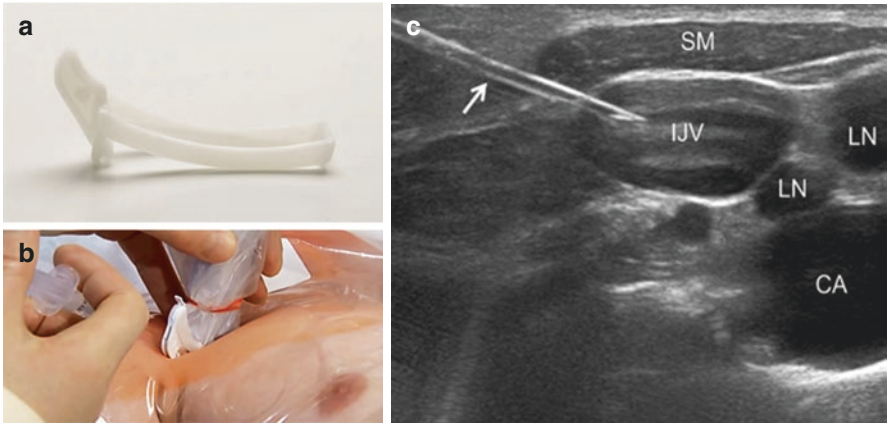

Fig. 16.16 The use of a needle guide controls the angle and depth of the needle during line insertion or drainage procedures, keeping the needle tip in view. (**a**) Snap on "in-plane" needle guide. (**b**) Needle guide on ultrasound probe during insertion. (**c**) Ultrasound image with needle visible for entire length; the arrow indicates the needle location. *SM* sternocleidomastoid muscle, *IJV* internal jugular vein, *LN* lymph node, *CA* carotid artery. Photos—Jay Doucet—Author

ultrasound to place peripheral intravenous catheters (IVs) has emerged as a leading way to reduce central line-days and CLABSI rates. Nurses, advance practice providers, and technicians can learn within 2 h how to place IVs with ultrasound into non-visible veins, such as the basilic vein, with very high success rates [48].

16.6.2 Paracentesis and Thoracentesis

Paracentesis and thoracentesis are made easier and safer with ultrasound [49–51]. Learning FAST skills first for the identification of intraabdominal fluid makes learning paracentesis skills a logical progression. In paracentesis, the bowel should be visualized floating within the peritoneal fluid to avoid mistaken attempts to tap intraluminal fluid in the bowel. Color Doppler imaging superimposed on the two-dimensional image should be used to assess the abdominal wall for blood vessels that might be accidentally lacerated at the puncture sight such as varices or the inferior epigastric artery. If abundant fluid is present, the proposed puncture site may simply be marked for the needle; otherwise a needle guide ensures the needle is placed into the desired area of fluid under ultrasonographic visualization.

Ultrasonography-guided thoracentesis reduces complications, including pneumothorax [52, 53]. After learning FAST and lung ultrasound, it becomes easy to recognize where the lung is in contact with the chest wall during a breathing cycle and to identify where pleural fluid exists. The use of ultrasonography instead of a blind paracentesis technique reduces costs and hospital length of stay [50].

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17 Nuts and Bolts of Interventional Radiology: A Valuable Adjunct for the Care of the ACS Patients in the ICU

Jonathan J. Morrison and Thomas M. Scalea

17.1 Introduction

Ever since Dr. Charles Dotter performed the world's first percutaneous angioplasty in 1964, interventional radiological (IR) techniques have become indispensable in modern medicine [1]. The basic principle of these percutaneous technologies is to use a needle to access a blood vessel, organ, or anatomical space and then using a combination of wires and catheters (the "Seldinger" technique) to navigate to the desired location to deliver an intervention [2]. The intervention is dependent upon the pathology encountered and the desired clinical effect but includes simple drainage of fluid, the relief of hollow organ obstruction, or the embolization of a vascular structure.

IR now constitutes a mature and broad specialty that contributes management options to a wide range of medical and surgical specialties, in both an elective and emergency setting. In the intensive care unit (ICU), there is a core set of IR procedures that are invaluable in the management of the acute care surgery (ACS) patients in the ICU: drainage of fluid collections as well as abdominal visceral and endovascular intervention. This chapter will discuss the "nuts and bolts" of these interventions—when they are indicated, what they entail, and where they fit into the management of the ACS patient in the ICU.

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17.2 Interventional Radiology and the Percutaneous Drainage of Fluid Collections

17.2.1 General Principles

The identification of fluid collections within the pleural, peritoneal, or retroperitoneal space in ACS patients in the ICU is a common occurrence. This is partly driven by the relative convenience and accessibility of computed tomography (CT) scanning [3–6]. The most common indication for imaging is in the evaluation of a septic patient following the development of a leukocytosis or pyrexia. The development of new organ failure should also trigger an evaluation of the patient which may also include the use of axial imaging.

Fluid collections can present in the context of the patients' primary pathology, e.g., a diverticular abscess, where drainage alone may lead to resolution of the episode, or secondary to a condition such as pancreatitis [7]. Broadly, drainage of a fluid collection is indicated when it is felt to be negatively contributing to a patient's clinical status. While this is generally related to sepsis, sterile collections can compromise organ function due to their local compressive effects or inflammatory reaction to them.

Provided there is no indication for operative intervention, the percutaneous drainage of a symptomatic collection provides a minimally invasive option for patients which can be lifesaving. This is especially useful in patients who are critically ill and/or those who have a limited ability to tolerate a larger surgical procedure [8].

17.2.2 Specific Considerations

17.2.2.1 Anatomical Suitability for Drainage

The anatomical location of a fluid collection is important in order to determine suitability for IR drainage. Within the peritoneal space, there are well-known dependent regions within the abdomen where fluid tends to coalesce under gravity: the subdiaphragmatic spaces, the Morrison's subhepatic pouch, the paracolic gutters, and the pelvis [9]. Anterior or lateral approaches can be utilized to access most collections above the pelvic brim [10]. The drainage of large collections can be guided by ultrasonography and can be accomplished at the bedside if clinical circumstances dictate. For smaller collection, especially those next to major vascular structures or those adjacent to gas-filled structures which interfere with ultrasound waves, CT guidance is preferred (Fig. 17.1).

Collections below the pelvic brim, depending on their size and location, may require more unusual approaches [11]. While a large collection that rises above the pelvic brim can be drained via an anterior approach, pre-rectal or presacral collections are more challenging, as the rectum, boney pelvis, and genitourinary organs limit access [12]. The optimal approach in this setting is via the posterior transgluteal route, which traverses the sacrosciatic notch. This is performed under CT guidance, in the prone position, with care taken to avoid the sciatic nerve and gluteal vessels

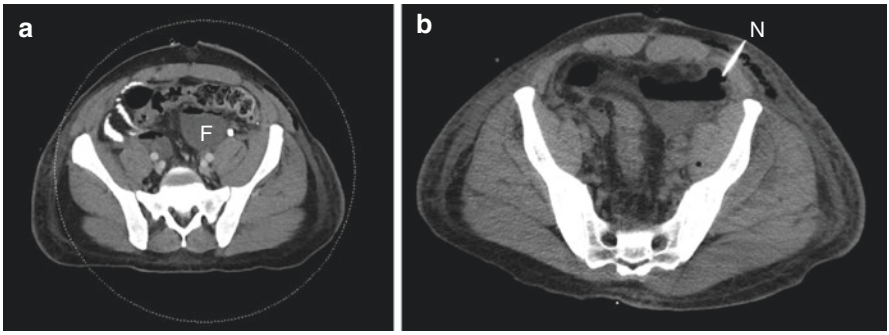

Fig. 17.1 A CT scan demonstrating an intra-abdominal fluid collection, denoted by "F" (**a**) treated by percutaneous CT-guided drainage, with needle being inserted, denoted by "N" (**b**)

[13]. Additional perineal approaches include the transrectal and transvaginal routes, which can be performed under ultrasound guidance in the lithotomy position.

Retroperitoneal collections, such as those arising from the pancreas, can be accessed via a lateral approach, anterior to the kidney [14]. This is an especially useful approach for the acute care surgeon, as percutaneous drain placement can facilitate access to the retroperitoneum for subsequent procedures such as percutaneous necrosectomy [15]. The only non-accessible sites are inter-loop collections, where fluid is surrounded by small bowel. The risk of concomitant hollow-organ injury is substantial, and thus a percutaneous approach is best avoided [16].

17.2.2.2 Incidental Fluid Collections

Clinicians occasionally find themselves in the scenario where they have a patient with non-specific or modest clinical signs and a CT scan demonstrating multiple fluid collections. This is most commonly seen in the context of a recent laparotomy, where the interpretation of multiple fluid collections requires caution. An option in such a scenario is to either observe or consider interval imaging to reassess. If clinically indicated, sampling the collections with a needle under radiologic guidance can help resolve any clinical quandary. Sterile collections can be aspirated without a drain placement, but frank pus mandates an appropriate sized drain [17].

17.2.2.3 Pleural Effusions

Ideally, pleural effusions should be identified by clinical examination, but frequently, they are an incidental finding on plain chest radiography. Assuming that the ACS patient has a primary abdominal problem, these findings may or may not be of significance. Bilateral effusion may represent cardiac failure or a low protein state and in general should not be tapped unless they are compromising ventilation. Unilateral effusions (Fig. 17.2) can represent para-pneumonic or sympathetic transudates from subdiaphragmatic pathology and are usually less benign than bilateral effusions.

While large effusions that compromise ventilation should receive an expeditiously placed surgical drain at the bedside, radiologically guided drains have an

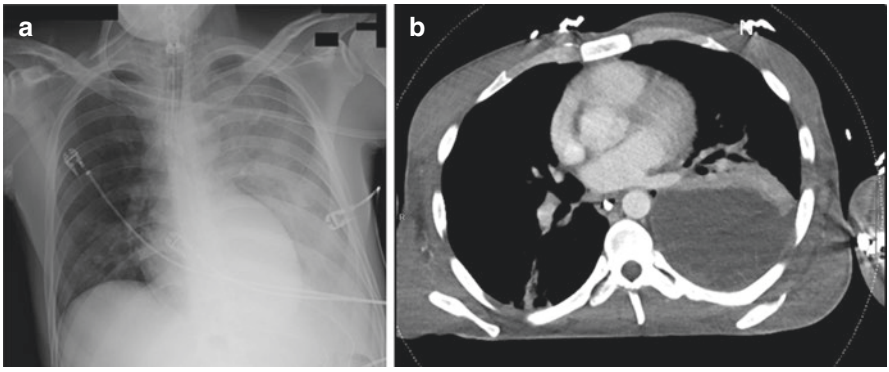

Fig. 17.2 A plain chest radiograph demonstrating a left pleural effusion (**a**) and CT scan demonstrating the left pleural effusion (**b**)

important role in helping resolve a diagnostic question or accessing difficult-to-reach anatomical areas. Imaging-guided thoracocentesis increases precision of sampling and reduces the risk of iatrogenic injury; this is especially the case in smaller effusions requiring sampling at the costophrenic angle. Furthermore, when formal drainage is required, a radiological drain permits the accessing of collections which are walled off or loculated. It is extremely important to remember that any drain in the chest should be drained into an underwater-sealed container—IR drains are no exception to this policy.

17.2.3 Procedural Considerations

17.2.3.1 Pre-procedure Preparation

Patients undergoing radiological drainage of a fluid collection should be optimized for the procedure. This includes the correction of any coagulopathy and the obtaining of informed consent. The patient, or an appropriate surrogate, needs to be aware of the complications that can arise from percutaneous drainage which include iatrogenic injury of major neurovascular structures and hollow viscus injury [16]. Patients also need to be able to tolerate the procedure, which can necessitate lying prone, depending on the approach required. If a procedure cannot be tolerated or the airway felt at risk, then the use of a general anesthetic and intubation should be considered if the procedure is considered urgent.

17.2.3.2 Technical Aspects

As a principle, the most dependent part of the collection should be tapped, so that it will drain under gravity. Furthermore, one body cavity should not be accessed via another cavity, e.g., the peritoneum should not be tapped via the pleural space. The initial tapping of a collection should be performed using a long needle, which can be used to confirm a safe route to the collection, as well

as the nature of fluid encountered. If the collection is benign in appearance, e.g., clear and straw colored, this can be aspirated dry, with a sample sent to the laboratory.

If the fluid has a suspicious appearance, e.g., pus, then a wire should be exchanged for the needle and a drain inserted over wire. If the collection is loculated, the wire can be used to break these up with gentle and systematic agitation of the wire in the cavity. The choice of drain is dependent upon the nature of the cavity, with a larger drain for thicker fluid, up to around 12 Fr.

17.2.3.3 Post-procedural Care

The most important task for an acute care surgeon post-drain placement is to reassess the patient. A deterioration may signify a complication from the drain, such as hemorrhage or hollow organ injury. Similarly, the disruption of an infective focus can precipitate a "septic response" with a bacteremia and pyrexia. In general, a patient's condition should improve following successful drainage of a symptomatic collection, so if there is no improvement, the treating team should consider reimaging to assess for an undrained focus or to look for a different pathology.

Drains need to be adequately secured to the patient. Drain function must be monitored, as well. It is best to mark a drain at the point where it exits the skin so that staff can be alerted to any change in position. Where fluid is viscous, the drain should be flushed with 10–15 mL of sterile saline, two or three times a day to ensure continued drainage. A non-draining drain is a blocked drain until proven otherwise.

The converse can also be encountered, when a drain output suddenly increases. This can relate to a shift in the collection and improved drainage, but the greater concern is the erosion of the drain into a hollow viscus and the formation of a fistula. The drain must not be removed, and the patient should be reimaged. This can be by plain imaging following the instillation of contrast down the drain or by CT, ideally with oral and rectal contrast, in addition to IV, in order the delineate the anatomy of the fistula.

A final point relates to the removal of an IR placed drain; the most common commercial drains have a pig-tail configuration, which is locked into place, so called "self-retaining" drains. This mechanism is propriety to each manufacturer but usually involves a thread held under tension at the proximal end of drain. Once released, the drain should be easily removed without resistance; if this is not the case, it is prudent to seek advice from the inserting IR unit.

17.3 Specific Visceral Radiological Intervention in the ACS ICU Patient

17.3.1 General Principles

While the ideal and ultimate aim in ACS patients is to perform a definitive procedure for their pathology, this may not be readily achievable due to the physiological state of the patient or the burden of comorbid disease. IR interventions can be

effective as they can be used either as a bridge to definitive intervention or as a way to help optimize comorbid problems, allowing definitive management when appropriate [8]. This section will provide an overview of some of the common hepatobiliary, gastrointestinal, and urological IR interventions that can be effective for ACS patients in the ICU.

17.3.2 Hepatobiliary Intervention

17.3.2.1 Percutaneous Transhepatic Cholecystostomy

This is indicated in patients with severe cholecystitis associated with significant organ failure, who are unsuitable for a definitive cholecystectomy [18]. Under ultrasound or CT guidance, a needle is inserted into the gallbladder through the liver parenchyma [19]. Such an approach reduces the rate of adhesions seen after a direct transperitoneal approach. This procedure can either be used as a bridge to cholecystectomy by draining a septic gallbladder or as a definitive procedure in frail patients where the tube is left to form a permanent fistula [20]. As this can be performed under ultrasound guidance, if necessary, it can be done at the bedside. The cholecystostomy tube can also facilitate diagnostic imaging of the biliary tree, which may aid in the planning of a definitive procedure.

17.3.2.2 Percutaneous Transhepatic Cholangiography

This procedure provides for the relief of biliary obstruction but is associated with a high mortality, largely due to the nature of the underlying diagnosis, which is frequency neoplastic [21, 22]. In patients presenting with biliary obstruction and jaundice, the preferred approach is to relieve the obstruction, allowing the antegrade flow of bile into the alimentary canal.

In the setting of a neoplastic lesion obstructing the common bile duct, biliary drainage is ideally accomplished via endoscopic retrograde cholangiopancreatography (ERCP) and the placement of a stent. In the stone disease, ERCP or operative bile duct exploration can be used to clear the duct of obstruction. Where these modalities fail, percutaneous transhepatic cholangiography (PTC) has a role (Fig. 17.3) [21].

The procedure consists of an ultrasound-guided approach, in conjunction with fluoroscopy, where an intrahepatic duct is accessed with a needle [23]. This facilitates the passage of a wire into the biliary tree, over which a catheter is advance. This can be used to facilitate biliary drainage, imaging, and intervention such as stent placement. To be successful, the biliary tree must be sufficiently dilated to enable access. A significantly jaundiced patient is also likely be coagulopathic, which should be corrected prior to instrumenting the liver.

17.3.2.3 Transjugular Intrahepatic Portosystemic Shunt

This is a complex intervention which permits the decompression of a hypertensive portal system into the hepatic venous system [24]. This is indicated in cirrhotic patients as a method of decompressing esophageal varices and in the treatment of

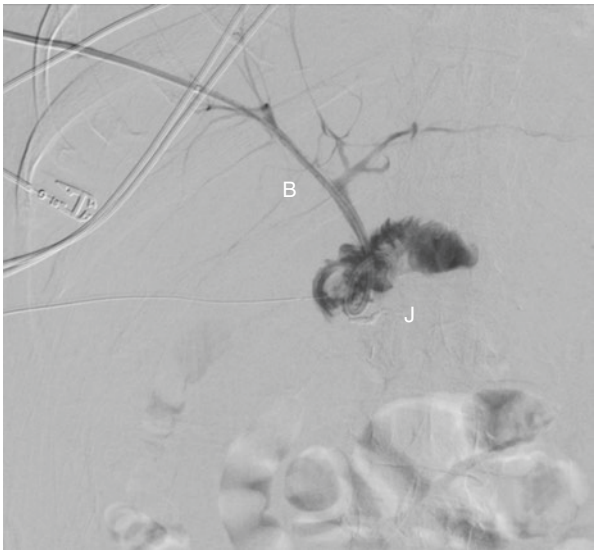

Fig. 17.3 A percutaneous transhepatic cholangiogram demonstrating the integrity of a choledochojejunostomy in a patient post Whipple resection. The letter "B" denotes the biliary tree and "J" the jejunum

refractory ascites. While these conditions may not be primarily cared for by acute care surgeons in every institution, cirrhotic patients can present with acute care surgical problems, complicated by portal hypertension.

Access via the internal jugular permits access to the hepatic portal vein, where, under fluoroscopic guidance, a needle is deployed into a portal vein, which is then cannulated with a wire. This allows for the deployment of a stent decompressing the higher-pressure portal system directly into the hepatic venous circulation. This is a technically challenging procedure, which is elegant in principle and avoids open surgical alternatives which are associated with a dismal survival [25].

The acute care surgeon needs to be aware of the metabolic and physiological consequence of a TIPS procedure [25]. Essentially, the portal vein now empties directly into the systematic circulation, shunting ammonia and other neurotoxins, which can precipitate an encephalopathy. Furthermore, the additional blood volume returning to the right side can stress the heart, inducing failure, unless the patient's volume status is adjusted appropriately.

17.3.3 Gastrointestinal Intervention

17.3.3.1 Enteral Access

While enteral access in ACS patients can usually be achieved by the simple passage of a large or small bore tube via the nose into the stomach, on occasion this can be more complex. IR has a small role in assisting the acute care surgeon with enteral access. For example, where jejunal feeding is required, a percutaneous endoscopic gastrostomy can be easily converted to a percutaneous gastrojejunostomy with the use of a wire and fluoroscopic guidance [26].

17.3.3.2 Supporting Endoscopic Intervention

Another role where IR can assist the acute care surgeon is by supporting endoscopic intervention [27]. A typical example is in the deployment of colonic stents across stenotic lesions, which can obviate the need for a colostomy. Typically, an endoscopist will advance the endoscope to the lesion, and a wire will be deployed across the lesion. The scope will be withdrawn, allowing for a stent to be deployed on the wire across the stenosis, where it will be deployed under fluoroscopic guidance. The administration of air and contrast can be used to confirm the position and patency of the stent.

17.3.4 Urological Intervention

17.3.4.1 Percutaneous Nephrostomy

The role of IR in the management of renal issues in the acute care patient is largely limited to the use of percutaneous nephrostomy in the decompression of an obstructed kidney. Similar to the biliary tree, obstruction can come about from stone disease and neoplasia [28]. Injury can also cause urologic obstruction. The relief of an obstructed kidney can permit the optimization of a patient's renal function, either prior to a more definitive procedure, e.g., en bloc resection, or as a definitive procedure in of itself.

The procedure is performed on the patient's lateral side, initially under ultrasound or fluoroscopic guidance, where the renal parenchyma is traversed with a needle, allowing access to the renal pelvis (Fig. 17.4) [29]. This is then followed up with a wire and drain in the standard fashion. The nephrostomy tube can be used for both drainage of the kidney and access for subsequent imaging and intervention.

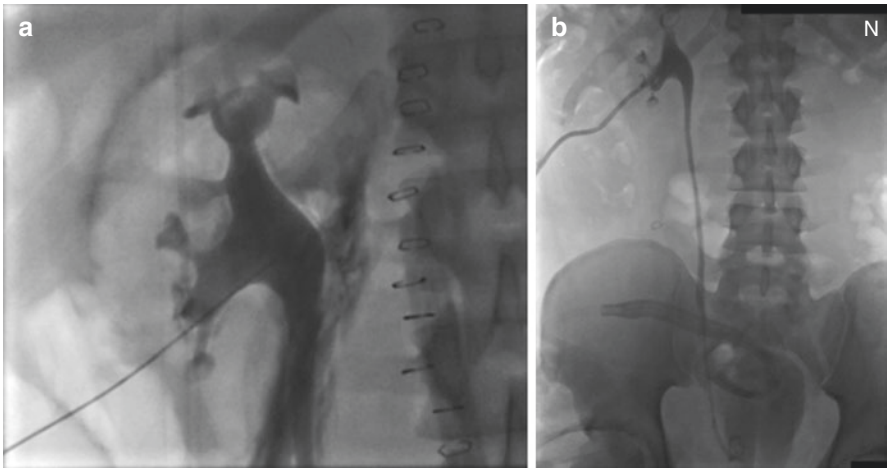

Fig. 17.4 A plain fluoroscopy image demonstrating (**a**) an initial puncture of the kidney and (**b**) a nephrostogram via the nephrostomy tube

17.4 The Role of Endovascular Intervention in ACS ICU Patients

17.4.1 General Principles

Endovascular techniques are minimally invasive and can prevent and/or correct some very significant problems in ACS patients. Acute care surgeons need to be aware of the strengths and limitations of endovascular intervention in order to optimize the care of their patients. Two major categories will be discussed in this section—the role of endovascular intervention in hemorrhage control and in the prevention of venous thromboembolism (VTE).

17.4.2 Endovascular Intervention in Hemorrhage

Hemorrhage can arise in the ACS ICU patient as a consequence of their primary pathology or as a complication of their ICU stay. Bleeding can present both as an acute event, with the typical features of tachycardia and hypotension, and as a more insidious process, with a gradual fall in hemoglobin, pressor dependence, and increasing transfusion requirements. The latter is a common presentation, and clinicians need to vigilant to occult bleeding.

When evaluating an ACS patient with signs of hemorrhage, in addition to assessing the whole patient, the patient's hemodynamic and coagulation status needs to be specifically defined as these parameters will guide management decisions. In general, a patient with a catastrophic cardiovascular collapse should be dealt with by operative intervention in parallel with a massive transfusion of balanced blood products. Patients with a significant coagulopathy should ideally have this corrected ahead of or in parallel with hemorrhage control. Any maneuver, be it via surgical, endoscopic, or endovascular mean, will be more effective when a patient can form stable clot.

In the absence of significant hemodynamic instability, a patient with suspected bleeding who is being considered for endovascular hemostasis should undergo a triple-phase contrast-enhanced CT scan, without oral contrast [30]. This consists of an unenhanced scan, followed by a contrast bolus injection and scanning during the arterial and venous phases. The arterial phase scan is obtained when contrast appears in the thoracic aorta, a so-called "bolus tracked scan," usually at a density of 100–150 Hounsfield units. The imaging is then repeated at around 40 sec, to allow image acquisition during the portal venous phase.

The CT technique is important for several reasons. The non-contrast scan enables the identification of any material that might be mistake for contrast extravasation. The arterial phase can identify a region of active hemorrhage by the appearance of contrast extravasation or "blush." In the setting of active hemorrhage, this "blush" would be expected to change in its appearance during the portal venous phase. If the source of bleeding is felt to be in the GI tract, then oral or contrast should be avoided, so that this does not interfere with the appearance of arterial bleeding.

Ultimately, the CT scan is to enable the identification of the anatomical source of bleeding and to help plan the procedure. Two broad categories of bleeding are considered below: gastrointestinal (GI) and non-gastrointestinal hemorrhage.

17.4.2.1 Gastrointestinal Hemorrhage

The primary modality for the control of GI hemorrhage is via endoscopic maneuvers such as epinephrine injection and electrocautery. However, some patients either cannot undergo endoscopy (e.g., access limitation or unsafe to insufflate the GI tract) or have failed endoscopic management. In which case, endovascular hemostasis becomes an attractive option [31].

Where the origin is an upper GI source, the arteries supplying the stomach and duodenum require angiographic interrogation in a systematic manner [32]. For duodenal bleeding the gastroduodenal artery (GDA) is a usual culprit due to its anatomical relationship with the posterior wall of the duodenum. To ensure hemostasis, due to the collateral flow through the GDA from both the celiac and superior mesenteric arteries, it is important to occlude proximal and distal to any demonstrable extravasation. Similarly, in the stomach, the commonest site of hemorrhage is from the left gastric artery, which has an excellent collateral supply (Fig. 17.5).

17.4.2.2 Non-gastrointestinal Hemorrhage

While non-GI hemorrhage is a less common source of bleeding in ICU patients than GI bleeding, it can be as important. Sources include splenic artery

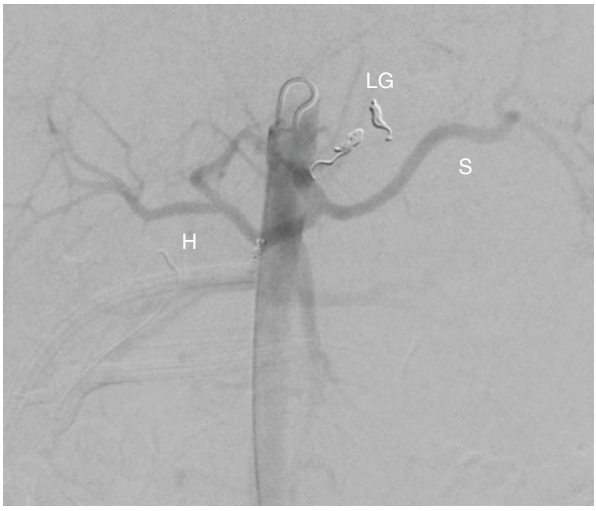

Fig. 17.5 A completion angiogram of the celiac trunk demonstrating the hepatic artery "H," the splenic artery "S," and a coil embolized left gastric artery "LG." This was performed for hemorrhage control from a gastric ulcer

pseudoaneurysms secondary to pancreatitis, secondary hemorrhage from surgical intervention, and the erosion of an abscess into a major vessel through to a spontaneous bleed in a coagulopathic patient. Many of these etiologies occur in patients who have a relatively hostile abdomen. While operative management takes precedence in profound hemodynamic instability, an endovascular approach can reduce the morbidity of intervention where there is time to obtain angiography.

A triple-phase CT scan is helpful in identifying the source of the hemorrhage and planning the procedure. The two major methods of endovascular hemostasis are routinely used—embolization and stent-grafting—the choice of which is dependent upon the location and morphology of bleeding. Embolization, using coils, liquid agents, plugs, etc., is a useful agent in occluding the flow of end arteries. In general such interventions can be delivered via standard catheters (4 or 5 Fr) and microcatheter systems (2.5 or 2.8 Fr).

Where flow needs to be preserved in an artery, a stent-graft can be used to exclude pathologies such as a false aneurysm. The issue with stent-grafting is that covered stents often require relatively larger delivery systems (6–12 Fr depending on diameter) compared to embolic agents. Furthermore, while the fabric used to cover the stent usually have an anticoagulant coating (e.g., heparin), they have significant thrombotic potential; thus most surgeons advocate the use of an antiplatelet agent in elective practice. This can be more complicated with emergent ACS patients, who may have a contraindication to such agents.

17.4.3 Endovascular Intervention in Venous Thromboembolism

17.4.3.1 Inferior Vena Cava Filters

An inferior vena cava (IVC) filter is a device that resembles an umbrella that can be deployed just below the confluence of the renal veins and IVC and catches embolic material (Fig. 17.6). The use of IVC filters has evolved substantially over the last decade, with current practice characterized by strict indications and an emphasis on patient follow-up for removal. An IVC filter is an indication when a patient has evidence of deep vein thrombosis (DVT) but cannot be anticoagulated or has evidence of a venous thromboembolism (VTE) despite anticoagulation [33].

IVC filters can be inserted using either a femoral, internal jugular, or basilic approach [33]. Typically, a venogram is obtained to characterize the optimum zone of deployment which is just below the renal veins, although intravascular ultrasound can also be used for this function. The acute care surgeon must be aware that an IVC filter does not entirely eliminate the risk of VTE, and should a patient deteriorate, further emboli should not be discounted. Clear documentation of the filter insertion is also strongly advised in order to track the patient, so that removal can be arranged.

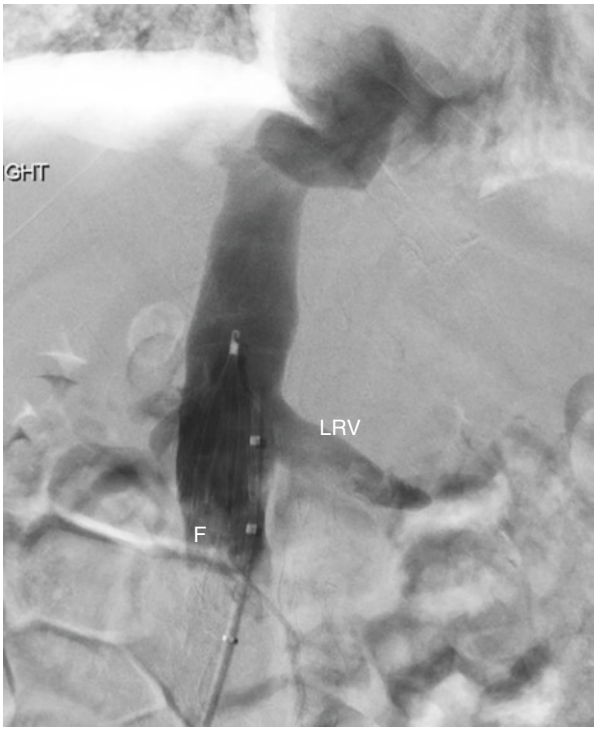

Fig. 17.6 A completion venogram demonstrating the placement of an inferior vena caval (IVC) filter "F" below the lowest renal vein "LRV"

17.5 Summary

Interventional radiology can undertake procedures which can significantly advance the management of the ACS patient in the ICU. This ranges from the drainage of simple sepsis through to complex procedure that can optimize patients with comorbidities. Frequently, IR procedures can help avoid further surgical insult or can temporize a pathology in order to facilitate the resolution of organ failure, allowing for a delayed definitive surgical procedure.

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18 Ethical Decisions and Dilemmas in the ACS Patients Requiring ICU: Understanding When to Start and When to Stop

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18.1 Introduction

The major goal of intensive care units (ICUs) is to offer patients optimal management that will ensure survival and quality of life in accordance with their wishes and values [1].

With the advances in medicine and technology, ICUs have now the capacity to treat patients who would have previously not been expected to survive and would therefore not have been managed in ICUs [2].

In recent decades, advances in medical technology have afforded intensivists a remarkable ability to extend life, even in the setting of critical illness [3]. This has led to extensive ICU utilization at the end of life, with an estimated one in five Americans admitted to the ICU prior to death [4].

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Moral dilemmas and challenges of end-of-life care surrogate decision-making and potentially futile interventions arise frequently when caring for critically ill patients [5].

18.2 Appropriateness on Healthcare

To choose appropriately is an everyday challenge in Acute Care Surgery and Intensive Care.

The "appropriateness" concept was introduced in 1984 by Woodward and Warren-Boulton. They defined "appropriate" a procedure that one expect to improve patient's health [6].

In 1997, a European Council Recommendation (nº 17/1997) entrusts all the countries to improve their healthcare quality, defining appropriateness as a fundamental element [7].

The most common definition of appropriateness on healthcare intervention is the RAND Corporation's one [8], on which they introduce the concept of balance between benefits and potential risk of a procedure. A procedure is appropriate if the expected benefits (life expectation, pain relief, improved quality of life) exceed its risks (death, disability, pain) [9, 10].

To quantify this balance, the RAND/UCLA Appropriateness Method was introduced to support physicians on their everyday decisions [11].

The WHO (World Health Organization) defined in 1948 health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

This definition involves the respect of human being as an absolute value, considering not merely the attention to reduce biological damage but the development of the patient's individuality, joining a moral value to the healthcare techniques.

The *deontological appropriateness* (physician/patient relationship) and *ethical appropriateness* (the patient's health interest identification) are the elements to the final decision (diagnostic or therapeutic) in clinical care.

During the 1990s, the appropriateness concept was integrated in the setting of care context, becoming the result of a decision process that guarantees the best benefit for the patient, in the context of the actual society resources [12].

In the same intent, Lavis and Anderson introduce the "setting appropriateness" of healthcare [13].

A setting is appropriate if it matches with the patient's needs and the healthcare techniques he/she deserves.

18.3 Appropriateness in ICU

In a society that rejects death as an integral part of life, the surgeon and intensivologist (who owns the decision to grant or refuse a patient's admission to ICU) have the hard work to reaffirm this inevitability [14].

The ICU physician is considered as the preferred intermediary in the decision to admit a patient to the ICU (or not), as well as for decisions regarding possible limitation or withdrawal of life-sustaining therapy because he/she has the best knowledge of the ICU and the life-support therapies that can be offered to the patient, he/she is best placed to evaluate the patient's prognosis according to the presence or absence of organ failure, and he/she is the most qualified to explain to the patient, as well as families and loved ones, the limitations and possible outcomes of ICU care [15].

The ICU physician must create new legitimacy through widening his/her field of competence multidisciplinarily in the context of intensive care and transdisciplinarily to human and social sciences in the field of care by the numerous ethical questions that arise [16].

To support the anaesthesiologist/ICU physician on these decisions, many Societies of Anaesthesia and Intensive Care produced guidelines on this argument.

The goal of intensive treatment is the complete recovery of health conditions, in a way to allow patient's social rehabilitation. Since this goal is impossible for some patients, the new goal must be the maintenance of their dignity and quality of life, leaving out excessive therapies and ICU admission. In the impossibility of intensive care to prolong life, but only to prolong an unavoidable death, ethics and clinical reasons suggest to prefer palliative care. In front of a dying patient, the priority is accompany him/her in assuring him/her the best quality of life: relief of pain and suffering is the goal. In this scenario, restricting the access to ICU is neither "euthanasia" nor abandoning the dying patient but the respect of his/her needs, according to ethics principles of autonomy, benevolence and absence of malice [17].

In case of Acute Care Surgery, the surgeon must balance too the need to alleviate pain and suffering and the avoidance of overtreatment, including considering treatment-related morbidity, acting in the best interest of the patient.

He has to consider the patient's prognosis, based on the status of underlying disease, the risk of the procedure and the patient's personal anamnesis.

In case of symptomatic patient, the surgeon must consider whether the patient could benefit from a palliative surgery.

It is important for the surgeon to prognosticate the outcome before surgical decision-making, incorporating the knowledge about underlying disease, the possible surgery outcome and the patient's preferences [18].

The decision is delicate, because palliative surgery procedures are associated with a high mortality rate. McCahill et al. published a score to quantify and predict the effectiveness of palliative treatments (palliative surgery outcome score (PSOS)) to support surgeon on these situations [19].

There are five major issues concerning decisions the surgeon should take in addressing a patient for ICU:

1. Admission
2. Treatment
3. End of life
4. Dismiss patient
5. Readmission

18.3.1 Admission

Although there are well-established criteria for patient admission in ICU with the maximum therapeutic intent for cure, there are at least four major clinical dilemmas with an ethical value. These are indications for admission: too-sick-to-benefit, or not sick enough to benefit; risk of loss of opportunity or risk of unreasonable therapeutic obstinacy; admission for curative or palliative therapy; and "readmission" from "non-readmission" [20]. The specificity of solving these dilemmas is that physicians are always working under pressure, taking decisions in no time. This obviously requires exceptional surgical expertize, where moral issues are sometimes of utmost importance.

Whereas multidisciplinary management approach to critically ill patients in ICU is a routine established and implemented practice, criteria for admitting and leaving ICU decision-making are not well defined [16]. Ethical aspects of admission, or non-admission, of a patient to the ICU according to the recommendations from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine include: stipulating the need for coordination between consulting physicians for the management of the patient, implementation and updating of protocols with regular training for healthcare staff, clearly defined criteria for admission and non-admission to the ICU, taking account of the legislative framework, the continued improvement of the quality and safety of care, participation in teaching and research activities and transparency vis-à-vis the patient, their families and society as a whole, where the ICU physician is a pivotal organizer of the patient's healthcare pathway and therapeutic project [21].

Current consensus acknowledges that patients should not be admitted to the ICU if the patient himself/herself does not wish to be admitted or if the therapeutic resources are no longer able to keep pace with the progression of the disease. Within a healthcare system that suffers from financial constraints as well as limits on access to ICU beds, it is the ICU physician's responsibility to define the objectives and conditions of ICU care for a given patient, in parallel to any ethical reflection. In an emergency, the decisions made by the ICU physician may be influenced by pressure from the patient and their family, who understandably want everything possible to be attempted, without knowing or imagining what can be offered or what ICU care may involve. This pressure stems from the fear of death and the failure to anticipate this finality, which may sometimes be expected, if not logical, given the patient's clinical situation [16].

In a systematic review where found 16 relevant articles analysing results of ethic consultations in ICU, based on surveys and interviews of user experiences, and the CEC (clinical ethics consultations) were helpful in 383/435, while stress disagreement with CEC were found in 113/431 patients [5]. Conclusively, CEC assists family and provider satisfaction and decision-making, alongside with reducing non-beneficial treatment, thus increasing the process and outcome in patient care.

18.3.2 Treatment

Programs to enable patients to learn about their rights relating to their own healthcare decisions, envisaging in particular the right to participate in discussions and partake of decisions relating to their healthcare, and the right to refuse treatment include: advance care planning (ACP) and advance directives (AD) [15]. ACP is a dynamic process in which the patient is encouraged to discuss and identify his/her values, beliefs and life goals, especially the healthcare trajectory he/she wishes to follow. AD are a written document, available in many countries, that a patient may prepare to consign, in writing, their wishes regarding end-of-life care, in case they subsequently become incompetent and unable to communicate their preferences [22].

The admission to the ICU, refusal to admit or readmit, should be integrated into the healthcare project in agreement with the patient, regardless of the stage of disease that the patient suffers from, where the ICU physician must guide patient choices when formalizing their healthcare preferences in the form of ACP or AD [15].

Complexity thinking for decision-making process throughout the patient's stay in ICU is a progressive process of critically adapting to novel ways of negotiation, interaction and exploration, by connection of the analytical way of thinking with the principle of conjunction [23].

Transdisciplinary teamwork led to qualitative richer comprehensions of the concerns of their common patient, allowing recognition of the conflicting prognosis: recovery or no recovery at all. Practitioners in ICU engage elements of complexity thinking in their decision-making, and although largely unaware of it and its benefits, they shift from an analytic to a complex approach.

18.3.3 End of Life

International data confirm the increased frequency of end-of-life decisions within an ICU setting. End-of-life decisions include holding or withdrawing potentially life-prolonging treatment and alleviation of pain or other symptoms with a possible life-shortening effect [24].

Around 20% of patients die in the ICU [4], and these deaths in the ICU are preceded in 53–90% of cases by a decision to withhold or withdraw life-sustaining therapies [25].

The decision to limit or withdraw life-support treatment is an integral part of the job of a physician working in the intensive care unit (ICU) and of the approach to care [26]. This decision is influenced by factors, such as resource availability and environment, ICU capacity strain, institutional culture, multidisciplinary care, communication strategies, cultural and religious differences, beliefs of the physicians, ICU family conferences, presence or not of surrogate decision-makers and ethics consultations.

Advance directives (AD) as a mechanism for assuring patient wishes in decision-making (93% agreement) must be respected and incorporated into their decision making, as well as using the standard of substituted judgment, communicate important medical information to patients and use shared decision-making procedures when deciding about end-of-life care for critically ill patients. Collegial decision-making process can be implemented when therapy fails, despite a well-conducted therapeutic strategy and optimal management, in patients with unfavourable outcome or if the patient directly or indirectly refuses the introduction or intensification of life-support therapies. Decision to limit or withdraw therapy should be carried out in a collegial manner, through collective and interdisciplinary deliberation, taking into account the opinions and reflections of all those involved in the patient's management, patient's and patient's family opinion [26].

Decision to continue or withhold life-sustaining measures must take into consideration many individual patient factors and therefore can only be done on a case-by-case basis [27].

The World Federation of Societies of Intensive and Critical Care Medicine in 2016 apprises the complexity of end-of-life care in the ICU, particularly relating to withholding and withdrawing life-sustaining treatment while ensuring the alleviation of suffering, within different ethical and cultural environments, and endorses and encourages the member societies to develop national guidelines and recommendations within each country [22].

Although there is lack of a standardized approach to end-of-life decision-making, the physician is the initiator and leader in end-of-life decisions with the family of ICU patients [2].

The consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study in 2014 stated that despite differences in geography, culture, religion, training and background, worldwide professional consensus was developed for the majority of end-of-life practices. Statements of consensus can help develop policies and procedures, develop directives and serve as areas for quality metrics to improve healthcare [28].

At the end of life, the patient is focused on two key points, namely, rejection of unreasonable therapeutic obstinacy and collegial decision-making [16].

In their systematic review, Mark et al. identified several publications describing end-of-life practices in almost 1000 ICUs on 6 continents, spanning three decades from 2015. They found substantial variability in the prevalence of withdrawal of life-sustaining treatment worldwide and on many levels where the overall percentage of deaths preceded by withdrawal of life-sustaining treatment varied between 0% and 84% [3].

Withholding and withdrawal of life-sustaining treatment are often considered to be ethically equivalent [28]. Withdrawal is an active process that often requires a written order and justification, and the initiation of withdrawal is therefore likely to be documented. Withholding, however, is the absence of an action, in many cases may not require an order and therefore may be less consistently documented [3]. Guiding and supporting a patient and their family through the process of deciding whether or when to limit or stop life-sustaining measures is one of the more difficult

and important tasks facing the critical care practitioner, and optimizing approaches to the limitation of life-sustaining treatment could greatly improve ICU care worldwide [3]. Variability in the limitation of life-sustaining treatment between regions, ICUs within a region and physicians within a single ICU necessitates to develop a consensus for end-of-life decision-making, to reduce this variability, ensuring respect of individual patient values and goals.

In a systematic review from 2016 by Oczkowski et al., exploring communication tools to assist in EoL decision-making of ICU clinicians, including traditional decision aids, structured meeting plans, educational interventions and the use of consulting services and complex quality improvement programmes, the authors found very low-quality evidence that the use of structured communication tools increases the number of documented goals-of-care discussions and low-quality evidence that they do not affect the number of patients with documented code status/DNR forms or decisions to withdraw/withhold life-sustaining treatments [29]. They also found very low-quality evidence that the use of structured communication tools results in reduced healthcare resource utilization compared to usual care.

Development of global consensus about end-of-life care will require open and continued discussion of these issues in international forums. The delivery of ethical and high-quality critical care requires training and emphasis on ethical decision-making, communication and collaboration throughout the interdisciplinary team, effective communication with patients and families and identification and resolution of conflicts within the team and with patients and families [30].

Patient-centred care is emphasized in today's healthcare arena. This emphasis is seen in the works of the International Alliance of Patients' Organizations (IAOP) who describe patient-centred healthcare as care that is aimed at addressing the needs and preferences of patients, with five principles which are foundational to the achievement of patient-centred healthcare: respect, choice, policy, access and support and information. Within the description of these five principles, the idea of shared decision-making is clearly evident [31].

Clinical judgement, clinical decision-making and metacognitive skills presenting surgeon's ability to recognize and reflect on their subconscious resolution vary enormously. Yet, this valuable skill, when present, enhances learning and teaching capability [32].

The teaching of decision-making in respect to the care of patients presenting as a surgical emergency is a topic that is still in its infancy but is currently being addressed, and further research will enlighten this area [33].

18.4 Conclusions

The surgeon and the anaesthesiologist, both responsible for the same patient, must share decisions, discussing and planning together the best strategy, with the patient and his family too.

The decision should involve also the necessity of ICU recovery after surgery, with all the previous consideration.

A study performed in Regione Emilia-Romagna (Italy) in cooperation with Bologna University and Jefferson University (Philadelphia, USA) during the year 2012, including 11,738 end-stage cancer disease, showed how 3.9% of these patients received an ICU recovery during their last 30 days of life. In the 53% of cases, ICU recovery followed a major surgery treatment (according to Agency for Healthcare and Quality classification definition of "major surgery" 2014) [34].

The reduction of inappropriate surgery and consequent inappropriate admission on ICU is a clinical and ethical goal to pursue, on patient's and global interest.

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Intensive Care for Emergency Surgeons: Mass Casualties

19

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19.1 Introduction: Disasters

Worldwide humanity is faced with multiple threats. Natural disasters in Central America and Southern Asia, terrorist attacks in Europe and North America and conflict zones in Middle East and Eastern Africa leave behind a huge death toll and mass casualties. By definition disasters are incidents that overwhelm the capacity in manpower and resources of a region, in which they are inflicted [1]. Disasters result from natural phenomena, manmade events or hybrid incidents [2]. According to International Disaster Database (EM- DAT) in the period 1996–2015, there have been recorded 7056 disasters worldwide [3]. Only during 2015 there have been

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reported 346 disasters, 22,773 people dead, 98.6 million people affected and US$ 66.5 billion economic damage [3].

19.2 Disasters and Healthcare System

In the dynamic and complex setting of disasters, healthcare systems struggle to manage the impact as well as to recover from the aftermath. While developing countries seem unprepared to meet growing demands in human and material resources, developed countries struggle also with a compromised technological network and huge influx of mass casualties.

Although there is a growing literature over disaster management and response, usually it addresses the needs of local communities, prehospital healthcare providers, emergency department personnel or hospital setting as one entity. There is a limited number of articles and texts over preparation, response and recovery of intensive care units to mass casualties [4, 5]. A robust MCI plan should be based on broadened system-based response, rather than in separate entities.

19.3 Mass Casualties and ICU

Although majority of disaster casualties do not need critical care [6], intensive care unit (ICU) participates in primary evaluation, resuscitation and postoperative management [7]. An ICU is a specialized department with a well-trained personnel and abundant resources, ready to provide high-quality care to every critical ill patient. But in times of mass casualty incidents (MCI) when a number of patients and duration of disaster are unknown, a more careful management of human and material resources is needed. In many countries the philosophy of MCI management is to save the maximum number of patients. In principle ICU may need to take difficult decisions and deny care to those unlikely to recover from lethal injuries or to patients with chronic illnesses in order to admit seriously injured casualties [8]. ICU personnel should constantly triage patients in order to assure a continuous flow to other departments or hospitals, preparing healthcare system for recovery phase [9]. Resources should be wisely used as well as allocated in areas with need for the maximum number of patients [10]. While all these mandate a preexisting plan setting minimum requirements and actions for effective care, this plan should be flexible upon existing conditions [8]. As Alan Lakein wisely stated, “Failing to plan is planning to fail.” In case of mass casualties, failure of planning in ICU can lead to inacceptable casualty care and problem in hospital disaster response [11]. Planning can be categorized in three groups: staff, stuff and space [12].

19.4 Preparation, Response and Recovery for Mass Casualty Incidents

In most mass casualty incidents, patients are evacuated or arrive on their own to the closest healthcare facility [13, 14]. Consequently every ICU needs to be prepared for a mass casualty incident at any time.

19.5 Plan

Integral part of preparatory phase is the development of a well-defined disaster plan for the ICU. A disaster plan should be based on a thorough threat and hazard vulnerability assessment (HVA) for the responsible hospital and ICU. Although there are numerous threats, a threat assessment should identify and include only those more likely to inflict on the greater area where the hospital is located to. In order to assess probability of a hazard, hospital's location, surrounding area, local industries, weather conditions, seasonal illnesses and demographics of the greater area should be taken under consideration [15]. Each catastrophic incident results in different epidemiology of injuries and requires different treatment options as well as level of medical expertise. As a consequence hazard vulnerability assessment should take under consideration the surge capacity of the ICU to respond effectively in each possible threat [16]. Surge capacity implies the ability of an ICU to admit a certain number of patients. It is determined by the number of resources (mechanical ventilators, medications, airway devices, substance isolation precautions, etc.), the personnel (qualified physicians, nurses, etc.) and space (number of beds). Although a prediction of patients' number is difficult to be made, it is considered acceptable in disaster planning to estimate for every one million population a number of 500 casualties above everyday capacity of ICU [17].

Undertaking a plan for every disaster is not possible; for this reason, an all-hazard approach is essential with flexibility in human resources to be customized upon existing circumstances. An ICU disaster plan should be designed with a clear chain of command, which should be integrated into the everyday hospital structure (Fig. 19.1). This integration increases the effectiveness of response in case of a major incident [19]. A useful resource for command structures remains the already existing literature in the management of MCI for other departments [15].

19.6 Staff

During response phase, medical care in ICU should be delivered promptly by well-trained trauma teams. Team approach is considered essential for accurate examination and prompt treatment [20]. Training in mass casualty triage and treatment is crucial for effective disaster response [21]. Because of shortage of well-trained intensive care personnel or inability of many intensivists to respond to a hospital disaster call, care of critically ill casualties becomes even harder [22]. Intensivists and well-trained physicians can be allocated to critically ill casualties, only when patients with minor injuries will be directed to community care facilities [17]. In shortage of personnel, well-trained nonintensivists can be responsible for general medical care of seriously injured (a nonintensivist cares for six patients), whereas intensivists take care of emergencies and ventilatory support (a intensivists supervises four nonintensivists) (Fig. 19.2) [5].

Expansion of ICU during MCI causes a need for highly qualified nurses. ICU administration can meet nursing needs by extending working hours, call off-duty staff, relocate nurses from other wards within hospital or utilize nurses from national disaster response teams, military nurses, Red Cross and nurse agencies [15, 23, 24].

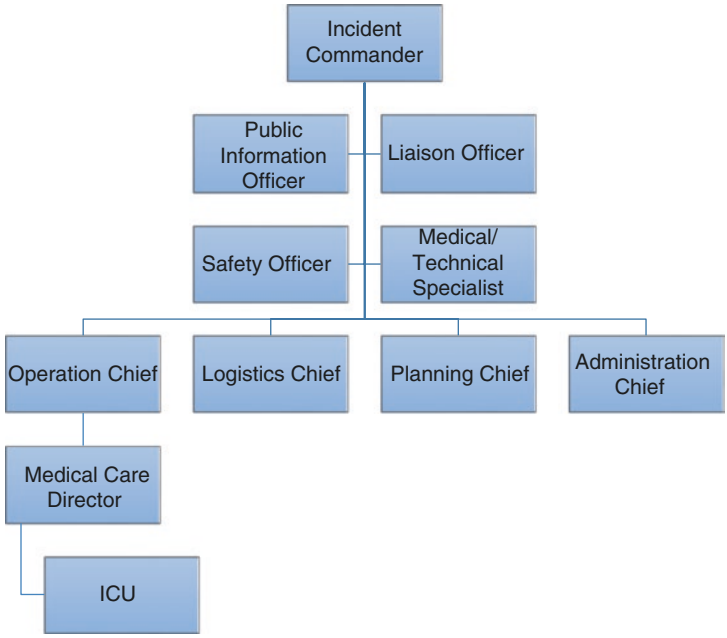

Fig. 19.1 Concise hospital emergency incident command system. ICU officer in hospital chain of command (modified from Hanfling and Andress [18])

Noncritical care nurses take care of two seriously injured casualties, whereas one critical care nurse supervises three noncritical care nurses (Fig. 19.3) [5]. Additional auxiliary personnel from Red Cross, volunteer emergency medical teams and NGO could be entrusted with care of casualties with minor injuries.

Long-lasting disaster response results in work exhaustion because of continuous stress and sleep deprivation. A structured shift roaster considering present and potential needs, available personnel and skills should establish a viable staff rotation. After a MCI staff working in ICU may present with behavioural changes, emotional and physical symptoms, underperformance and low morale [25, 26]. Early recognition of these symptoms and prompt management with counselling and psychological support are considered crucial [27]. Especially susceptible are considered inexperienced staff and nurses, those handling dead bodies and those working with end-stage patients or children [28].

19.7 Stuff

Stockpiling maintenance and medical resources is crucial for ICU in disasters. Any ICU should be autonomous in food, water and basic supplies for at least 48 h during an MCI. Medical resources usually depend on the type of disaster. Apart from a basic inventory of anaesthetic and analgesic medications, resources for respiratory

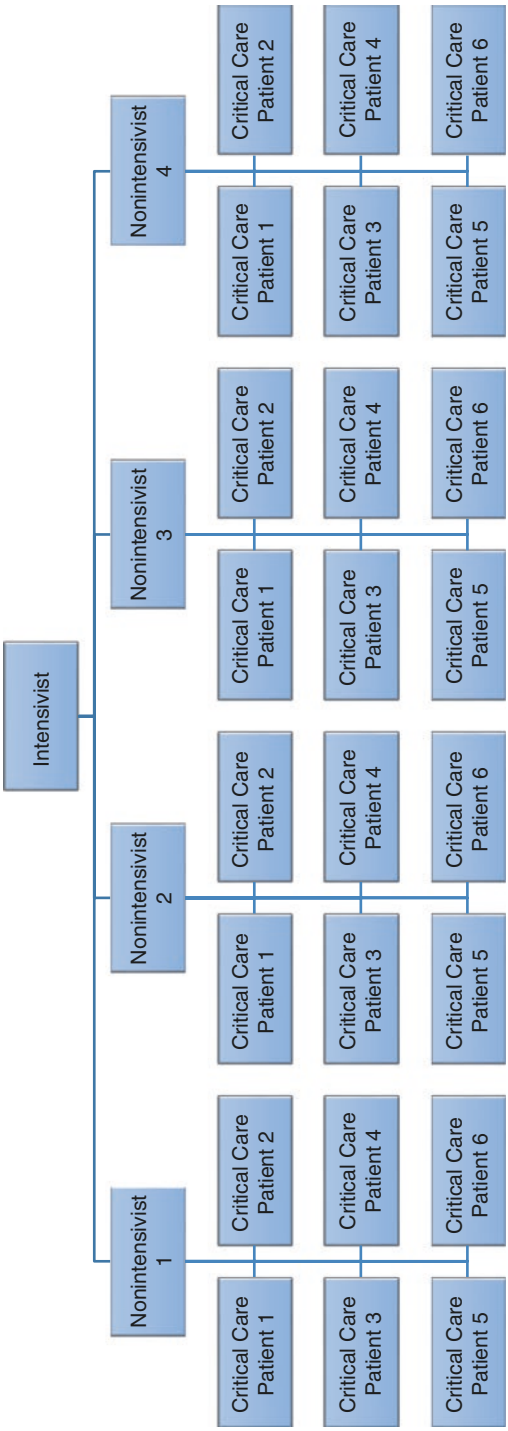

Fig. 19.2 Suggested ICU physician allocation in MCI (modified Rubinson et al. [5])

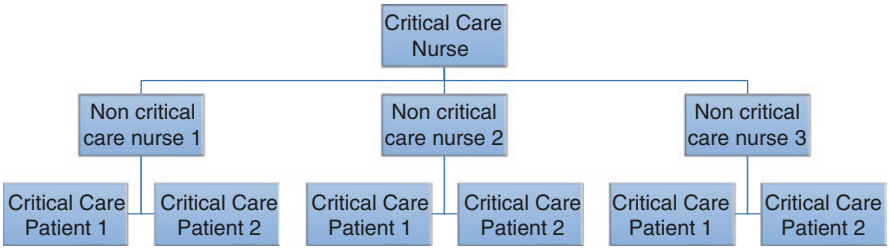

Fig. 19.3 Suggested ICU nurse allocation in MCI (modified Rubinson et al. [5])

Table 19.1 Essential ICU resources for MCI response (modified Rubinson et al. [5])

Number	Type	Drugs
1	Bronchodilators	Anticholinergic, beta-agonist
2	Crystalloids	0.9% NaCl, LR
3	Vasopressor	Upon hospital preference
4	Analgesics	Benzodiazepines
5	Analgesics	Opioids
6	Sedatives	Succinylcholine
7	Sedatives	Non-depolarizing agents
8	Antibiotics	Guidelines of Infectious Disease Society of America or American Thoracic Society
9	Anticoagulant	Upon hospital preference
10	Hormone	Insulin
11	Hormone	Hydrocortisone/fludrocortisone

support, hemodynamic management and antibiotic prophylaxis are considered essential (Table 19.1). Extra resources can be attained upon interhospital cooperation and private sector agreements in times of MCI [5].

Continuous oxygen supply and mechanical ventilators are considered essential for respiratory management. In case of shortage, an ICU may modify ventilators to support more than one patient, utilize postoperative care devices and noninvasive positive pressure ventilators or ask for national stock support [29]. Oxygen availability in bulk, portable liquid systems, compressed gas cylinders and oxygen concentrators are important, since many ventilatory support devices are incompatible with some types of oxygen delivery devices [30].

Existing infrastructure for adjusting temperature in ICU may be compromised in disasters, which may result in diagnostic device malfunction, threaten patients' health or result in suboptimal staff performance [31, 32]. Deployable heating systems and air-conditioning devices should assure a comfortable environment [24]. Air-conditioning devices should be placed away from heating devices or generators, since they may cause CO poisoning by accumulation of CO in ICU [33]. Shutters in windows ensure staff as well as patients' protection from flying debris and wind [16]. During disasters, resources packed in special supply carts can be deployed wherever there is a need. These carts contain equipment for resuscitation, monitoring and wound care [34].

ICU should take provision to admit paediatric and neonatal patients. Paediatric patients are admitted more often than other casualties in ICU [35]. For this reason,

a paediatric ICU (PICU) should expect to receive a huge number of patients after a MCI. Equipment and medications should be available for paediatric use, and medical personnel trained in paediatric emergency care should be present [36]. Paediatric ICU should have an autonomy for 10 days, focusing on reduction of cold stress, ventilatory support, IV fluid administration and vasoactive medications, sedatives, antibiotics and critical care procedures [37].

19.8 Space

High influx of patients in ICU mandates adequate bed capacity. With ICU capacity in many hospitals almost occupied by everyday workload [38], actions should focus on increasing bed vacancy and expanding to other wards. An ICU can free up beds by limiting admittance in emergency department prior to natural disasters, discharging patients from wards ready to go home within 24 h, cancelling elective surgeries, calling in off-duty personnel and transferring patients to another ICU [17, 39, 40]. ICU medical officer should establish high- and low-intensity care areas. Expansion could take place in units with monitoring equipment, oxygen, body heaters, rapid infusion devices, electricity and vacuum capabilities as emergency rooms, dialysis units, post-operation monitoring units, 1-day surgery units, coronary care units und hospital wards with telemetry as well as telemedicine equipment [17]. Clustering of severely injured patients in one area should be avoided, since it may lead to resource depletion and burnout of the personnel. In case of communicable diseases, ventilator deflectors for negative pressure could be deployed in isolation rooms or wards [41]. This expansion should be based on backup equipment, and services are needed (e.g. ventilators, generators, oxygen concentrators, etc.) and continuous patient flow to other medical facilities [42].

19.9 Procedures Management

Hospital management for an MCI begins at the time of the incident. The first 20 min after a disaster are called “latent period,” and a hospital should collect information regarding the number of casualties, trauma patterns, severity of injuries, location, time of the day, etc. This period provides adequate time to clear ER, ICU and wards from patients ready for discharge and plan ICU expansion [43]. An ICU medical officer should establish an ICU coordination cell (Table 19.2) in senior nursing office in order to organize tasks, dispatch runners and collect information, where a physician or nurse could develop a database for patients and resources. ICU coordination cell could serve as multidisciplinary meeting point of surgical, trauma and resuscitation teams for updating and patient management decision-making. ICU coordination cell should always be updated from emergency department, whenever there is a new MCI response activation, and holds the responsibility to inform on time other departments (e.g. haematology, blood bank) [44]. Effective internal and external communication is decisive for ICU operation during MCI. On-call ICU personnel can be informed via cellular phones, beepers and computerized system

Table 19.2 ICU medical officer action card (modified Shirley and Mandersloot [44)

No	ICU medical officer (action card page … of …)
Purpose	Effective response of ICU to MCI, cooperation with incident hospital medical commander for effective hospital MCI response
Role by	ICU senior consultant
Report	
	• Attend Hospital Incident Command Cell meetings • Cooperate with medical care director and operations chief
Key actions	
Major incident stand by	• Get information about the incident • Assess needs for ICU additional equipment, human resources and bed capacity expansion • Contact with medical care director to decide a major incident declared • Once a major incident is declared, activate ICU plan for mass casualties
Major incident declared	• Establish ICU coordination cell • Liaise with anaesthesia and surgery medical officer for patient management • Liaise with ICU senior nurse for effective communication, coordination, resources and patient management • Expand ICU bed capacity • Establish alternative communication channels • Assure continuous patient flow through ICU • Allocate ICU specialist in resuscitation and operation area for triage purposes and decision-making • ICU patients tracking in different departments (operation room, radiology department, etc.) • Liaise with Medical Care Director for continuous supply of resources and personnel • Ensure quality care for all ICU patients
Major incident cancelled	• Debriefing—evaluation existing plans • Ongoing support to personnel, patients and relatives

with recorded messages. Emphasis should be given to those who reside close to the hospital. Whenever during response the fixed communication network is overwhelmed, ICU may use, for in-hospital communication "runners," two-way radios for internal communication and internal mail and for external communication cell phones, satellite phones, mails and internet [20, 24, 44]. Provision for backup system is crucial.

19.10 Triage

During a MCI usually ICU is overwhelmed with multiple casualties with numerous care needs. Triage is an attempt to establish order in a chaotic dynamic environment. Triage can be performed either to casualties in order to identify those requiring immediate care or to resources for managing shortage in stuff while providing emergency care [45].

First step in hospital triage process is patient identification. In a MCI, patient identification may be problematic, because prehospital triage system does not

comply with in-hospital coding. In this case, day-to-day standard hospital procedures should be employed, without additional documentation [46]. Accurate patient triage is important for effective ICU function. Overtriage has a linear correlation with increased mortality, because of consumed resources, delayed care and overwhelmed ICU surge capacity [47]. Therefore triage officer should be an experienced physician in MCI management with good understanding of injury patterns, required emergency interventions and resource allocation [7]. Triage in emergency department should be performed by senior general surgeon. However there may be need for consultancy from an ICU specialist in emergency room, as well as in other triage areas like resuscitation room and operation theatre [44]. An ICU consultant in ER can evaluate patients and give useful information regarding type and severity of injuries. This is helpful in planning for ICU bed expansion. Regarding triage prior to ICU admission, MCI casualties can be divided into three priority categories, immediate, delayed and minor. Immediate casualties present with life-threatening injuries and have poor prognosis. In case of resource shortage, these patients should be provided expectant management in emergency room. When situation allows, they can be upgraded to ICU care and more resources can be allocated. Delayed casualties are considered those with severe injuries and can survive if urgent care is provided.

These can be transferred to ICU for further critical care [48]. Casualties with minor injuries should be triaged and treated away from the hospital, and patients seeking shelter in hospitals should be redirected to organized centres in order to preserve manpower and resources for ICU patients (Fig. 19.4). This is possible by establishing trauma stabilization points close to disaster, as those deployed in Gaza during conflicts in March 2018. Lack of these can overwhelm hospital capacity, as happened in hurricane Katrina [16, 49]. Patient flow should be continuous

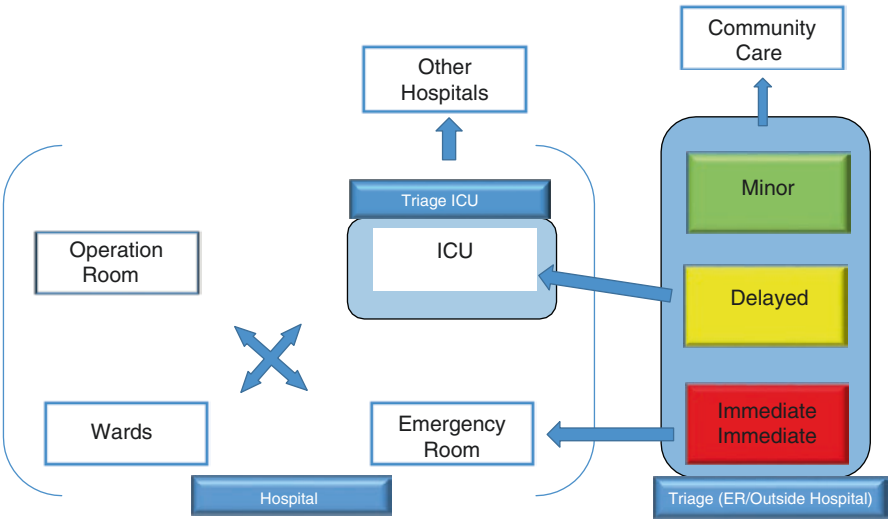

Fig. 19.4 Patient triage [24]

Table 19.3 Resource allocation framework (modified White et al. [51])

Principle	Basis	Points			
		1	2	3	4
Save most lives	Prognosis short-term survival (SOFA score)	<6	6–9	10–12	>12
Save most life years	Prognosis long-term survival	No comorbidities which limit long-term survival	Minor comorbidities with small impact on long-term survival	Major comorbidities with substantial impact on long-term survival	Severe comorbidities; likely death within 1 year
Life cycle principle	Prioritize those who have had the least chance to live through life's stages. (Age)	12–40	41–60	61–74	>75

Patients with the lowest cumulative score are considered to have priority to receive critical care in a limited resource setting

from operation room to ICU and from ICU to other wards or other affiliated hospitals [50]. Wise use of public ambulances prehospitally at scene or use of private ambulance companies may assure an undisruptive interhospital patient transfer [14]. Although in initial patient assessment in ICU, there is always possibility of missed injuries, for this reason, experienced surgeons should re-evaluate patients the following day after the disaster.

Triage of resources is imperative either in shortage of resources or an MCI ongoing with high influx of casualties, and a conservative management of resources is essential. Equipment triage raises ethico-legal issues because of survival implications to casualties. Exclusion criteria remain controversial and vary among nations. A utilitarian approach suggests as criteria, saving the most lives, maximizing life years and life cycle principle (Table 19.3) [51].

19.11 Treatment

The vast majority of casualties may need only basic wound care, tetanus and antibiotic prophylaxis. Blunt abdominal trauma results rarely in intrabdominal organ rupture [52]. Even 38% of casualties from low velocity penetrating abdominal injuries may be treated conservatively in an ICU setting without need of an operation [53]. However casualties with trauma in four or more body regions are considered severe injured and may need ICU admittance [54]. Medical care in ICU can be categorized in early phase and later phase. In early phase because of continuous influx of seriously injured casualties, damage control care is provided, aiming to address

life threats and preserve resources. Damage control care complies with international guidelines in fluid administration and other resuscitation efforts [55, 56]. At a later phase, when no more casualties arrive to ICU, a more aggressive treatment can be initiated. In the same way could radiology department and operation room function for a better management of human and material resources [57]. ICU physicians should be able to predict bottlenecks and consult accordingly. The end of a disaster does not necessary signals the end of ICU readiness. The majority of hospitals have a disaster casualty care plan for the first 6 h. However an ICU should develop also a prolonged care plan. Extensive injuries may take time to heal, or additional operations may be needed. Nonetheless a second wave of casualties from minor hospitals should be expected or from chronic ill medical patients, because the compromised fresh water and sewage system may give rise to infectious diseases or exacerbation of chronic health problems [58]. In this case preventive medicine principles should be applied.

19.12 Training

Another important factor is the speed of response, because many seriously injured will succumb to their wounds in the first 4 h, if not given appropriate care [59]. Response can be improved with continuous training on disaster plans. Training should incorporate various adult learning methodologies (Fig. 19.5).

19.13 Special Circumstances: Terrorist Attacks

In terrorist attacks, casualties can sustain burns, blunt force injuries or penetrating trauma. Often inflicted injuries result from more than one mechanism of injuries. ICU admittance is approximately four casualties per suicide bomber attack

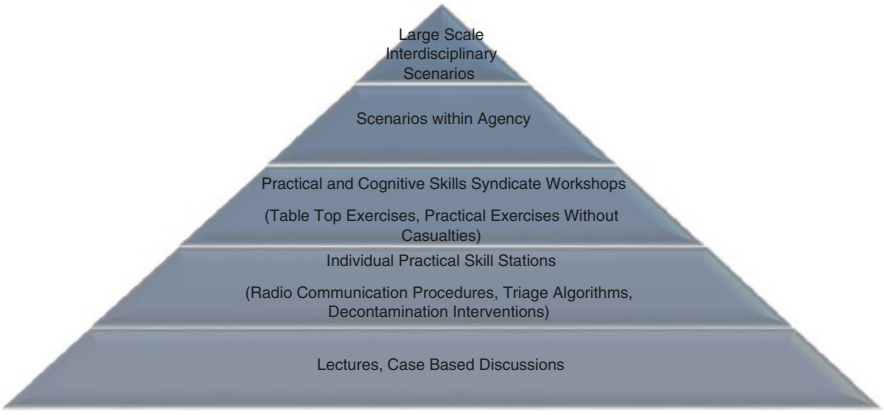

Fig. 19.5 Adult learning approach in MCI training [60]

(range 1–9) [43]. The majority of casualties arrive at the nearest hospital within 2 h after a mass shooting incident usually with minor injuries [47]. In IED explosions the majority casualties present symptoms of blast lung, traumatic brain injury, penetrating and multiorgan injuries [61]. Explosion in confined spaces results in multiple severely injured casualties [62]. Blast incidents tend to be overtriaged regarding ICU admission. This should be avoided because of the reasons stated above [63].

19.14 Burn Incidents

Majority of burn patients never reach a burn centre, because they get treatment by the receiving hospital. However it is advised that a burn patient should be evaluated by a burn surgeon in a burn centre within the first 24 h after a major incident.

Burn ICU is expected to receive burn patients within "intermediate" time of a burn disaster (6–120 h) through interhospital distribution [64]. In burn incidents digital photographs of injuries from the incident or in emergency department and mailed to burn ICU personnel can speed up preparation of operating theatres and ICU admittance. Burn patients need a multidisciplinary approach, since they will most likely need extensive surgery and ICU management [65].

19.15 CBRN

Casualties from a CBRN MCI present with different symptoms. ICU personnel should be trained to identify and treat adequately contaminated patients. Training should include recognition of injury patterns, use of personal protective equipment, decontamination procedures and management of special pathology [66]. Initial patient management may focus on basic support of oxygenation, ventilation and perfusion, while switching later to individual care based on clinical condition with bedside toxicology and monitoring of chemical agents [67]. Contrary to other disasters, pandemic diseases appear over a period of time, providing flexibility for early preparation. Safety in infectious diseases presents a crucial factor, since it may hinder availability or competency of medical staff. In case of aerosolized highly communicable pathogens, protection should include negative pressure respirators [27]. Resources in biological MCI should be disease customized based on threat analysis, and supply relies on basic stock and inter-institutional agreements [68].

19.16 Summary

ICU is a highly trained and specialized hospital unit which has a substantial role in hospital disaster response. A well-designed multidisciplinary ICU disaster response plan should be incorporated in already existing hospital preparedness plan.

Provisions should be made for staff, stuff and space considerations. Continuous training of ICU and non-ICU personnel ensures a rapid response, accurate triage and effective communication. Allocation of resources rises ethical dilemmas which should be discussed and settled in the preparatory phase. ICU surge capacity presents always a challenge and should be managed through interdisciplinary cooperation within hospital and with other healthcare facilities. ICU should be flexible in responding to various major disasters from natural phenomena to terrorist attacks and CBRN incidents. ICU will always be a shelter, where every critical injured casualty will receive best treatment available.

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The ACS Patient in Resource-Limited Setting: How to Get the Maximum from the Minimum!

20

Alain Chichom-Mefire, Liban Wehliye, and Susan I. Brundage

20.1 Background: Access, Limitations, and Systems Development

An environment where healthcare providers cannot operate and provide basic resuscitation is usually referred to as an "austere" environment [1]. An austere environment is defined as an underdeveloped setting (whether infrastructure, human resources, and technology) with harsh working conditions due to the physical environment of an isolated location and/or exposure to climate. Austere environments also can be situations which include the stress and danger associated to armed conflict zones [2]. It is estimated that over 75% of surgeons in the world practice under such challenging conditions. The working environment in these austere settings is characterized by variable degrees of deficit in health infrastructures, equipment, supplies, consumables, and human resources. Other challenges include frequent failures of power and water supply, absence of protection mechanism against sudden weather changes, and sometimes major security issues. Also, many countries in the world, especially in sub-Saharan Africa, do not provide basic universal health coverage, and access to health is financed by out-of-pocket patient's contribution. This makes the care of the acute care surgery (ACS) patient even more challenging.

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These shortcomings result in major disparities in the qualitative and quantitative delivery of surgical services as compared to the western world and even among low- and middle-income countries [3, 4]. These differences also result in poorer outcomes in patients displaying similar surgery-related conditions. Globally, 234 million surgical operations are estimated to be performed annually. However, the poorest third of the world's population receive only a small fraction of these surgical operations at 3.5% [5]. When analyzing the specific field of injury, it was recently estimated that for a similar injury, a patient attended to in a resource-limited setting is twice as likely to die from their injury as another one taken care of in a western country [6].

Consequently, the daily challenge for surgeons working under these conditions is to be able to define a relevant and practical standard of care of the ACS patient which is considered acceptable without compromising quality of care. This challenge is especially difficult in the absence or inappropriateness of intensive care units (ICUs) in most places at the peripheral level. While health systems should be tailored toward meeting the World Health Organization (WHO) recommendations for providing quality surgical care at the tertiary (district) level, the management of the complex ACS patient should always be oriented toward organizing safe transfer to a center possessing a properly equipped ICU when indicated. This orientation is supported by the fact the absence of important resources and technology including laboratory indicators of resuscitation success such as serum lactate levels and estimation of base deficit limits proper tailoring treatment and implementing corrective measures for a better outcome.

While organizing for this referral, the surgeon or the available healthcare provider should be able to ensure basic life support with emphasis on airways and breathing and circulatory stability ensuring appropriate oxygen supply to peripheral organs and tissues to preserve life and limit irreversible organ damage. To this regard, some of the major specific challenges include the initial management of the injured, initiating resuscitative measures including availability of the blood and blood products, and the fight against sepsis and its consequences. Consideration of the current Surviving Sepsis Guidelines including antibiotics use and the fight against antimicrobial resistance is crucial [7].

The aim of this chapter is to provide the healthcare provider managing an ACS patient in resource-limited settings with tricks that could be useful in facing some of the shortcomings related to their specific conditions of practice.

20.2 Initial Resuscitation and Maintaining Life Until Referral and Transfer

The main goal should always be to maintain airways and efficient ventilation and stabilize hemodynamic parameters compatible with adequate oxygen supply to peripheral tissues. In addition, particular attention should be paid to controlling temperature and ensuring minimum nutritional requirements. While there should always be an attempt to follow existing gold standard guidelines, the healthcare

provider needs to use some tricks to face the shortcomings related to the absence of some basic equipment and consumables. A comprehensive list of resources for both trauma and emergency care is outlined in multiple WHO publications including the Integrated Management for Emergency and Essential Surgical Care (IMEESC) toolkit. These resources from WHO are available freely online and as downloadable content (http://www.who.int/surgery/publications/en/).

In the absence of mechanical ventilation, manual ventilation can be performed safely and sometimes could be aided by the quick training of a family member to face the shortage of trained staff. Chest decompression by placement of finger thoracostomy followed by placement of a chest tube controlled by a simple locally made underwater seal system is usually possible everywhere when necessary [8]. The underwater seal system has proven to be even more efficient than suction in preventing air leak [9]. The absence of oxygen supply could be supplemented by using a simple oxygen extractor which relies on environmental air free of charge. This equipment is usually available or can be easily acquired.

Care providers should always remember that two large bore (never one only!) peripheral venous accesses could be substituted to a central venous access for rapid vascular filling. Although strong evidence suggests that standard hemodynamic parameters are not sufficient to assess the degree of physiological derangements [1], the monitoring of efficacy of correction of circulatory failure can rely on these simple monitoring parameters such as blood pressure, pulse, and diuresis when laboratory parameters such as serum lactate are not available. Depending on the etiology of shock, hemorrhage, and hypovolemia versus sepsis, adjustments of circulatory failure can also be aided by an appropriate dose of adrenalin in the absence of other vasoactive substances considered to be more adapted.

Limited evacuation systems are capable of providing separate blood components in civilian prehospital environments. Even when prehospital blood products are available, the impact on outcomes is unclear when studied in various settings [10–13]. Lack of prehospital transfusions is particularly true in austere settings. When the need for blood transfusion arises, in the absence of more acceptable alternatives, whole blood transfusion remains a valid lifesaving option [1, 10, 14–16]. Fresh whole blood could also be envisaged to address specific issues such as coagulation problems as it is suggested that coagulations properties of stored blood could be preserved for as long as 2 weeks in austere environments [17]. It could be useful to remember that O rhesus negative blood can be used as a lifesaving option without requiring all usual matching procedures. Consequently, this type of blood could be stored and kept for as long as possible to await acute situations. Tranexamic acid (TXA) is a relatively inexpensive plus an easily portable and stable drug. Numerous studies have shown an improvement in mortality when TXA has been administered as an adjunct for presumed hemorrhagic shock within 3 h from the time of initial injury. Conversely, TXA treatment greater than 3 h from injury has been associated with significantly worse mortality rates. Although controversy does surrounding the administration of TXA due to concerns of potential untoward thromboembolic events, at this point in time, globally TXA has become a standard adjunct in face of hemorrhage on the basis of strong evidence from the CRASH and MATTERS

studies [18–20]. TXA should be considered for administration only within 3 h of time from injury and using locally designed protocols which adhere to the most currently available evidence.

Anemia is a frequent finding in many tropical areas and must be carefully identified and corrected as it is likely to greatly impact outcomes especially in ACS patients in need of surgical intervention [21]. Recognition of the potential for sickle cell disease and trait also needs to be taken into account with regard to treatment of anemia and the decisions surrounding transfusion processes.

Surgical action such as laparotomy or thoracotomy should only be considered as a lifesaving intervention and performed in the damage control spirit, giving priority to correction of physiological derangements rather than anatomical repair of lesions [1]. This approach has demonstrated its ability to save life in desperate situations [22]. Definitive treatment would preferably be best organized in a setting with appropriate ICU facilities.

Some specific actions which could not be delayed to await referral include laparotomy with splenectomy for exsanguinating splenic injury and the drainage of an extradural hematoma for which exploratory burr hole could still be safely considered as a useful tactical approach [23].

Protecting the patient against hypothermia is possible with a very simple trick: application of blankets and warm water in plastic bottles which are placed beside the patient after they have been wrapped in linen to prevent direct contact with the skin and burn injury.

Blood sugar is not usually considered a major concern in the first 24 h of management of the ACS patient as it does not seem to impact mortality at that point [24]. However, after this initial period, great attention should be paid to glycemic control as it is associated with poorer outcomes especially in patients with trauma [25]. In the absence of contraindications, the most cost-effective option would be enteral nutrition through a nasogastric tube which should be envisaged as soon as possible without requiring the services of a nutritionist.

Finally, patient safety should always be a major concern as medical errors are more likely to occur when facing such critical emergency situations. Whenever possible and in the absence of specific guidelines adapted to the working environment, the use of safety tools such as the WHO operating room checklist or the emergency department safety checklist should be encouraged and generalized [26].

20.3 Organizing Safe Referral and Transfer

Surgery-related conditions are known to be the most important providers of ICU admissions especially in resource-limited settings [27]. A careful selection of patients to be referred to a center with ICU is indispensable to avoid unnecessary referrals as interhospital transfer has been identified as an independent predictor of mortality in the ACS patient even in developed countries [28, 29]. It is also suggested that ICU referrals or admission during afterhours or weekend is clearly associated with poorer outcomes [30] and this must also be taken into account when organizing

referral without resulting in overdue patient retention. Whenever possible, transfer should not be initiated without providing a proper referral by contacting the receiving ICU to ensure availability of admission space and qualified personnel including essential subspecialties optimal for management of the specific condition. Standard referral pathways, processes, and communication routes for transfers to higher levels of care should be pre-established to avoid confusion and time delays.

Frequently, an ambulance is not available, and the transfer has to be done using non-specific vehicles. Whatever the mode of transportation, the patient must be assisted during transfer by a healthcare provider, ideally a doctor. The physician or medical officer's mission would be to ensure ventilation and vascular stability during the trip. They need to be prepared to face any unexpected event during transfer by taking along enough intravenous fluids, some ready-to-transfuse blood kept in a cooler, and vasoactive agents, among other items.

Special attention should be paid to appropriate documentation of all clinical findings and actions undertaken before referral, preferably in the form of a complete handoff. This costs nothing and has proven to improve outcomes, especially in the patient admitted in an intensive care unit after a surgical procedure [31].

20.4 Some Specific Situations

20.4.1 The Patient in Sepsis

20.4.1.1 Initial Evaluation and Decision-Making

The patient with a surgery-related sepsis represents a special challenge in austere settings. It is estimated that up to 70% of cases of sepsis originate from the abdomen and will be very significant contributors to death toll [32]. Also, survivors of sepsis frequently display major permanent disability [33, 34].

The fight against sepsis in general is currently centered around principles such as early recognition and diagnosis, appropriate and rapid resuscitation measures, source control whenever possible, and proper initiation of antimicrobial therapy [35].

The criteria to be used for decision-making would be best inspired by existing validated guidelines based on clinical evaluation alone and not on sophisticated laboratory findings. To this regard, the quick Sequential Organ Failure Assessment (qSOFA) score which simply uses blood pressure, respiratory rate, and Glasgow Coma Scale (GCS) is a good alternative to more comprehensive scores such as SOFA or various versions of the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score. The best approach to early diagnosis is systematic suspicion in all patients with a situation which could potentially lead to a septic condition. In the absence of comprehensive laboratory work-up, assessment of severity and monitoring of sepsis in austere setting could rely on a purely clinical scoring system such as qSOFA score. This score is gradually being validated as a useful tool for assessment of sepsis despite some controversies especially on its use in the emergency setting [36–38].

20.4.1.2 Source Control

Source control often requires a surgical action such as laparotomy or abscess drainage. The surgeon often faces extreme situations with the moribund patient in severe sepsis and multiorgan failure not responding to standard resuscitation measures. This is usually a consequence of major delays in initiation of care. It is suggested that in selected cases, breaking the vicious circle of sepsis in such patients by suppressing the source of infection could be associated with improved survival rate [22]. When the decision to operate on the moribund is taken, the spirit of that intervention should always be damage control with the goal of correcting only physiological abnormalities which are likely to contribute to immediate survival.

20.4.1.3 Antibiotic Choice and Timing of Administration

Antibiotics play a key role in these physiological corrections. It is critical for surgeons and other workers in low- and middle-income countries to join the international medical community in the current stewardship in favor of the timely and appropriate use of antibiotics and the fight against antimicrobial resistance [7]. Whenever possible, a sample should be obtained for organism identification and sensitivity testing by microbiology to help the choice of antibiotics on the condition that it does not delay the initiation of antimicrobial therapy. The Surviving Sepsis Guidelines have just been updated in 2018 [39] and currently recommend broad-spectrum antibiotics be administered as part of a 1-h "sepsis bundle." The components recommended in the 1 h sepsis bundle include lactate measurement, obtaining blood cultures prior to starting broad-spectrum antibiotics, and crystalloid resuscitation combined with vasopressors to maintain a mean arterial blood pressure (MAP) >65 mmHg. Antibiotic choice should ultimately be de-escalated to the sensitivities specific to the offending organism once identified. Such sample could be conditioned and taken along with the patient during referral. Despite scarcity of data, selection of antimicrobials to be used in empirical initiation of therapy should rely as much as possible on local microbiological ecology. Excellent educational resources outlining the up-to-date expectations and standard for sepsis management are provided freely online via the Surviving Sepsis Campaign materials [39]. In the long run, efforts should be tailored toward implementing a systematic method of reducing sepsis-related ICU admissions by preventing its occurrence in the first place [40].

20.4.2 The Injured Patient

In austere settings, it is of critical importance to rely on systematic and validated approach such as Advanced Trauma Life Support (ATLS®) when attending to every patient with an injury. Decisions of referral are best taken after secondary survey which alone permits accurate identification of lesions to be mentioned on the handout document and proper preparation of transfer.

The challenge of maintaining circulation is a critical issue and most often relies on controlling bleeding. In this regard, the use of mechanical hemostatic adjuncts

such as various forms of tourniquets could be lifesaving [1]. There is increasing evidence in favor of the use of injectable hemostatic adjuncts such as TXA (see above). Training civilian first responders is recognized as a major global need. Lay first responders optimize "time critical" care. Formal civilian first responder training programs launched in the past year to large acclaim include the "Stop the Bleed" initiative [41, 42] designed for use in countries with developed emergency response systems. The WHO details the success of first responder care in low-to-middle-income countries (LMICs) in *Pre-hospital Trauma Care Systems* publication (http://www.who.int/emergencycare/trauma/success-stories/en/) [43]. This document highlights the key role that first responders play within a prehospital trauma care system, especially in low-income countries. A significant body of evidence from countries without formal emergency response systems shows that training lay first responders significantly improves the outcomes of injured patients [44]. Recognition of potentially life-threatening extremity injuries and appropriate use of tourniquets in both the prehospital and accident and emergency department settings should be considered. A number of programs training civilians and first responders such as police forces, fire brigades, and civilians in the proper application of tourniquets have been undertaken in both developed and austere settings with positive impacts.

In the trauma patient with an intra-abdominal or intrathoracic bleeding, it is still considered safe and reliable to resort to autotransfusion and other intraoperative blood salvaging methods in the absence of contraindications. These methods have proven to be efficient and cost-effective [45–49].

While selective non-operative management of abdominal traumatic bleeding has shown to be feasible in high-income settings and is being gradually extended even to gunshot wounds [50], this option should be considered with a lot of caution in setting with limited possibility of repeated advanced imaging and shortage of human resources as this treatment option requires more monitoring. In particular, it should never be envisaged in the absence of appropriate transfusion capacity.

Careful evaluation of the patient with a burn injury must be conducted, and no compromise from existing criteria for admission in a burn center should be accepted as the death toll is extremely high. Unfortunately, there is a high incidence of life-threatening as well as disfiguring injuries and functional limitations from burn contractures in austere environments secondary to frequent use of open fires for cooking and heat provision. Although understanding the prevention and management of burns is essential in austere conditions, burn care is outside the scope of this chapter and will not be covered in detail. Excellent educational materials and important links can be found on the American Burn Association (ABA) as well as the International Society for Burn Injuries (ISBI) and the South African Burn Society's online resources.

There should always be an attempt to grade overall severity of injury. Simple purely physiological scores such as Revised Trauma Score or Kampala Trauma Score would generally suffice in the emergency setting. Also, according to a recent report from Brazil [32], independent early predictors of mortality in trauma patients include arterial hemoglobin oxygen saturation, diastolic blood pressure,

serum lactate level, GCS, infused crystalloid volume, and presence of traumatic brain injury [51]. At least four of these criteria could be easily obtained in the least equipped health facility, and we suggest the immediate referral of every patient displaying any of these characteristics. No patient with head injury and a GCS of 12 or less should be retained at the peripheral level.

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