Multisystem Trauma

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LEARNING OBJECTIVES

1. Justify the role of the pharmacist in optimizing pharmacotherapy for acutely ill patients with multisystem trauma.
2. Design an acute resuscitation plan—including appropriate coagulopathy management—based on the current literature and guideline recommendations.
3. Assess differences in pharmacotherapy for patients with multisystem trauma based on specific organ injuries.
4. Develop pharmacotherapy to address challenges in the prevention and management of trauma-related complications.

ABBREVIATIONS IN THIS CHAPTER

ACCP	American College of Chest Physicians
Anti-Xa	Serum antifactor Xa concentration
ATLS	Advanced Trauma Life Support
BTF	Brain Trauma Foundation
CPP	Cerebral perfusion pressure
GCS	Glasgow Coma Scale
ICP	Intracranial pressure
ISS	Injury Severity Score
IVC	Inferior vena cava
LMWH	Low-molecular-weight heparin
MODS	Multisystem organ dysfunction syndrome
PE	Pulmonary embolism
RSI	Rapid sequence intubation
SBP	Systolic blood pressure
SCI	Spinal cord injury
TBI	Traumatic brain injury
UFH	Unfractionated heparin
VTE	Venous thromboembolism

Table of other common abbreviations.

INTRODUCTION

Injury is a serious public health problem associated with significant morbidity, mortality, and economic burden. In 2016, unintentional injuries were the third-leading cause of death and the leading cause of death among people aged 1–44 years in the United States (CDC 2018). Unintentional injuries, violence-related injuries, and injuries from undetermined intent accounted for more than 231,000 deaths (Xu 2018). Victims of nonfatal injuries made more than 32 million ED visits and had 2.88 million hospitalizations. The CDC estimates that total lifetime medical and work-loss costs resulting from both fatal and nonfatal injuries amounted to $671 billion in the United States in 2018 (CDC 2018). Those total medical and work-loss costs were more than twice as high for nonfatal injuries compared with fatal injuries (CDC 2018).

Trauma Types

Mechanisms of injury are commonly classified as blunt, penetrating, burn, or blast. Blunt injuries are caused by exertional forces with rapid acceleration and deceleration. Those types of trauma include motor vehicle collisions and falls. Penetrating injuries include stabbings and gunshot wounds resulting in direct tissue damage at the point of physical impact as well as projectile-associated damage (Marr 2017). Injuries related to blunt and penetrating trauma are the major focus of this chapter.

Injury Severity Scores

The Injury Severity Score (ISS) is an internationally recognized scoring system for describing injury extent based on anatomic locations. The Abbreviated Injury Scale (AIS) assigns a score for each body region with higher scores indicating greater injury. The ISS is calculated as the sum of the squares of the three highest injured body

regions (Box 1). A score of greater than 25 indicates severe trauma with a maximum score of 75 indicating patient death (Champion 2017). The ISS and AIS are used primarily in research settings as methods to compare or control for severity of injury between patient groups; however, it may be used in clinical practice to provide objective information regarding patient prognosis, resource allocation, and risk assessment tools (e.g., venous thromboembolism prophylaxis).

Pharmacist Role

Pharmacists are integral members of a multidisciplinary trauma team and serve as pharmacotherapy experts by aiding in protocol and guideline development and reducing adverse drug events and costs. Pharmacotherapy interventions include dosing and alternative-therapy recommendations, avoidance of unnecessary therapies, and drug information responses (Patanwala 2010). Pharmacists demonstrate expertise in acute trauma therapies such as resuscitation; prevention of associated complications of pain, agitation, and delirium; provision of antimicrobial stewardship; hemorrhage management; and appropriate VTE chemoprophylaxis (Scarponcini 2011). Clinical pharmacist interventions as part of Level I trauma service are associated with more than $500,000 in cost savings annually (Hamblin 2012).

Box 1. Injury Severity Score and Abbreviated Injury Scale

AIS Severity and Description

Points	Injury
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Unsurvivable

ISS Body Regions

Head or neck
Face
Chest
Abdomen/pelvis
Extremities
External/skin

AIS = Abbreviated Injury Score; ISS = Injury Severity Score.

Information from: Champion H, Moore L, Vickers R. Injury severity scoring and outcomes research. In: Moore EE, Feliciano DV, Mattox KL, eds. Trauma. New York: McGraw-Hill, 2017:71-95.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of various shock states and vasopressor agents
- Consequences of shock states on end-organ damage
- Available blood components and their uses
- Uses of anticoagulants to prevent venous thromboembolism
- Basic understanding of available reversal agents
- Basic understanding of pathophysiology in traumatic brain injury

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Vincent JL, De Backer D. Circulatory Shock. N Engl J Med 2013;369:1726-34.
- WHO. Clinical Transfusion Practice.
- Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients. Chest 2012;141(Suppl 2):e227s-e277s.
- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. Neurocrit Care 2016;24:6-46.
- Vella MA, Crandall M, Patel MB. Acute management of traumatic brain injury. Surg Clin North Am 2017; 97:1015-30.

ADVANCED TRAUMA LIFE SUPPORT

Deaths attributable to multisystem trauma follow a trimodal distribution (ACS 2018). The initial peak happens within seconds to minutes after initial injury. Prevention is the best method for minimizing early deaths. However, educational efforts such as the Stop the Bleed awareness campaign to train bystanders on basic control of external bleeding in mass-casualty disasters are increasing.

The second peak occurs minutes to hours after initial injury. The golden hour following trauma forms the basis for the Advanced Trauma Life Support (ATLS) guidelines (ACS 2018).

The third mortality peak occurs days to weeks after initial injury, typically caused by sepsis, with multisystem organ dysfunction syndrome (MODS) or worsening of traumatic brain injury (TBI). Emphasis is placed on initial management of the patient with multisystem trauma in order to prevent negative outcomes (ACS 2018). For more on TBI monitoring modalities, see the Online Appendix.

Primary Survey

The primary survey of trauma patients is systematic and logical so as to prioritize the identification of life-threatening conditions that can rapidly progress to death. The ABCDE

acronym is used in ATLS to prioritize the sequence of care and ensure that critical injuries are not missed.

Airway Maintenance

Maintaining a functional airway is one of the most critical aspects of managing the patient with multisystem trauma. Failure to rapidly identify airway issues leads to inadequate oxygenation, which deprives vital organs and the brain of oxygen-rich blood and impairs ventilation. The inability to identify and secure an adequate airway because of obstruction is one of the leading causes of early, preventable deaths in trauma patients (ACS 2018).

When the decision is made to establish a definitive airway with an endotracheal tube, the pharmacist should know which sedatives and paralytics can be used safely in trauma patients. Rapid sequence intubation (RSI), which involves the administration of an induction sedative followed by a neuromuscular blocking agent to achieve motor paralysis is the most common technique for placing an endotracheal tube (Patanwala 2016).

Etomidate has historically been the favored induction agent because of its rapid onset of effect, short duration of action, and stable effects on hemodynamics. However, given concerns about the association of etomidate with short-term adrenal insufficiency, there has been renewed interest in the use of other sedative agents for RSI in trauma patients (Cotton 2008). Ketamine has traditionally been avoided in trauma patients because it may increase intracranial pressure (ICP) and it may lower cerebral perfusion pressure (CPP) in patients with TBI (Patanwala 2016). A recent systematic review suggested that ketamine caused neither sustained increases in ICP nor reductions in CPP. Another systematic review reported no differences in mortality, neurologic outcome, or ICU length of stay between use of ketamine and that of other induction agents (Cohen 2015). Finally, a retrospective analysis of trauma patients that compared ketamine and etomidate for RSI reported no differences in hospital mortality, ICU-free days, or ventilator-free days (Upchurch 2017). Although prospective studies comparing ketamine and etomidate are still needed to determine the optimal induction agent in trauma patients, available data suggest that either agent is likely safe and effective.

Succinylcholine and rocuronium are the two most commonly used neuromuscular blocking agents for RSI (Patanwala 2016). Both agents are associated with high levels of first-intubation-attempt success, but concerns have been raised about the use of both agents in trauma patients. Drug labeling for succinylcholine suggests that transient increases in ICP are possible, and the longer duration of action with rocuronium may prevent the timely assessment of neurologic function in patients with TBI and delay operative intervention. In a retrospective multivariate analysis, succinylcholine-treated patients with head AIS scores of 4 or greater had increased mortality compared with rocuronium-treated patients (Patanwala 2016). Although this was a retrospective analysis that looked at a specific subgroup, the trial raises important questions regarding the safety of succinylcholine in patients with severe TBI, and it spotlights the need for a prospective trial. In the meantime, the risks of using succinylcholine for RSI in patients with severe TBI must be balanced against the benefits (earlier assessment of neurologic function) when selecting the most-appropriate paralyzing agent. When rocuronium-based RSI is used, pharmacists should be aware of the longer duration of neuromuscular blockade and implement early postintubation sedative to minimize the risk of a conscious but pharmacologically paralyzed patient. Pharmacist presence during rocuronium-based RSI has been associated with shorter time to implementation of sedative use compared with pharmacist absence (Amini 2013).

Breathing and Ventilation

Disorders of oxygenation and ventilation in trauma patients can be caused by a number of factors such as neurological injuries and injuries that compromise respiratory mechanics. For example, patients with severe TBI may have altered breathing patterns that lead to abnormal ventilation, and those with cervical spinal cord injury (SCI) may have difficulty oxygenating and ventilating because of paralysis of the diaphragm, intercostal muscles, and abdominal muscles (ACS 2018).

Circulation with Hemorrhage Control

Trauma patients may present with various types of shock, including hypovolemic, cardiogenic, obstructive, and neurogenic. Rapid identification of the cause of shock is critical to the successful management of trauma patients. The most common form of shock following trauma is hemorrhagic, which is a form of hypovolemic shock. Treatment of hemorrhagic shock involves identification and control of bleeding in addition to volume repletion to restore adequate perfusion to vital organs (ACS 2018).

Disability

After initial stabilization, the trauma patient should be evaluated for neurological injury (e.g., TBI, SCI). Abnormalities in Glasgow Coma Scale (GCS) score, in pupillary size and reaction, and extremity movement or sensation, as well as lateralizing signs (e.g., headache, dizziness) may indicate neurologic injury (ACS 2018).

Exposure and Environmental Control

To identify all potential injuries, the patient should be completely undressed. Practitioners should carefully keep the patient normothermic by applying warm blankets or external warming devices and using warmed intravenous fluids (ACS 2018).

HEMORRHAGIC SHOCK

Hemorrhagic shock occurs in the setting of severe blood loss leading to impaired oxygen delivery at the cellular level. The

mismatch between tissue oxygen demand and consumption leads to a cumulative oxygen debt. Rapid identification and correction of the oxygen debt are critical in the trauma patient with hemorrhagic shock (Cannon 2018).

Pathophysiology and Complications

Response to tissue injury and blood loss at the cellular level is complex. Proinflammatory molecules and damage-associated molecular patterns are released from intracellular locations. Although this adaptive mechanism to stimulate an inflammatory response and tissue repair is initially beneficial, it is believed that those changes may lead to compensatory anti-inflammatory-response syndrome and prolonged immunosuppression that increases the risk of nosocomial infections and MODS in trauma survivors (Cannon 2018).

Trauma patients presenting with hemorrhagic shock attempt to maintain adequate organ perfusion by a number of compensatory mechanisms. At the tissue level, hypovolemia triggers vasoconstriction through activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. That compensatory mechanism is initially adequate to maintain hemodynamic stability, but continued hemorrhage and hypoperfusion can lead to MODS and death. The stages of hemorrhagic shock as described in the ATLS guidelines inform practitioners of the expected physiologic responses based on amount of expected blood loss (Table 1). The presence of hypotension typically indicates advanced stages of hemorrhagic shock due to a failure of compensatory mechanisms to maintain blood pressure. Alteration of physiologic measurements such as heart rate, respiratory rate, and urine output are likely to result in earlier identification of hemorrhage (Cannon 2018).

Hemorrhagic shock causes activation of platelets and the clotting system to form a hemostatic plug at the injury site. The endothelium and blood act synergistically to attempt to achieve thrombus formation and cease bleeding. With continued hemorrhage and mounting oxygen debt, the vascular endothelium becomes damaged. The glycocalyx, which consists of membrane-bound glycoproteins and proteoglycans, is a protective border found on endothelial cells. It regulates endothelial permeability and shear stress and exhibits heparinlike activity. Glycocalyx shedding in addition to excess plasmin activity can result in pathologic hyperfibrinolysis and coagulopathy. Although many of those responses are adaptive changes designed to facilitate hemostasis, many of the downstream effects tend to be maladaptive in the setting of continued bleeding (Cannon 2018). In addition, the changes represent potential pharmacologic targets for reversing those maladaptive responses.

Damage Control Resuscitation

Damage control resuscitation (DCR) refers to a bundle of interventions used in hemorrhaging trauma patients to prevent further accumulation of oxygen debt and ensure timely repayment of oxygen debt through the identification and cessation of bleeding and the restoration of intravascular volume. The main tenets of DCR can be found in Box 2. Damage control surgery is commonly discussed in the setting of DCR. In damage control surgery, operative procedures are staged in a manner to control hemorrhage and minimize contamination (e.g., feculent material from injured bowel) and are followed

Table 1. Signs and Symptoms of Hemorrhage by Class

Parameter	Class I	Class II (Mild)	Class III (Moderate)	Class IV (Severe)
Approximate blood loss	<15%	15–30%	31–40%	>40%
Heart rate	↔	↔/↑	↑	↑/↑↑
Blood pressure	↔	↔	↔/↓	↓
Pulse pressure	↔	↓	↓	↓
Respiratory rate	↔	↔	↔/↑	↑
Urine output	↔	↔	↓	↓↓
Glasgow Coma Scale score	↔	↔	↓	↓
Base deficit[a]	0 to –2 mEq/L	–2 to –6 mEq/L	–6 to –10 mEq/L	–10 mEq/L or less
Need for blood products	Monitor	Possible	Yes	Massive Transfusion Protocol

[a]Base excess is the quantity of base (HCO_3– in mEq/L) that is above or below the normal range in the body. A negative number is called a base deficit and indicates metabolic acidosis.

Reprinted from American College of Surgeons. Advanced Trauma Life Support (ATLS) Student Manual, 10th ed. Chicago: American College of Surgeons, 2018.

Box 2. Principles of Damage Control Resuscitation

Primary principles of DCR

- Minimization of crystalloid infusions during early resuscitation (<3 L in the first 6 hours)
- Permissive hypotension in select patient populations
- Resuscitation with blood products that closely mimic whole blood

Other principles of DCR

- Avoidance and/or correction of hypothermia
- Avoidance of delays in surgical or angiographic hemostatic procedures
- Development and implementation of massive transfusion protocols
- Minimization of blood loss during transport and initial evaluation with tourniquets and hemostatic gauze
- Selective use of pharmacologic adjuncts to reverse prehospital anticoagulant medication and correct ongoing coagulopathy
- Use of functional laboratory measure of coagulation such as thromboelastography to guide the transition from empiric to targeted therapy

DCR = damage control resuscitation

Information from Cannon JW. Hemorrhagic shock. N Engl J Med 2018;378;370-9; Cannon JW, Khan MA, Raja AS, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg 2017;82:605-17.

by definitive surgery within 24 hours to repair anatomic abnormalities (e.g., reconnecting sections of injured bowel that were left in discontinuity). Resuscitation using DCR techniques occurs between operative procedures (Cannon 2018, Cannon 2017). Finally, there has been an increased utilization of angiography and selective embolization of bleeding vessels to minimize operative procedures or control bleeding that is difficult to approach because of location (e.g., retroperitoneal bleeding with pelvic fractures).

Permissive Hypotension

Permissive hypotensive resuscitation is defined as the intentional maintenance of low blood pressure by restricting crystalloid fluid administration until surgical control of bleeding can be achieved. Aggressive fluid administration before achieving hemostasis may result in (1) further bleeding by dislodging a hemostatic clot, (2) dilutional coagulopathy, (3) hypothermia from cold crystalloid solutions, and (4) worsening acidosis by administration of isotonic crystalloid solutions (Cannon 2018, Tran 2018).

A landmark study compared the outcomes of immediate versus delayed fluid resuscitation in patients with penetrating trauma to the torso and prehospital SBP of less than 90 mm Hg. Patients were randomized to either the immediate-resuscitation group with Ringer's acetate solution, used for maintaining SBP greater than 100 mm Hg before operative intervention, or the delayed-resuscitation group, where fluids were withheld until the patient arrived in the operating room. The delayed-resuscitation group had a higher rate of survival compared with the immediate-resuscitation group (Bickell 1994).

In recent years, prospective studies evaluating hypotensive resuscitation in populations of heterogeneous trauma patients, including blunt trauma, have been published. In addition, the studies addressed previous concerns about withholding fluid administration in blunt trauma patients and allowed for small-volume resuscitation when certain physiologic parameters were met (Carrick 2016). Systematic reviews suggest that liberal fluid administration before adequate hemostasis is associated with higher mortality (Albreiki 2018, Wang 2014). Another systematic review and meta-analysis demonstrated that hypotensive resuscitation was associated with decreased mortality, blood product utilization, blood loss, and crystalloid volume (Tran 2018).

In clinical practice, most trauma systems are using some form of hypotensive resuscitation. The method whereby hypotensive resuscitation gets achieved tends to be variable because consensus statements and guidelines either differ on the target blood pressure goals or provide no specific target. The ATLS guidelines advocate controlled resuscitation that balances the goals of maintaining perfusion while minimizing the risk of clot dislodgement. Those guidelines advocate small volumes of resuscitation (1 liter of crystalloid) compared with previous versions, which advocated up to 2 liters (ACS 2018). European guidelines on the management of bleeding and coagulopathy following trauma recommend maintaining an SBP of 80–90 mm Hg until major bleeding has been controlled in non-TBI patients or a mean arterial pressure of at least 80 mm Hg in patients with severe TBI (Rossaint 2016). The Eastern Association for the Surgery of Trauma (EAST) guidelines recommend avoiding fluid administration if the patient is coherent and has a palpable radial pulse. Small-volume resuscitation to achieve those end points should be administered. In a patient with suspected TBI, the EAST guidelines advocate maintaining an SBP greater than 90 mm Hg (Cotton 2009).

Blood Transfusions

The emphasis on resuscitation in hemorrhaging trauma patients has shifted from a fluid-based focus to a blood-based focus. Studies have demonstrated that crystalloid resuscitation after initial trauma has been associated with dilution of existing coagulation factors, worsening acidosis, and hypothermia, all of which contribute to the lethal triad and vicious cycle of continued bleeding. Those complications contribute to increased risk of acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), abdominal compartment syndrome, and mortality (ACS 2018, Cannon 2018). Given the negative outcomes associated with crystalloid resuscitation,

blood products are the mainstays of intravascular volume expansion in the acutely bleeding trauma patient.

Massive Transfusion and Blood Product Ratios

In recent years, major trauma centers have developed systems that enable physicians to activate a massive transfusion protocol that facilitates the rapid administration of blood products. Although triggers to activate massive transfusion protocols vary, the definition typically used in research studies is an anticipated need for 10 or more units of red cells within 24 hours. The protocols have evolved over the years to provide a balanced ratio of plasma, platelets, and red blood cells.

The evolution of blood product ratios was initially based on outcomes in military studies emphasizing whole-blood resuscitation while minimizing crystalloid solutions. Because blood products are fractionated into various components in the United States, studies in civilian patient populations evaluated giving the separate components to mimic whole-blood resuscitation. Two prospective trials and a systematic review of available literature demonstrated that high ratios of plasma and platelets to red blood cells reduced short-term mortality (Cannon 2017, Holcomb 2013; Holcomb 2015). The PROPPR trial was a multisite, randomized clinical trial of 680 severely injured trauma patients. Patients were randomized to receive blood products in a ratio of 1:1:1 (plasma/platelets/red blood cells) or a 1:1:2 ratio. No significant difference in mortality at 24 hours or 30 days was detected between the groups; however, the authors did find lower rates of exsanguination and higher achievement of hemostasis in the 1:1:1 group. In clinical settings, an approach that mimics administration of whole blood by using a 1:1:1 ratio of blood products is most commonly utilized (Holcomb 2015).

Prehospital Plasma

The use of blood products, including plasma, in the prehospital setting as a method to correct early coagulopathy and permit earlier initiation of DCR strategies has sparked recent interest. The implementation of DCR practices in the prehospital setting in order to minimize downstream complications may improve mortality in trauma patients with suspected hemorrhagic shock. The PAMPer study was a prospective trial involving patients with suspected hemorrhagic shock based on hemodynamic assessment. Patients were randomized during air transport to receive either standard-care resuscitation or 2 units of thawed plasma. The group that received prehospital plasma had lower mortality, and Kaplan–Meier estimator curves revealed early separation between the groups beginning 3 hours after randomization (Sperry 2018). Implementation of the practice is logistically challenging given the need for cold storage, short shelf life once thawed, and limited availability to provide adequate supplies for all emergency medical service personnel.

Intravenous Fluid Resuscitation

Intravenous fluids are used only infrequently in acute resuscitation of the hemorrhaging trauma patient. However, intravenous fluids remain an important treatment option when blood products are unavailable (e.g., in the prehospital setting) or for continued resuscitation after active bleeding has been controlled. Pharmacists should have an understanding of the risks and benefits of various solutions in trauma patients.

Crystalloids

There is a paucity of data from large randomized controlled trials comparing various isotonic crystalloid solutions in trauma patients. As a result, fluid selection is frequently based on theoretical benefits or known adverse-effect profiles of the various crystalloid solutions rather than on data from prospective trials. Historically, lactated Ringer's has been the most frequently used crystalloid in trauma patients.

In recent years, small prospective studies have compared balanced crystalloids with normal saline in trauma patients. The studies demonstrated that balanced crystalloids resulted in greater increases in base excess, reduction in hyperchloremic metabolic acidosis, and similar intracranial pressure compared with those who received a chloride-rich solution such as normal saline (Roquilly 2013, Young 2014).

Data from large randomized controlled trials involving critically ill patients provide additional information regarding crystalloid selection in trauma patients. The SMART trial was a prospective study that randomized patients to either normal saline or a balanced crystalloid (multiple-electrolytes injection or lactated Ringer's). Trauma patients represented more than 20% of the total sample size (n=3,413). In the trauma subgroup, the composite end point of major adverse kidney events (death from any cause, new renal replacement therapy, or persistent renal dysfunction at 30 days) was similar between the balanced-crystalloid group (8%) and the normal-saline group (8.4%) (Semler 2018). However, in the overall population, the risk of major adverse kidney events was lower in the balanced-crystalloid group compared with the normal-saline group.

Although additional studies comparing various crystalloid solutions in trauma populations are needed, subgroup analysis of SMART suggests that it may be difficult to find clinically important differences between various crystalloid solutions in this patient population. The difficulty may be related to the emphasis on blood product resuscitation in the hemorrhaging trauma patient and on minimization of crystalloid volume during initial hours following the initial injury—when the risk of mortality is highest. In clinical practice, balanced crystalloids are used more frequently than normal saline because of issues related to hyperchloremic metabolic acidosis with higher volumes of normal saline. In patients with severe TBI, normal saline or multiple-electrolytes injection

may be preferred over lactated Ringer's when the goal is to avoid hyponatremia that could worsen cerebral edema and increase ICP.

Colloids

Albumin has traditionally been considered the reference colloid for volume resuscitation and has been studied in trauma patient populations. The SAFE trial compared 4% albumin with normal saline for volume resuscitation in a heterogeneous population of critically ill patients and found no difference in mortality between the two groups (Finfer 2004). Subgroup analysis of trauma patients (n=1186) demonstrated that the relative risk of death favored saline over albumin (p=0.06). A post hoc analysis of patients with TBI (n=460) reported higher mortality in patients who received albumin compared with saline. In addition, patients with severe TBI who received saline had more-favorable neurologic outcomes as defined by the Glasgow Outcome Scale extended (GOSe) at 24 months compared with those who received albumin (Myburgh 2007).

Because albumin has not been shown to be associated with improved outcomes in trauma patients and is associated with higher costs compared with crystalloids, the use of albumin should be limited. The use of albumin should be avoided in patients with TBI given concerns about increased mortality compared with the use of crystalloids. Hydroxyethyl starches are considered colloid solutions and are used in military-trauma applications. However, in civilian trauma starches are not used because of concerns related to AKI, increased need for renal replacement therapy, and coagulopathy (Myburgh 2012).

Hypertonic Saline

The use of hypertonic saline compared with normal saline has been studied as a resuscitative fluid in the prehospital setting in two randomized controlled trials involving different trauma patient populations. In both trials, patients were randomized to receive either a 250-mL bolus of normal saline, 7.5% saline, or 7.5% saline with dextran. The first trial involved patients with blunt trauma and severe TBI. The study was halted early based on prespecified futility criteria following the enrollment of 1331 patients. The authors reported no differences in 6-month favorable GOSe or survival at 28 days between any of the groups (Bulger 2010).

The other study was to evaluate patients with prehospital shock, but enrollment was halted early because of likely futility and concerns related to higher mortality among patients who received hypertonic fluids and no blood transfusions during the initial 24 hours. Among all of the randomized patients, there were no differences in mortality at 28 days between any of the study groups (Bulger 2011).

Data from those two trials suggest that there are no benefits to using hypertonic saline in the prehospital setting and that there is, potentially, harm to subgroups of trauma patients with severe shock. At this time, hypertonic saline in the prehospital setting should not be used for resuscitation. However, it may be considered when out-of-hospital transport times are prolonged and the patient has a suspected severe TBI with high ICP.

End Points of Resuscitation

After initial hemostasis has been achieved, (1) continued monitoring for reversal of shock and for signs and symptoms of ongoing bleeding, (2) correction of hypothermia, and (3) normalization of coagulation parameters are critical in the trauma patient. Although there is no universally accepted end point of resuscitation in trauma patients, there has been extensive research on the role of various hemodynamic, global, and regional markers of perfusion completed in this patient population.

In clinical practice, global measurements of resuscitation are more readily available and used compared with regional assessments (e.g., gastric tonometry). Even though standard hemodynamic parameters (e.g., blood pressure, heart rate) are used in monitoring patients, they are poor markers for quantifying the degree of physiological derangement given the body's compensatory mechanisms to maintain pressure (Cannon 2018). As a result, more-advanced measures of global resuscitation (e.g., bedside echocardiography, pulse pressure variation) and laboratory measures of global perfusion (e.g., lactate, base deficit) are used more commonly. To date, laboratory-based end points of resuscitation have been more extensively studied in trauma patients. Two of the laboratory measurements more commonly used in trauma patients are serum lactate and base deficit, which is defined as the amount of base needed to be added to a liter of whole blood to bring the pH to 7.40 in the presence of acidosis. Both initial lactate levels and rate of lactate clearance have been correlated with mortality in trauma patients (Rossaint 2016). Base deficit values can be indirect measures of impaired perfusion and tissue acidosis. Initially elevated base deficit levels have been correlated with increased mortality, and base deficit changes over time may correlate with higher MODS, increased transfusion requirements, more metabolic and coagulation abnormalities, and higher risk of death. Following trends in lactate clearance and base deficit is likely most effective at guiding ongoing resuscitation in trauma patients. A combination of assessment of hemodynamic measures and basic measures of resuscitation can result in important information that can help determine whether ongoing shock is occurring regionally (Feinman 2014).

Pharmacologic Adjuncts for Bleeding

Tranexamic Acid

In addition to hemostatic responses to injury, compensatory responses stimulate clot breakdown or fibrinolysis away from the site of hemorrhage to minimize microvascular thrombosis (Cannon 2018). Because excessive fibrinolysis may be associated with coagulopathy and hemorrhage, the use of

antifibrinolytic agents has been investigated to reduce mortality and blood product administration.

The CRASH-2 trial was a randomized controlled study of 20,211 trauma patients with or at risk of significant bleeding (Shakur 2010). Patients received either tranexamic acid (1 g intravenously once over 10 minutes followed by 1 g intravenously infused over 8 hours) or placebo within 8 hours of injury. Study enrollment was governed by the uncertainty principle, meaning that the responsible treating physician enrolled the patient only if uncertain whether to treat the patient with tranexamic acid. Death from any cause at 28 days and death caused by bleeding were reduced in patients who received tranexamic acid. Vascular occlusive events were similar between the tranexamic acid group and the placebo group. Based on post hoc analysis, the benefit of tranexamic acid was limited to patients treated within the first 3 hours following injury, and the risk of death increased when tranexamic acid was given after 3 hours (Roberts 2011). The CRASH-2 trial has been criticized by experts based on the use of the uncertainty principle for enrollment that can increase the risk for selection bias, the failure to show a reduction in blood transfusions between the groups, high rate of patients who did not receive any transfusions (approximately 50% in both groups), a modest reduction in mortality (14.5% vs. 16%), and lack of laboratory measurements of fibrinolysis to determine the need for tranexamic acid.

The use of tranexamic acid in military applications was the focus of a retrospective study. The MATTERs study reported that patients who received tranexamic acid based on the need for emergency-release blood products—which consist of universal donor red cells that have not been crossmatched—or patients with evidence of hyperfibrinolysis had lower rates of inpatient mortality compared with patients who received no tranexamic acid before implementation of this protocol (Morrison 2012).

Several recently published retrospective studies have been unable to replicate reductions in mortality with tranexamic acid reported in the CRASH-2 and MATTERs trials. Using propensity scoring, a subgroup analysis of patients enrolled in the PROPPR study who received tranexamic acid were matched to patients who did not receive tranexamic acid. The study showed a reduction in mortality at 6 hours, but the benefit did not persist beyond that point, and there were no differences in transfusion requirements between groups (Khan 2018). Another propensity-score-matched, retrospective review of a trauma registry showed no difference in mortality between patients who received tranexamic acid and those who did not. However, among patients who received red blood cells in an ED, mortality was lower for those who received tranexamic acid (Boutonnet 2018).

The identification of trauma patients most likely to benefit from tranexamic acid administration remains controversial in clinical practice, with some clinicians advocating empiric administration in severely injured patients and others advocating more-selective administration because about 50% of trauma patients have fibrinolysis shutdown and may not benefit from the administration of an antifibrinolytic agent (Moore 2016). Additional research is required to resolve those issues, but it is reasonable to use tranexamic acid in patients receiving massive blood transfusions or those with evidence of fibrinolysis based on thromboelastography.

Recombinant Factor VIIa

The use of recombinant factor VIIa has been evaluated in two randomized controlled trials as a pharmacologic adjunct in bleeding trauma patients. One study randomized trauma patients—after the patients received their eighth unit of red blood cells—to receive either recombinant factor VIIa (200 mcg/kg followed by 100 mcg/kg at 1 hour and 3 hours) or standard treatment. In patients with blunt trauma, recombinant factor VIIa reduced red blood cell transfusion (p=0.02) and the need for massive transfusion, defined as greater than 20 units (p=0.03). However, there were no statistically significant differences in the penetrating trauma patients (Boffard 2005). The CONTROL trial randomized trauma patients who continued to have active bleeding to receive factor VIIa (200 mcg/kg followed by 100 mcg/kg at 1 hour and 3 hours) or placebo after receiving four units of red blood cells. The trial was terminated early for futility, given lower-than-expected mortality rates. There were no differences in overall mortality between the two study groups. Patients with blunt trauma received fewer transfusions in the factor VIIa group; however, there were no statistical differences in transfusion requirements for patients with penetrating trauma (Hauser 2010). Because of lack of proven benefit on mortality and high cost, factor VIIa is not generally considered as an adjunctive medication in severely bleeding patients.

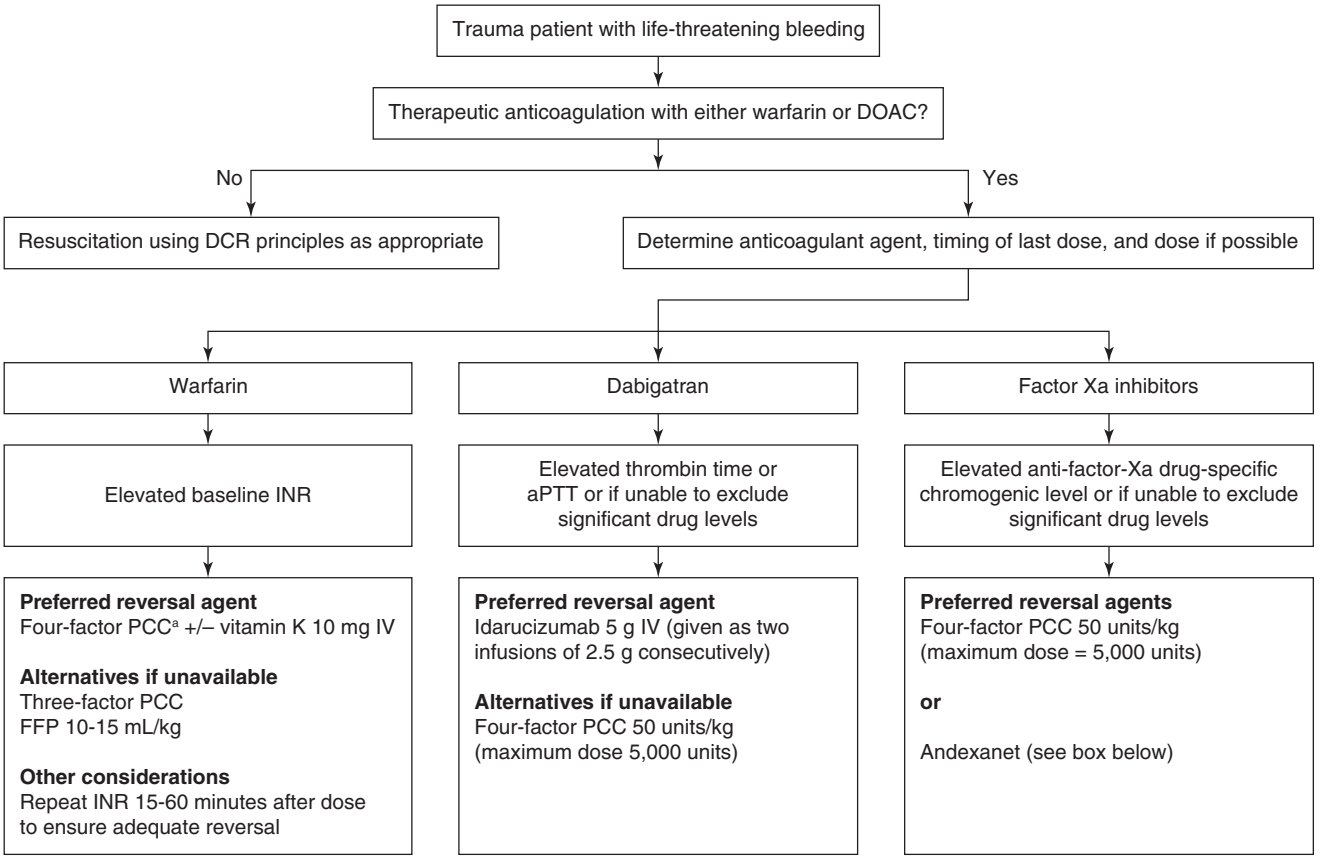
Management of Drug-induced Coagulopathy

Pharmacists are usually the sources of recommendations for the most appropriate agents and doses to reverse the pharmacologic effects of anticoagulants patients are receiving before hospitalization (Figure 1).

Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran (free and thrombin bound) with an affinity 350 times stronger than that of thrombin. It was granted accelerated status by the FDA in April 2015 based on an interim analysis of the REVERSE-AD study.

The RE-VERSE AD study was a prospective, open-label study that evaluated the efficacy and safety of idarucizumab in reversing the anticoagulant effects of dabigatran in patients with uncontrolled bleeding or patients who had to undergo urgent procedures (Pollack 2017). Dabigatran reversal was evaluated based on the percentage of patients who had normalization of either dilute thrombin time or ecarin clotting time within 4 hours following the end of idarucizumab



PCC dosing for warfarin reversal (round to nearest vial)[a]

Baseline INR	PCC dose	Maximum dose
2–3.99	25 units/kg	2,500 units
4–6	35 units/kg	3,500 units
>6	50 units/kg	5,000 units

Andexanet dosing

Dose	Initial IV bolus	Continuous infusion
Low dose	400 mg at rate of 30 mg/min	4 mg/min for up to 120 minutes
High dose	800 mg at rate of 30 mg/min	8 mg/min for up to 120 minutes

Factor Xa inhibitor	Factor Xa inhibitor dose	<8 hours or unknown	≥8 hours
Rivaroxaban	≤10 mg	Low dose	Low dose
Rivaroxaban	>10 mg/unknown	High dose	Low dose
Apixaban	≤5 mg	Low dose	Low dose
Apixaban	>5 mg/unknown	High dose	Low dose

Figure 1. Algorithm for anticoagulant reversal.

[a]Dosing for three-factor PCC is derived from package insert dosing for four-factor PCC as the optimal dose has not been identified.

aPTT = activated partial thromboplastin time; DCR = damage control resuscitation; DOAC = direct oral anticoagulant; FFP = fresh frozen plasma; INR = international normalized ratio; IV = intravenous; PCC = prothrombin complex concentrate.

Information from Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. Neurocrit Care 2016;24:6-46.

infusion. Both of those laboratory tests correlate linearly with dabigatran concentrations. A total of 503 patients were enrolled in the two study cohorts. In the uncontrolled-bleeding cohort, about one-quarter of patients were enrolled because of trauma. Idarucizumab rapidly reversed the anticoagulant effects of dabigatran in more than 98% of patients evaluated. The rate of thrombotic events was 4.8% in the two study cohorts. Despite the lack of a comparison group and relatively small numbers of trauma patients enrolled in the study, idarucizumab is commonly used to reverse the effects of dabigatran in bleeding trauma patients.

Andexanet

Andexanet is a modified recombinant decoy protein that resembles human factor Xa and binds and sequesters factor Xa inhibitors. By binding to factor Xa inhibitors, human factor

Xa is able to cleave prothrombin to thrombin and restore normal hemostasis.

Andexanet was granted accelerated approval by the FDA in May 2018 for reversal of apixaban and rivaroxaban because of life-threatening or uncontrolled bleeding. The approval was based on the results of two studies involving healthy volunteers and an interim analysis of factor-Xa-treated patients with acute major bleeding (ANNEXA-4). In healthy volunteers, andexanet reduced anti-factor-Xa activity by 94% in apixaban-treated patients and by 92% in rivaroxaban-treated patients (Siegal 2015).

The full results of ANNEXA-4 were recently published and provide additional insight into the safety and efficacy of andexanet to reverse Xa inhibitors. The study was a prospective, single group study that enrolled adult patients with acute major bleeding while receiving factor Xa inhibitors (e.g., apixaban, rivaroxaban) within the previous 18 hours. Andexanet dosing was dependent on the specific Xa inhibitor the patient received, dose of the Xa inhibitor, and time of last dose. Anti-factor-Xa activity was reduced by 92% in both apixaban- and rivaroxaban-treated patients. Hemostasis was found to be good to excellent in 82% of those who could be evaluated for that end point, and thrombotic events occurred in 10% of the population (Connolly 2019).

Although andexanet has been shown to adequately reverse anti-factor-Xa activity in apixaban- and rivaroxaban-treated patients, several areas of uncertainty exist. The ANNEXA-4 trial was conducted without a comparator group, and it evaluated a surrogate marker as its primary end point. However, the study revealed no significant relationship between anti-factor-Xa activity and hemostasis, which raises a question about whether this is the most appropriate surrogate end point. Patients with GCS scores of less than 7 were excluded from the study, which limits the generalizability to patients with severe TBI who would likely be candidates for andexanet. Clinical experience with andexanet is minimal because of limited distribution, which makes it difficult to determine the importance of potential rebound antifactor activity given the short half-life of andexanet and the thrombotic risks outside a clinical trial. Finally, andexanet dosing is complicated—especially in trauma patient populations that have TBI or are acutely hemorrhaging because the ability to gather information regarding last administration time and dose of the specific Xa inhibitor is challenging. This will likely have the result that the higher dose of andexanet will become the default dose in a substantial number of trauma patients, which could have significant financial implications given the high cost of andexanet (low dose=$27,500; high dose=$49,500).

Pharmacists will likely play an important role related to formulary decisions and in the determination of appropriate uses for andexanet based on the published literature. For institutions that decide to add andexanet to their formularies, pharmacists will be key players when it comes to the decision to initiate andexanet, to provide dosing recommendations, and to provide recommendations for alternative reversal agents when appropriate.

Prothrombin Complex Concentrate

Prothrombin complex concentrate (PCC) is available as a three-factor, a four-factor, and an activated product. All PCC products contain clotting factors II, VII, IX, and X but differ in the amounts of the individual factors and whether the clotting factors are active or inactive. Three-factor products contain inactive factors and very small amounts of factor VII. Four-factor PCC also has inactive factors but differs in that it contains significant amounts of factor VII, and many contain small amounts of the anticoagulant protein C, protein S, and heparin. In trauma patient populations, PCC products are commonly used for reversing the anticoagulant effects of warfarin and the factor Xa inhibitors.

A four-factor PCC product was approved for warfarin reversal in the United States in April 2013 based on the results of two phase IIIb studies. Sarode et al. performed a prospective noninferiority trial of patients with acute major bleeding taking warfarin who were randomized to receive four-factor PCC or plasma. The results demonstrated that four-factor PCC was non-inferior to plasma for effective hemostasis; however, INR correction with four-factor PCC was significantly shorter, and that trend persisted up to 24 hours after infusion (Sarode 2013). Another study demonstrated the superiority of four-factor PCC over plasma to achieve effective hemostasis and for rapid INR correction in patients in need of urgent surgical or invasive intervention while on warfarin (Goldstein 2015). The combined rate of thromboembolic events in the four-factor PCC groups was 7.3% compared with 7.1% in the plasma groups. Based on those results, four-factor PCC products are preferred over plasma to reverse warfarin in patients with severe hemorrhage or bleeding in critical sites (e.g., intracranial). Guidelines for anticoagulation reversal support those recommendations (Frontera 2016, Tomaselli 2017). In addition, the use of PCC allows smaller volumes of fluid to be administered relative to plasma.

Four-factor PCC has been used off-label for the reversal of oral-factor-Xa inhibitors in trauma populations given the lack of specific reversal agents until recent years. As a result, trauma facilities have gained significant experience in using these agents to reverse the laboratory abnormalities associated with taking oral-factor-Xa inhibitors. Majeed et al. published a prospective study evaluating the efficacy of four-factor PCC to achieve adequate hemostasis in patients with acute major bleeding who were taking rivaroxaban or apixaban. Hemostasis was effective in 69.1% of patients, and the thromboembolic rate (confirmed or suspected) was 3.8%. The median dose administered was 2,000 units (Majeed 2017). Another prospective observational study evaluated the efficacy of four-factor PCC at a fixed dose of 2,000 units to achieve hemostasis in acutely bleeding patients on

rivaroxaban or apixaban. Hemostasis efficacy was judged to be good or moderate in 85% of patients, and the thromboembolic rate was 7.6% (Schulman 2018). Guidelines advocate the use of four-factor PCC 50 units/kg for the reversal of factor Xa inhibitors (Frontera 2016); further studies are needed to determine the optimal dose. Although direct comparisons of four-factor PCC and andexanet are not available—and caution should be exercised by comparing patients from different studies—data that are available suggest similar hemostasis rates and thromboembolic rates between four-factor PCC and andexanet.

MANAGEMENT OF SPECIFIC INJURIES

After initial stabilization of life-threatening injuries identified in a primary survey, a secondary survey is performed to identify and treat injuries that can range in severity from mild to life threatening (ACS 2018).

Traumatic Brain Injury

Traumatic brain injury is defined as a disruption or alteration in brain structure or function caused by external forces. It represents a major cause of death and disability as demonstrated by the 2.5 million ED visits, 282,000 hospitalizations, and 56,000 deaths that were attributed to TBI in 2013 (Taylor 2017). Patients with TBI are categorized as having either mild (GCS score of 13–15), moderate (GCS score of 9–12), or severe (GCS score of 3–8) injuries, with the associated likelihood of permanent disability increasing with higher severity (Vella 2017).

Pathophysiology

The pathophysiology of TBI follows the principles of the Monro–Kellie hypothesis, which represents the pressure/volume relationship between cerebrospinal fluid (CSF), brain tissue, and blood. Significant injury to the brain results in an elevated ICP, with compensatory reductions in cerebral blood flow (CBF) and secondary neurologic injury (Vella 2017).

Primary and Secondary Injury

Primary injuries in patients with TBI occur immediately after the initial trauma. Treatment of patients with TBI focuses primarily on limiting secondary injury, which can occur as a result of hypotension, hypoxia, hypercarbia, hyperthermia, cerebral edema with elevated ICP, and ischemia resulting from changes in CBF. The Brain Trauma Foundation (BTF) provides updated recommendations on the management of patients with TBI, including monitoring and options to treat complications and thereby minimize the risk of secondary injury. General concepts include avoidance of hypotension (SBP greater than 100 mm Hg for patients 50–69 years of age and SBP greater than 110 mm Hg for all other patients), securing an appropriate airway, maintaining oxygen saturation of at least 90%, maintaining arterial partial pressure of oxygen of at least 60 mm Hg, and providing adequate analgesia and sedation (Carney 2016).

Pharmacists play an important role in analgesia and sedation selection. Appropriate analgesia and sedation can improve ventilator synchrony, prevent blood pressure and temperature elevations, and minimize agitation and pain that can contribute to increased ICP and secondary injury. The argument that pain is allowable because treatment obscures neurologic examination should not be accepted. Short-acting analgesics (e.g., fentanyl, sufentanil) and sedatives (e.g., propofol) should be used preferentially to facilitate rapid clearance when frequent neurologic examination is necessary. Propofol has been shown to reduce cerebral metabolism and oxygen consumption and may be neuroprotective (Vella 2017). Current BTF guidelines recommend propofol because it improves control of ICP; however, it has not demonstrated improved mortality outcomes or 6-month neurologic outcomes. Benzodiazepines are typically avoided because of their lengthy duration of action and because they limit assessment of neurological status. Physicians should carefully avoid analgesia- and sedative-associated hypotension so as to avoid paradoxical decreases in CPP (Carney 2016).

Intracranial Pressure Monitoring and Goals

Published data evaluating indications for ICP monitoring are primarily observational, which makes it difficult to develop definitive recommendations regarding which patients should receive monitoring. However, it remains clear that elevated ICP contributes to secondary injury. Although the ICP monitor itself does not necessarily improve outcomes, the information provided guides treatment, which in turn results in patient care optimization. The BTF guidelines advocate ICP monitoring in severe TBI injuries in order to reduce inpatient and 2-week mortality (Carney 2016).

Intracranial pressure monitoring can be accomplished using a variety of invasive and noninvasive techniques (see Online Appendix). External ventricular drains are often used because they facilitate either continuous or intermittent measurements of ICP and drainage of CSF, which can reduce ICP. Intraparenchymal ICP monitors can be used to measure the ICP of patients with TBI without high risk of hydrocephalus; however, the monitors are not capable of draining CSF (Carney 2016; Vella 2017). Noninvasive monitors are gaining popularity based on ease of use, but further research is necessary to evaluate patient outcomes (Volovici 2018).

Intracranial hypertension has traditionally been defined as a sustained ICP greater than 20 mm Hg (normal 5–15 mm Hg), which has represented the threshold for the implementation of therapy. However, current BTF guidelines advocate initiation of treatment when ICP is greater than 22 mm Hg because that represents the threshold for improved mortality and favorable outcomes (Carney 2016). Despite the recommendation, however, clinical judgment should always be exercised when considering the threshold for implementation of ICP-lowering therapy.

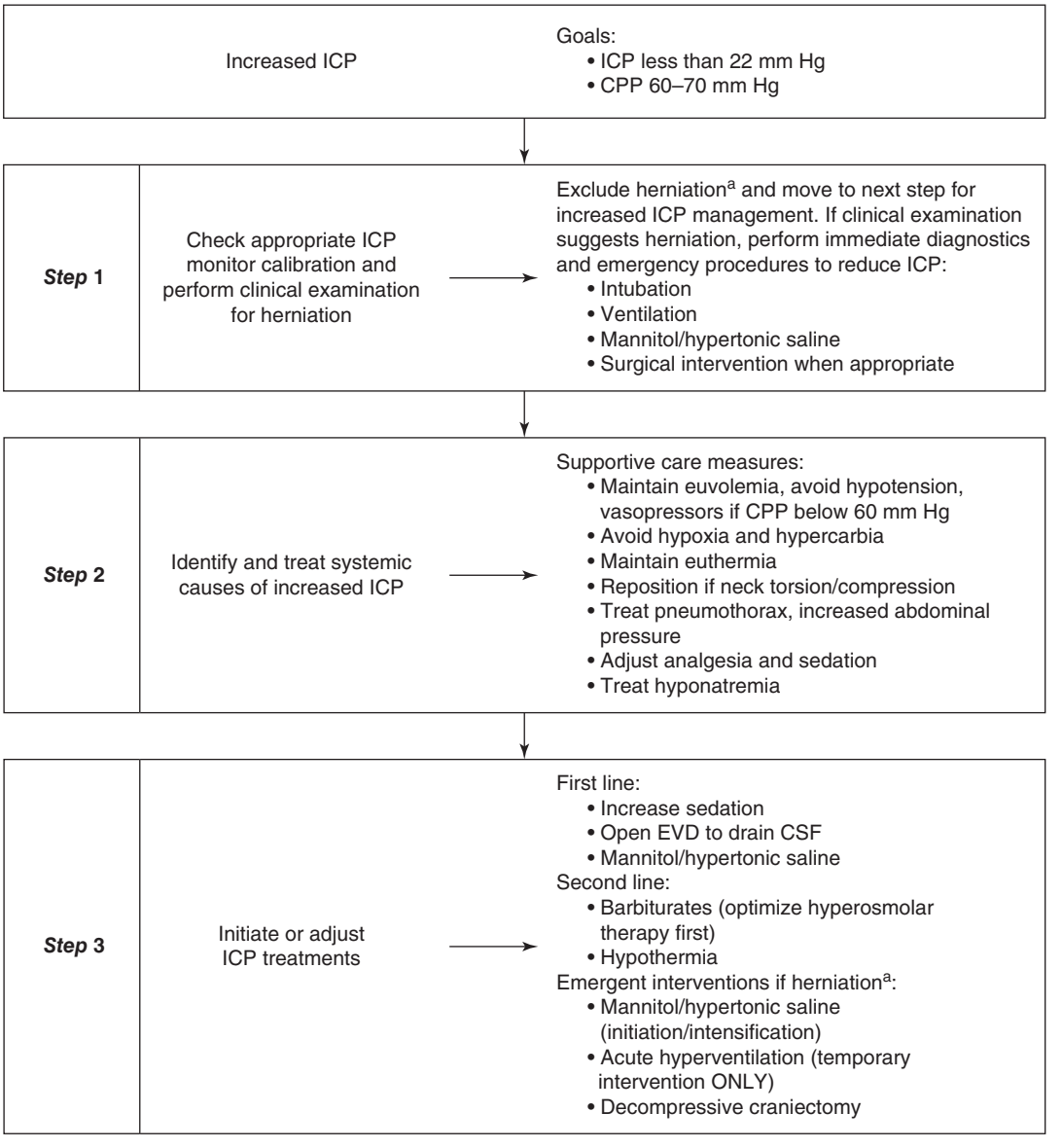


Figure 2. Stepwise approach to treating intracranial hypertension.

[a]Clinical examination should be routinely monitored for herniation with emergent treatment should it occur. Herniation syndromes occur because of displacement of brain tissue from areas of high pressure to low pressure. Early signs of herniation include pupillary dilation without light reactivity and impaired consciousness. Brain stem compression results in bradycardia, arterial hypertension, and respiratory irregularity that progresses to apnea.

CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; EVD = external ventricular drain; ICP = intracranial pressure.

Information from Stocchetti N, Maas AIR. Traumatic intracranial hypertension. N Engl J Med 2014;370:2121-30.

Cerebral perfusion pressure is used as a surrogate marker of CBF and brain tissue oxygenation (Carney 2016; Vella 2017). The CPP can be calculated by subtracting ICP from mean arterial pressure. The goal CPP is 60–70 mm Hg because that range has been associated with higher survival rates and more-favorable outcomes in patients with TBI. Lower CPP goals have been associated with higher risk of cerebral ischemia, and higher CPP goals have increased the incidence of ARDS (Carney 2016). Emerging monitoring devices, such as those directly measuring autoregulation and partial pressure of brain tissue oxygen (PbO_2), may provide more-accurate monitoring of cerebral perfusion and oxygenation in the future.

Treatment of Elevated Intracranial Pressure

Patients with intracranial hypertension should undergo stepwise treatment (Figure 2).

Table 2. Comparison of Mannitol and Hypertonic Saline for Elevated Intracranial Pressure

Agent	Available strengths (mOsm/L)	Dosing	Reported ICP Effect	Considerations	Adverse Effects
Mannitol	20% (1098 mOsm/L) 25% (1375 mOsm/L)	0.25–1 g/kg every 4–6 hours	Range: –1.5 ± 7.1 to –8 ± 6.7 For each increase in dose by 0.1 g/kg, ICP decreased by 1 mm Hg	Achieves hyperosmolarity by dehydration (serum osmolarity 300–320 mOsm/L) Monitor serum osmolality and osmolar gap Avoid in hypotensive patients Mannitol storage on patient care units difficult due to crystallization	Rebound ICP increase Acute kidney injury Hyperkalemia Hypernatremia
		2–2.5 mL/kg	–8.9 ± 8.4		
Hypertonic saline	3% (1026 mOsm/L; sodium 513 mEq/L)	250- to 500-mL bolus	–7.1 ± 7.4[a] –8.7 ± 7.3[b]	Achieves hypernatremic, hyperosmolar state (serum sodium 145–160 mEq/L; serum osmolarity 310–320 mOsm/L) Monitor serum sodium to avoid rapid increase in patients with hyponatremia	Rebound ICP increase Acute kidney injury Hypokalemia Hypernatremia Central pontine myelinolysis Rebound hyponatremia Metabolic acidosis/alkalosis Coagulopathy Skin sloughing if extravasation[d]
		2.5 mL/kg bolus	–10.1 ± 8.7		
		1–2 mL/kg/hour	Not reported		
	7.5% (2556 mOsm/L; sodium 1283 mEq/L)	1.5- to 2–mL/kg bolus	–14 ± 7.8[a] –15 ± 5[c]		
	23.4% (8808 mOsmL; sodium 4004 mEq/L)	30 mL bolus over 15–20 minutes	–8.8 ± 2.2 ~50% reduction		

[a]Response at 1 hour postinfusion.

[b]Response at 2 hours postinfusion.

[c]Response at 1.5 hours postinfusion.

[d]Central line administration may be the preferred method for dosing hypertonic saline, however peripheral administration via a large bore catheter is acceptable for acute elevations of intracranial pressure to avoid treatment delays and secondary brain injury

ICP = intracranial pressure.

Information from Alnemari AM, Krafcik BM, Mansour TR, et al. A comparison of pharmacologic therapeutic agents used for the reduction of intracranial pressure after traumatic brain injury. World Neurosurg 2017;106:509-28; Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, ed 4. Neurosurgery 2017;1:6-15. Diringer MN, Zazulia AR. Osmotic therapy: fact and fiction. Neurocrit Care 2004;1:219-33; Hinson HE, Stein D, Sheth KN. Hypertonic saline and mannitol therapy in critical care neurology. J Intensive Care Med 2013;28:3-11; Ropper AH. Hyperosmolar therapy for raised intracranial pressure. N Engl J Med 2012;367:746-52.

Medical Management

The main pharmacologic interventions for elevated ICP are hyperosmolar agents such as mannitol and hypertonic saline (Table 2). Hyperosmolar agents exert their activity through plasma volume expansion, improved blood viscosity, and reduced brain water content to improve CBF. Increased plasma osmolality creates a gradient across the blood–brain barrier for osmosis toward systemic circulation away from the brain. Although hyperosmolar therapy improves ICP, the literature is not clear on the ideal agent, the ideal dose, or continuous versus intermittent administration (Burgess 2016; Carney 2016). Hyperosmolar therapy targets a serum sodium of 145–160 mEq/L and a serum osmolality of 300–320 mOsm/L (Hinson 2013, Ropper 2012).

Mannitol is an osmotic diuretic sugar moiety that causes sustained hyperosmolarity by dehydration. The onset of ICP lowering occurs within 10–15 minutes while an osmotic gradient gets established, and the peak effect occurs within 20–60 minutes. Lower dosing is usually used for maintenance therapy, whereas high dosing is used in emergency situations (Table 2).

To avoid nephrotoxicity, mannitol administration is traditionally held if serum osmolarity is greater than 320 mOsm or if total daily dosing is more than 200 g (Carney 2016; Ropper 2012).

Osmolar gap, which is calculated by subtracting the calculated serum osmolality from the measured serum osmolarity, has been proposed as a surrogate method to monitor mannitol concentrations, to determine when it is safe to redose, and to reduce the incidence of AKI. Although osmolality can be calculated with different formulas, the best formula that correlates with mannitol levels is equal to 1.86(Na + K) + (glucose ÷ 18) + (blood urea nitrogen ÷ 2.8) + 10 (Hinson 2013). If the osmolar gap is normal, the patient has likely cleared mannitol to allow for safe redosing (Diringer 2004; Hinson 2013).

In recent years, hypertonic saline has been increasingly used as the primary agent for reduction of ICP in TBI, and that use is supported by small studies. Theoretically, hypertonic saline has a lower risk of worsening cerebral edema and causing rebound intracranial hypertension because it does not cross the blood–brain barrier (i.e., reflection coefficient 1 versus 0.9 for mannitol). This has not been extensively validated in critically ill trauma patients, but mannitol has been found in the brain after repeated dosing (Diringer 2004). Hypertonic saline has a rapid onset, with ICP reduction within 5 minutes of infusion, and the effects can last up to 2 hours. Patients with responsiveness beyond 2 hours following a 3% saline bolus were associated with decreased mortality and improved outcomes (Alnemari 2017).

No studies to date have elucidated the optimal dosing strategy for hypertonic saline. Bolus doses have shown promise for ICP reduction—especially with higher sodium concentrations (e.g., 7.5%, 14.6%, 23.4%)—in the face of severely elevated ICP or patients refractory to other treatments (Alnemari 2017). As with mannitol, bolus dosing theoretically prevents the reestablishment of a new osmotic set point so that the intracellular and extracellular compartments avoid reequilibration (Hinson 2013). A recent analysis found continuous infusion was associated with improved survival and 90-day functional outcomes when compared with bolus therapy. However, continuous infusions of hypertonic saline should not be used for acute elevations of ICP. Results from the ongoing COBI trial may provide more guidance for continuous hypertonic saline therapy for elevated ICP (Roquilly 2017).

Barbiturate coma has been used to control ICP by preventing unnecessary movement, coughing, and straining against tubes while suppressing metabolism and altering cerebral tone. Other protective mechanisms include improvement in regional blood flow and inhibition of oxygen radical lipid peroxidation (Carney 2016). Pentobarbital is the most studied barbiturate and is typically administered with a loading dose (e.g., 10 mg/kg over 30 minutes followed by 5 mg/kg/hour for 3 hours) followed by a maintenance infusion (e.g., 1 mg/kg/hour). High-dose barbiturate coma is recommended only in patients with elevated ICP refractory to standard medical and surgical treatment who are hemodynamically stable with continuous electroencephalogram monitoring (Carney 2016).

Surgical Management

Surgical management of elevated ICP includes the evacuation of mass lesions, CSF drainage, and decompressive craniectomy, which involves the removal of a skull portion to allow cerebral edema progression without herniation (Stocchetti 2014). The BTF guidelines recommend a large over a small craniectomy in order to reduce mortality and improve neurologic outcome. Craniectomy is not recommended to improve outcomes in patients with severe TBI, with diffuse injury, or with persistently elevated ICP greater than 20 mm Hg for more than 15 minutes in a 1-hour period refractory to other therapies (Carney 2016). After publication of the guidelines, the RESCUEicp trial reported lower mortality but higher rates of vegetative state and severe disability at 6 months in patients who had received craniectomy for refractory ICP compared with standard medical care (Hutchinson 2016). Although research is needed to identify the patients most likely to survive with good neurological function following a decompressive craniectomy, in clinical practice this is typically reserved for patients in whom nonsurgical measures have failed.

Adjunctive Agents

Posttraumatic seizures are typically categorized as early (within 7 days of injury) or late (after 7 days of injury), with an estimated incidence of 12%. Risk factors for early posttraumatic seizure include a GCS score of 10 or less, immediate seizures, posttraumatic amnesia lasting longer than 30 minutes, linear or depressed skull fracture, penetrating head injury, subdural or epidural or intracerebral hematoma, cortical contusion, age of 65 years or less, and chronic alcoholism. Early seizures have not been associated with worse outcomes. Phenytoin is recommended to decrease the incidence of early posttraumatic seizures when the benefits outweigh the complications associated with that treatment. However, prophylaxis is not recommended beyond that early period because phenytoin does not reduce the risk of late seizures. As a result, pharmacists can recommend discontinuation of seizure prophylaxis after postinjury day 7 provided the patient does not have a seizure. The duration of treatment for patients who experience early posttraumatic seizure is not well-defined (Carney 2016).

Although phenytoin is the agent recommended by BTF guidelines, levetiracetam is commonly used to prevent early seizures given lack of serum monitoring, fewer drug-drug interactions, and more-predictable kinetics. Post-TBI cognitive dysfunction may also be potentiated by phenytoin, theoretically supporting levetiracetam use (Beghi 2003). Current guidelines cite insufficient evidence to provide recommendation for or against the use of levetiracetam (Carney 2016).

Blunt Cerebrovascular Injury

Blunt cerebrovascular injury (BCVI) is defined as nonpenetrating injury to the internal carotid or vertebral arteries causing intimal disruption, dissection, pseudoaneurysm, and possible occlusion of cerebrovascular circulation. Such

Patient Care Scenario

A 25-year-old man (weight 83 kg) involved in a rollover motor vehicle collision at highway speed presents to the ED. The patient's GCS score is 5. He is hemodynamically stable on arrival at the hospital. The patient receives a head CT scan, which reveals an 8-mm subdural hematoma and scattered subarachnoid hemorrhage. An external ventricular drain (EVD) is placed to measure intracranial pressure, with an opening pressure of 35 mm Hg. What is the most appropriate therapeutic intervention to acutely manage the patient's elevated intracranial pressure (ICP) while operative intervention is considered?

ANSWER

The patient's ICP exceeds the recommended threshold of 22 mm Hg as described in Brain Trauma Foundation (BTF) guidelines for the treatment of patients with severe TBI. While operative intervention is being considered, pharmacologic intervention to reduce ICP would be appropriate, assuming that ICP remains high despite adequate sedation and analgesia, head of bed is elevated to facilitate improved venous blood return from the brain, and the EVD is appropriately calibrated and set to drain cerebrospinal fluid. Hyperosmolar therapy in the form of either hypertonic saline or mannitol would be the initial recommendation, according to BTF guidelines. In clinical practice, hypertonic saline is more commonly used especially in the resuscitation phase of trauma because it avoids issues related to excessive diuresis with mannitol. The optimal dosing regimen for hypertonic saline remains unclear, and selection is limited by the number of concentrations that are commercially available. Even though the compounding of specific concentrations of hypertonic saline remains possible at some institutions, it should not delay treatment given the risk of secondary injuries. A reasonable approach would be to administer a bolus of 250 mL of 3% hypertonic saline. The dose could be repeated if ICP remains higher than 22 mm Hg.

1. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurg 2016;0:1-10.
2. Burgess S, Abu-Ladan RB, Slavik RS, et al. A systematic review of randomized controlled trials comparing hypertonic sodium solutions and mannitol for traumatic brain injury: implications for ED management. Ann Pharmacother 2016;50:291-300.

injuries can result in ischemic stroke, with rates as high as 64% if left untreated and as low as 0.5% with prompt treatment. The majority of strokes occur within the first 72 hours of injury (Burlew 2018). Despite low BCVI-related mortality (<1%), the development of stroke results in decreased activity, decreased cognitive function, and decreased mobility at a mean follow-up of 5 years postinjury (Shahan 2018).

Screening and Diagnosis

Blunt cerebrovascular injury is often present with distracting injuries that reduce injury identification, and the implementation of a screening protocol for at-risk patients increases diagnosis. Four-vessel cerebral angiography is considered the gold standard for diagnosis of BCVI, but computed tomography angiography (CTA) with at least 16-slice technology is typically used because it is less invasive and less resource

Box 3. Expanded Denver Screening Criteria for Blunt Cerebrovascular Injury

CTA is indicated if one or more features are present:

1. Signs/symptoms
   - Arterial hemorrhage from neck/nose/mouth
   - Cervical bruit in patients younger than 50 years
   - Expanding cervical hematoma
   - Focal neurological deficit
   - Neurological examination incongruous with head CT findings
   - Stroke on secondary CT scan
2. Risk factors for BCVI
   - High energy transfer mechanism
   - Le Fort II fractures (involve maxilla, nasal bones, and medial orbits)
   - Le Fort III fractures (craniofacial dissociation involving maxilla, zygoma, nasal and ethmoid bones, and skull base)
   - Mandible fracture
   - Complex skull fracture/basilar skull fracture/occipital condyle fracture
   - Severe TBI with GCS score <6
   - Cervical spine fracture, subluxation or ligamentous injury (any level)
   - Near hanging with anoxic brain injury
   - Clothesline injury or seat belt abrasion, with significant swelling, pain, or altered mental status
   - TBI with thoracic injury
   - Scalp degloving
   - Thoracic vascular injury
   - Blunt cardiac rupture
   - Upper-rib fracture

BCVI = blunt cerebrovascular injury; CT = computed tomography; CTA = computed tomographic angiography; GCS = Glasgow Coma Scale; TBI = traumatic brain injury.

Information from Burlew CC, Biffl WL, EE Moore, et al. Blunt cerebrovascular injuries: redefining screening criteria in the era of noninvasive diagnosis. J Trauma 2012;72:330-7; Geddes AE, Burlew CC, Wagenaar AE, et al. Expanded screening criteria for blunt cerebrovascular injury: a bigger impact than anticipated. Am J Surg 2016;212:1167-74.

intensive (Biffl 2009; Bromberg 2010). The expanded Denver Criteria currently recommend screening CTA be completed in patients with signs and symptoms of BCVI and in patients with the stated high-risk features (Box 3).

Classification, Treatment, and Monitoring

Blunt cerebrovascular injury should be graded based on the Biffl classification (Table 3). Stroke risk increases with higher-grade injuries, and injury grading standardizes severity and guides treatment (Bromberg 2010; Stone 2018) (Figure 3).

Treatment modalities consist of antithrombotic therapy or injury repair. Antithrombotic therapy (i.e., unfractionated heparin infusion titrated to an activated PTT of 40–65 seconds) and antiplatelet therapy (i.e., aspirin 81–325 mg daily or clopidogrel 75 mg daily) are equivocally recommended (Biffl 2009; Bromberg 2010; Cothren 2009; Stone 2018). In addition, the recent CADISS trial demonstrated no difference between antiplatelet therapy and anticoagulant therapy in death or stroke within 3 months, but only 25% of the study population had had trauma within the past 28 days (Markus 2019). Prompt or even immediate initiation of antithrombotic therapy is recommended for grades I through IV injuries for stroke reduction; however, concomitant blunt solid-organ injury management, SCI management, and TBI management should be balanced against antithrombotic-initiation timing (Bromberg 2010, Stone 2018). Antithrombotic therapy should be considered once patients have been stabilized and active bleeding is under control. Pharmacists can play a role at the bedside by discussing the risks versus the benefits of antithrombotic-therapy choice. Low-dose unfractionated heparin without bolus dosing may be considered in patients with a need for rapid reversibility because of hemorrhagic complications and in patients at risk of bleed in critical sites such as those anticipating neurosurgical or spine operations. Once the risk of bleeding has abated, patients should be transitioned to antiplatelet therapy, which uses less-intensive administration, has lower costs, and provides high tolerability (Stone 2018).

Thoracic Injuries

Thoracic trauma contributes to substantial morbidity and mortality, with up to 20% to 25% of trauma-related deaths related to thoracic injuries. Most of the immediate deaths caused by motor vehicle collisions result from myocardial-wall or aortic rupture. In patients who survive and receive medical attention, the identification and treatment of complications such as tension pneumothorax, cardiac tamponade, airway obstruction, and hemothorax can prevent early deaths (ACS 2018).

Complications Related to Thoracic Injuries

Pneumothorax and hemothorax are common complications in patients presenting with blunt trauma or penetrating trauma. Pneumothorax, which occurs when air accumulates in the pleural space, can result in a collapsed lung and disorders of ventilation or perfusion. Hemothorax involves blood in the pleural space and can be a cause of hemorrhagic shock in trauma patients. Treatment depends on the type and severity of the pneumothorax or hemothorax, but the mainstays of treatment involve chest tube placement and treatment of underlying hemorrhagic shock in the case of hemothorax (ACS 2018).

Antibiotic prophylaxis in the setting of chest tube placement remains controversial. Based on its review of seven prospective and retrospective studies in trauma patients, EAST concluded that the data are insufficient to recommend either for or against presumptive antibiotics around the time of chest tube insertion for the prevention of pneumonia or empyema (Moore 2012). Another systematic review of 12 prospective studies concluded that prophylactic antibiotics reduced the risk of pneumonia and of empyema (Ayoub 2019). Interpretation of that systematic review is complicated by the inclusion of trials that are more than 40 years old, differences in duration and antibiotic selection, and differences in injury type (penetrating trauma vs. blunt trauma). Providing an evidenced-based recommendation about the

Table 3. Biffl Blunt Cerebrovascular Injury Classification with Stroke Incidence

Grade	Findings	Stroke Incidence (%)	
		Carotid	Vertebral
I	Luminal irregularity or dissection with less than 25% luminal narrowing	3–8	6–19
II	Dissection or intramural hematoma with 25% or more luminal narrowing, intraluminal thrombus, or raised intimal flap	11–14	38–40
III	Pseudoaneurysm	26–33	13–27
IV	Occlusion	44–50	28–33
V	Transection with free extravasation	100	100

Information from Biffl WL, Moore EE, Offner PJ, et al. Blunt carotid and vertebral arterial injuries. World J Surg 2001;25:1036-43; Stone DK, Viswanathan VT, Wilson CA. Management of blunt cerebrovascular injury. Curr Neurol Neurosci Rep 2018;18:98.

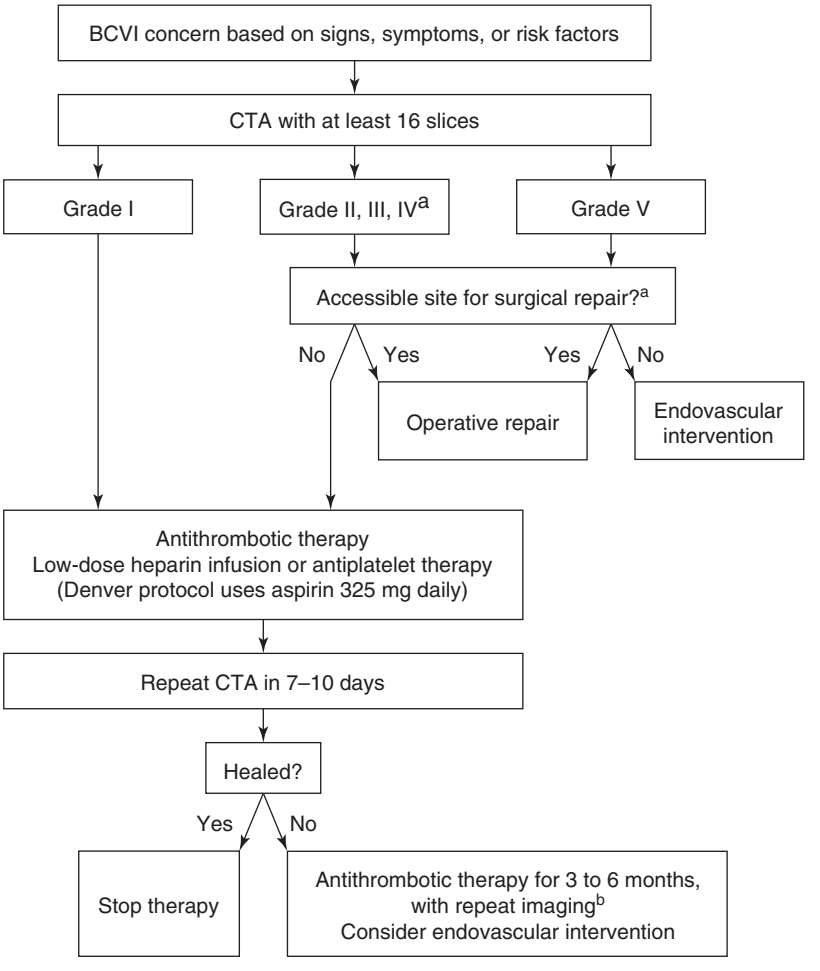


Figure 3. Treatment algorithm for the patient with blunt cerebrovascular injury.

[a]Consider surgical repair or endovascular intervention if (1) grade II with neurologic symptoms, dissection progression, or refractory; (2) grade III pseudoaneurysm 1 cm or larger; (3) grade IV with stroke recognized within 6 hours; should consider thrombectomy with or without stenting; and (4) grade V injury.

[b]Lifelong antiplatelet therapy for stroke prevention recommended if the lesion persists or stents placed.

CTA = computed tomographic angiography.

Information from Geddes AE, Burlew CC, Wagenaar AE, et al. Expanded screening criteria for blunt cerebrovascular injury: a bigger impact than anticipated. Am J Surg 2016;212:1167-74; Stone DK, Viswanathan VT, Wilson CA. Management of blunt cerebrovascular injury. Curr Neurol Neurosci Rep 2018;18:98.

role of prophylactic antibiotics is difficult given inconsistent results between trials and severely underpowered trials. If prophylactic antibiotics are given, available data suggest that a first-generation cephalosporin before chest tube insertion is likely adequate. Pharmacists should be involved in making recommendations for antibiotic agents and for ensuring that antibiotics do not get continued beyond 24 hours at most.

Blunt Traumatic Aortic Injuries

Blunt traumatic aortic injuries (BTAIs) occur in 8,000–9,000 patients annually in the United States. The severity of BTAI can range from an intimal tear or intramural hematoma of the artery (grade I) to free rupture (grade IV). Mortality rates vary depending on the severity of the aortic injury, but the vast majority of patients with ruptured BTAIs will die at the scene of the accident or shortly after arriving at the hospital (Demetriades 2016).

The management of hemodynamically stable patients with BTAIs has changed in recent years from immediate to delayed aortic injury repair. In addition, the definitive management of aortic injuries has shifted from open repair to endovascular repair. A recently completed systematic review completed by the EAST group found that endovascular repair reduced the risk of mortality and paraplegia compared with open repair (Fox 2015).

In patients managed by means of delayed aortic repair, medical management to control blood pressure and heart rate is critical. With appropriate management of blood pressure, the risk of aortic rupture is reduced to about 1.5%. The optimal blood pressure and/or heart rate goals are not clear based on published literature and guidelines. The therapeutic goals for blood pressure and heart rate are commonly derived from studies that compared early and delayed aortic injury repair rather than comparisons of different blood pressure and heart rate intensities. For the most part, studies targeted a systolic blood pressure of 100–120 mm Hg and a heart rate of less than 100 beats per minute. Several guidelines address blood pressure control in patients with aortic dissection, but those recommendations are not specific to patients with BTAIs. The European Society of Cardiology, the Japanese Circulation Society, and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines all advocate for SBP between 100 and 120 mm Hg. Additionally, the AHA/ACC guidelines recommend a heart rate goal of less than 60 bpm until operative or interventional repair of the aortic injury has been completed (Erbel 2001, Hiratzka 2010, JCS Joint Working Group 2013).

Intravenous beta-blockers are generally considered the first-line agents given their ability to reduce shear forces on an injured aorta. Esmolol is frequently selected given its short duration of action and ability to titrate to the desired hemodynamic end point; however, comparative studies of different agents are lacking. Labetalol is a less-expensive option that may be considered in patients requiring intermittent doses of blood pressure medications to maintain therapeutic goals or in patients receiving excessive volumes of fluid from esmolol. If additional blood pressure control is required in the acute management of BTAI, a vasodilator such as nicardipine or nitroprusside is usually used. However, it is important that a patient's heart rate be under adequate control before the start of the use of vasodilators because vasodilator agents can cause reflex tachycardia, which leads to increased shear forces on the aortic injury. Pharmacists are frequently involved in selecting intravenous blood pressure medications for the acute medical management of BTAI.

Tight blood pressure and heart rate control is typically maintained until definitive repair using endovascular stents has been achieved. Most clinicians relax blood pressure and heart rate goals once definitive repair has been accomplished. Optimal blood pressure goals in this situation are not clear based on published literature. In the case of a lower-grade BTAI, the physician may elect to pursue medical management rather than endovascular repair. In patients with lower-grade BTAI who do not receive endovascular repair, long-term management of blood pressure typically involves the use of beta-blockers to reduce shear force on the aorta followed by the use of vasodilators to decrease blood pressure. Pharmacists may play an integral role in the selection and titration of those oral antihypertensives following the acute management with intravenous agents.

Rib Fractures

The incidence of rib fractures among hospitalized trauma patients has been reported to be up to 10%. Injuries involving rib fractures and blunt thoracic injuries in general are associated with substantial morbidity. Pulmonary complications such as pneumonia, severe pain, prolonged ICU and hospital lengths of stay, and increased health care costs have been associated with chest trauma and rib fractures (Galvagno 2016).

Pain Management and Multimodal Approaches

Inadequately treated pain is one of the main contributors to morbidity associated with rib fractures. The optimization of analgesia is essential for early mobilization and proper breathing mechanics. A variety of different pain management strategies have been deployed in patients with blunt thoracic trauma, including epidural analgesia, thoracic paravertebral blockade, and intrapleural analgesia, as well as multimodal analgesia strategies that incorporate regional, systemic, and analgesic adjuncts. The majority of published data about patients with blunt thoracic trauma includes epidural analgesia and multimodal strategies. A meta-analysis comparing those two modalities reported lower mean pain scores at 48 hours and shorter weighted mean duration of mechanical ventilation among patients who received epidural analgesia (Galvagno 2016). However, mean pain scores at 72 hours, postoperative pulmonary complications, mortality, and hospital and ICU lengths of stay were not significantly different between the two groups. The authors provided a conditional recommendation for epidural analgesia over multimodal nonregional strategies. In addition, the 2013 edition of the pain, agitation, and delirium guidelines provide only a weak recommendation for epidural analgesia based on moderate-quality data in trauma patients with rib fractures and cite improvement in pain scores and reduction in pneumonia using that modality (Barr 2013). However, the 2018 guidelines do not address the use of epidurals in patients with traumatic rib fractures (Devlin 2018).

Retained Hemothorax

Posttraumatic retained hemothorax has been identified as a risk factor for the development of empyema, and it contributes to ongoing respiratory compromise. The most common treatment of posttraumatic retained hemothorax is video-assisted thoracoscopic surgery, which has success rates approaching those of open thoracotomy (DuBose 2012). However, many trauma patients who develop retained hemothorax are poor operative candidates. Nonoperative management of retained hemothorax has traditionally involved placement of additional chest tubes. But interest in using intrapleural alteplase in trauma patients has been explored in only

small retrospective studies, and the optimal dose of alteplase has not been clearly established in trauma patient populations. Reported doses of alteplase in patients with retained hemothorax ranged from 6 mg/dose to 100 mg/dose, and frequency of administration has varied from once daily to twice daily for up to 3 days (Holsen 2019). Although dornase alfa has been used in parapneumonic effusions with empyema given the large amount of deoxyribonucleoproteins found in this fluid, addition of this therapy to alteplase in the setting of noninfected retained hemothorax has not been studied and from a mechanism-of-action standpoint, would not seem to provide additional benefit (Rahman 2011).

Abdominal Injuries

The identification and evaluation of intra-abdominal injuries are challenging during the initial evaluation of a trauma patient. Despite significant intra-abdominal blood loss in many situations, there may not be dramatic changes in hemodynamics or obvious peritoneal signs (ACS 2018).

Diagnosis of intra-abdominal injuries is based on clinical features, physical examination, and diagnostic testing. A focused-assessment-with-sonography-for-trauma examination uses ultrasound to identify free intraperitoneal fluid or blood in the abdomen and thorax. Diagnostic peritoneal lavage is another rapid study that can identify hemorrhage or GI contents by means of lavage and the aspiration of warm saline into the peritoneal cavity. Computed tomography is sensitive (98%) for identification of intra-abdominal injuries, but the lengthier transport and procedure times may preclude its use in patients who are unstable (ACS 2018).

Suspected hollow viscus injuries generally require surgical intervention. The use of prophylactic antimicrobial therapy for penetrating abdominal trauma requiring therapeutic laparotomy is generally considered the standard of care. The antibiotic selected should include both aerobic and anaerobic coverage given the high rate of anaerobic infections that result after an antibiotic with only aerobic coverage has been selected. The EAST guidelines on prophylactic antibiotic use in penetrating abdominal trauma provide a level 1 recommendation that a single, preoperative dose of antibiotics with broad-spectrum aerobic and anaerobic coverage should be administered to all patients (Goldberg 2012). Selection of the optimal antibiotic agent is limited by relatively few adequately powered studies that compared different antibiotic regimens and the application of those studies to current practice because the majority of data was published more than 20 years ago. Antibiotic regimens that would be appropriate based on the available data and current antibiotic susceptibility include cefoxitin, ceftriaxone plus metronidazole, or an aminoglycoside plus clindamycin. Based on several studies that demonstrated no difference in infection rates with short- and long-course antibiotics, the guidelines provide a level 1 recommendation that antibiotics not be continued for more than 24 hours after source control. Two prospective randomized controlled trials demonstrated that surgical-site infections were not reduced with 5 days of antibiotics compared with 24 hours (Bozorgzadeh 1999, Kirton 2000). Although those trials evaluated patients with penetrating abdominal trauma, it is common in clinical practice to continue antibiotics for only 24 hours in patients with bowel injuries that resulted from blunt abdominal trauma. The Infectious Diseases Society of America recommends that bowel injuries caused by either blunt or penetrating trauma be treated with no more than 24 hours of antibiotics, provided the bowel injuries are repaired within 12 hours of injury (Solomkin 2010).

Solid-Organ Injuries

Injuries to solid organs such as the spleen, kidney, and liver are frequently encountered in patients with abdominal trauma. The management of solid-organ injuries has evolved from a primarily operative approach to the achievement of hemostasis (e.g., hepatorrhaphy, splenectomy) to a predominantly nonoperative approach (i.e., observation and serial hemoglobin monitoring) in the hemodynamically stable patient. The American Association for the Surgery of Trauma (AAST) developed the Organ Injury Scaling system for solid organs based on magnitude of anatomic disruption. The injuries are graded from minimal (grade 1) to lethal (grade 6); the AAST website has more information. With management shifting from an operative to an observational approach, pharmacists must be cognizant that the initiation of VTE prophylaxis may have to be delayed for at least 24 hours following the stabilization of hemoglobin (Van 2016).

When it comes to a patient who requires splenectomy as a result of significant injury, the pharmacist plays an important role in ensuring the administration of postsplenectomy vaccines to minimize the risk of overwhelming postsplenectomy sepsis. Patients should receive vaccinations for *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Neisseria meningitidis*, and an annual influenza vaccine. The best time for vaccine administration in order to achieve optimal immunological response following traumatic splenectomy appears to be at least 2 weeks following injury (Shatz 1998). The CDC website has the most-up-to-date information regarding the timing and selection of vaccines to be given in patients with asplenia. Trauma patients are often lost to follow-up in the outpatient setting, so the opportunity to vaccinate while patients are still in the hospital setting should not be lost among patients who are discharged before 2 weeks—despite the possibility of lower antibody response.

Extremities

Open Fractures and Antibiotic Prophylaxis

An open fracture, defined as the presence of bone protruding through an open wound or a break in the skin near the site of a fractured bone, commonly occurs in trauma patients with high—impact injuries. Open fractures are commonly

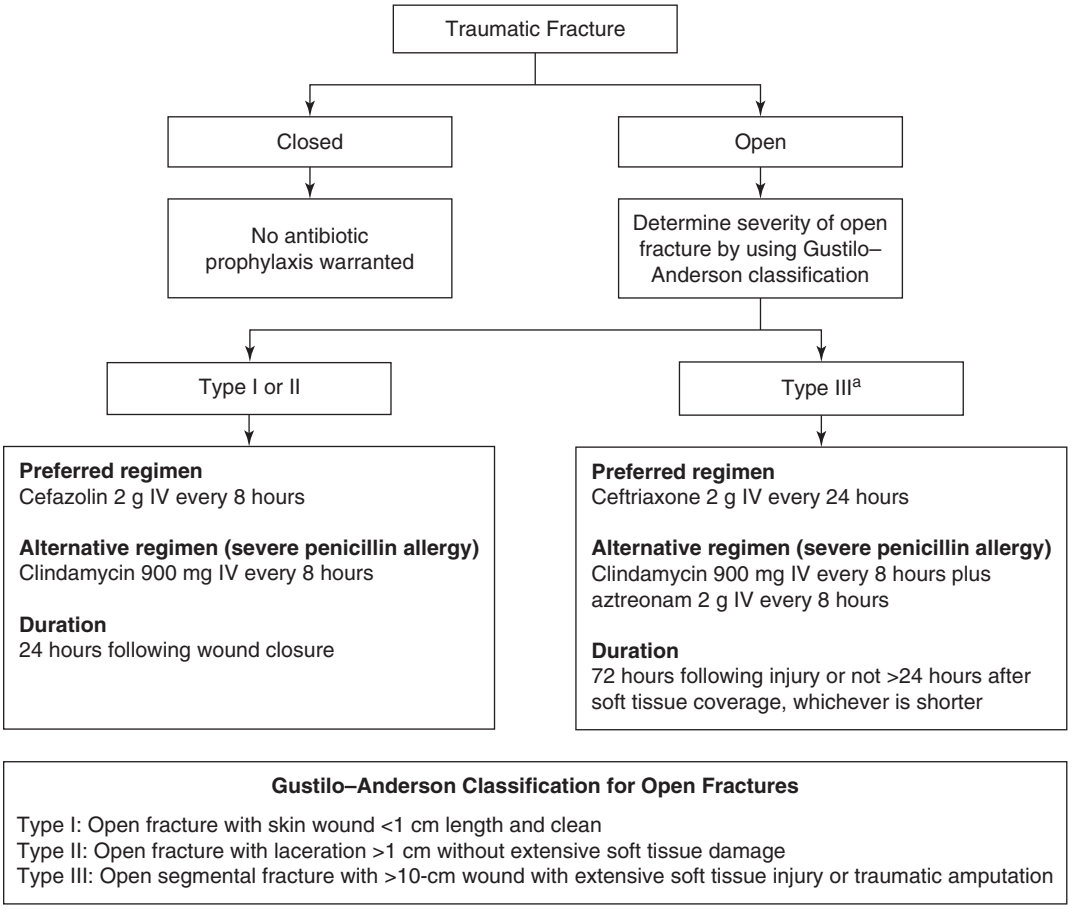


Figure 4. General approach to the management of open fractures in trauma patients.

[a]Consider addition of metronidazole 500 mg IV every 8 hours in grade III open fractures with heavy contamination of soil or fecal material.

IV = intravenous.

Information from: Hoff WS, Bonadies JA, Cachecho R, et al. EAST practice management guidelines work group: update to practice management guidelines for prophylactic antibiotic use in open fractures. J Trauma 2011;70:751-4; Rodriguez L, Jung HS, Goulet JA, et al. Evidence-based protocol for prophylactic antibiotics in open fractures: improved antibiotic stewardship with no increase in infection rates. J Trauma Acute Care Surg 2014;77:400-7.

classified according to size of wound, degree of contamination, and degree of soft tissue injury. The Gustilo–Anderson classification system is the most commonly used grading system for open fractures (Figure 4). The risk of infection and nonunion of a fracture increases with the level of severity of the open fracture (Cross 2008).

Treatment of open fractures includes prompt antibiotic therapy, early irrigation and debridement of the wound, and early soft tissue coverage with wound closure. Antibiotic therapy is directed at the most-common pathogens that cause infections according to the of the open fracture. The most-common pathogens isolated from open fractures are *Staphylococcus aureus* and *Streptococcus* species. For type I and II fractures, antibiotic therapy typically is directed at those pathogens. Patients with type III fractures have a higher risk of gram—negative pathogens, including *Enterobacteriaceae* species. Although debate continues regarding the benefits of additional gram-negative coverage in type III open fractures, this practice is typically followed in most civilian trauma centers (Hauser 2006, Ryan 2013).

For antibiotic recommendations based on severity of open fracture, see Figure 4. Cefazolin is recommended for type I and II fractures, which is supported by the EAST and Surgical Infection Society guidelines for antibiotic prophylaxis in open fractures (Hauser 2006, Hoff 2011). Antibiotic therapy of type III fractures is more controversial. Historically, cefazolin plus an aminoglycoside has been recommended for type III fractures, although comparative studies looking

at the addition of aminoglycosides to cefazolin are lacking. Uncertainties related to nephrotoxicity with aminoglycosides have prompted additional research into alternative antibiotics. A prospective, randomized controlled trial in patients with type IIIa open fractures demonstrated similar infection rates between patients who received ciprofloxacin/cefazolin compared with gentamicin/cefazolin (Janmohammadi 2011). However, uncertainties related to delayed union and nonunion of fractures may limit the implementation of fluoroquinolone-based therapy (Hoff 2011). Another study evaluated the impact of a new protocol wherein aminoglycosides, vancomycin, and penicillin were removed from their guidelines in a before-and-after study design. Ceftriaxone was used in place of aminoglycosides for type III fractures. The study demonstrated that no increased risk of infection with the new protocol after controlling for risk factors (Rodriguez 2014). Ceftriaxone may offer an attractive alternative for gram-negative coverage compared with the more-controversial aminoglycoside and fluoroquinolone options while providing the desired gram-positive coverage.

Pharmacists play an important role in antibiotic stewardship activities for patients with open fractures by providing antibiotic recommendations based on the severity of the open fracture and by ensuring the right duration of therapy. Extended durations of antibiotic use are generally of limited value in patients with open fractures—even in patients with type III fractures (Dunkel 2013).

Injuries and Rhabdomyolysis

Crush injury is an injury that occurs as a result of prolonged pressure on a part of the body. Crush injuries have been described following motor vehicle collisions, collapsed mines, earthquakes, assaults, and heavy-equipment injuries (Brown 2004).

Rhabdomyolysis from crush injury—frequently called crush syndrome—is the clinical manifestation of the injury. As a result of prolonged pressure on a muscle, cells get stretched, and contents such as myoglobin, urate, creatine kinase (CK), phosphate, and potassium get released. Leaking membranes contribute to muscle swelling leading to hypovolemic shock. Acute kidney injury occurs as a result of decreased renal perfusion, precipitation and tubular obstruction from myoglobin in the distal tubules, and the direct toxic effects of excessively elevated myoglobin in the kidneys (Smith 2003).

Creatine kinase levels are monitored as surrogate markers for the development of rhabdomyolysis because such monitoring is readily available in most hospital laboratories. Abnormal CK levels can be found in more than 85% of critically injured trauma patients when screened on a broad level (Brown 2004). The level of CK associated with the development of AKI has not been defined consistently, but data suggest that the risk is low in trauma patients with admission CK levels less than 15,000 IU/L (Bosch 2009). However, clinicians should remain vigilant about trauma patients with severe traumatic injuries and CK levels greater than 5000 IU/L (Brochard 2010, Brown 2004).

The mainstay of treatment for rhabdomyolysis and AKI from crush syndrome involves early, aggressive volume resuscitation with isotonic crystalloid fluids. The optimal amount of fluids to administer has not been clearly defined, but 10–24 liters may be required in the first 24 hours, with titration to a goal urine output of 200 mL/hour (Bosch 2009, Smith 2003). Other interventions proposed include bicarbonate-based fluid resuscitation to increase the solubility of myoglobin and forced diuresis with mannitol. A retrospective study of critically ill trauma patients admitted to a single trauma center compared bicarbonate-based resuscitation plus mannitol with standard resuscitation. Among patients at the highest risk of AKI—defined as a peak serum creatinine greater than 2.0 mg/dL—there were no differences in AKI, need for dialysis, or mortality between patients who received bicarbonate/mannitol or standard resuscitation (Brown 2004). Other, smaller studies have reported similar findings (Bosch 2009, Brochard 2010). At this time, the use of bicarbonate-based fluids or mannitol should not generally be used in lieu of standard isotonic crystalloid solutions.

PREVENTION AND TREATMENT OF COMPLICATIONS IN THE PATIENT WITH MULTISYSTEM TRAUMA

Venous Thromboembolism Prophylaxis

Venous thromboembolism is associated with high morbidity, mortality, and economic burden (ISTH 2014). When compared with medical populations, trauma patients are described as one of the groups at highest risk of VTE, with an incidence of 40% to 80% without thromboprophylaxis (Geerts 2008). Spinal cord injury, pelvic fracture, femur facture, obesity, high-energy blunt trauma, TBI, Greenfield Risk Assessment Profile (RAP) of five points or greater (Table 4), and ISS greater than nine have been proposed to increase or identify high VTE risk (Byrne 2017, Gould 2012, Gearhart 2000, Geerts 2008). Increasing age has classically been identified as a risk factor; however, recent data suggest VTE risk increases up to age 65 and then plateaus or diminishes (Nastasi 2017). Contemporary estimates of deep vein thrombosis (DVT) and pulmonary embolism (PE) are around 5% and 2%, respectively, for adult patients with severe injury who are receiving thromboembolism prophylaxis (Byrne 2017).

Modalities for VTE prevention include chemoprophylaxis, mechanical prophylaxis (e.g., sequential compression devices), or IVC filters (Gould 2012, Rogers 2002) (Figure 5). Mechanical prophylaxis is an adjunct to chemoprophylaxis for high-risk patients and is recommended over no prevention if chemoprophylaxis is contraindicated (Geerts 2008, Gould

Table 4. Greenfield Risk Assessment Profile

	Weight
Underlying conditions	
Obese (>120% Metropolitan Life Insurance Tables)	2
Malignancy	2
Abnormal coagulation factors at admission	2
History of thromboembolism	3
Iatrogenic factors	
Central femoral line >24 hours	2
Four or more transfusions during the first 24 hours	2
Surgical procedures >2 hours	2
Repair or ligation of major venous injury	3
Injury-related factors	
AIS >2 for the chest	2
AIS >2 for the abdomen	2
Spinal fractures	2
AIS >2 for the head	3
Coma (GCS score <8 for >4 hours)	3
Complex lower-extremity fracture	4
Pelvic fracture	4
Spinal cord injury with para- or quadriplegia	4
Age	
≥40 but <60	2
≥60 but <75	3
≥75	4

Reprinted with permission from Greenfield LJ, Proctor MC, Rodriguez JL, et al. Posttrauma thromboembolism prophylaxis. J Trauma 1997;42:100-3.

2012). Placement of mechanical prophylaxis devices is limited to application on noninjured extremities. Placement of IVC filters may reduce the incidence of PE in patients who are unable to receive chemoprophylaxis, but data are mixed. The American College of Chest Physicians (ACCP) recommends against routine use of IVC filters, whereas the EAST guidelines recommend consideration for very high-risk patients who cannot receive chemoprophylaxis for 5–10 days after injury (Gould 2012, Rogers 2002).

Lower-extremity venous duplex surveillance has been proposed to promote early therapeutic intervention and decrease PE rates in asymptomatic, high-risk trauma patients. The EAST guidelines recommend screening of high-risk patients (Rogers 2002). The ACCP guidelines do not recommend periodic screening for asymptomatic VTE (Gould 2012), and subsequently published data are mixed. Routine VTE screening in trauma patients remains an area for debate because the benefit versus the cost of monitoring has not been clearly demonstrated.

Timing of Prophylaxis

Early chemoprophylaxis is essential because the risk of VTE increases when initiation is delayed beyond the first 24 hours (Byrne 2017). Venous thromboembolism increases threefold in severely injured patients when prophylaxis is started later than 4 days after hospital admission (Nathens 2007), and PE risk increases by 80% with delayed chemoprophylaxis when compared with initiation on day one (Byrne 2017). Delays in prophylaxis occur because of the delicate balance between clot prevention and bleeding propagation. Contraindications to early chemoprophylaxis initiation include intracranial hemorrhage, incomplete SCI with spinal hematoma, and ongoing hemorrhage (Geerts 2008) (see Figure 5). Consensus opinion for initiation timing is lacking, and a multidisciplinary or even interdisciplinary team approach may be necessary when considering chemoprophylaxis in complex, critically ill trauma patients.

Several retrospective studies and literature reviews of blunt solid-organ injuries demonstrate that early chemoprophylaxis initiation within 48 hours of admission reduces VTE without increasing bleeding (Kwok 2016, Murphy 2016, Rostas 2015, Van 2016). Clinical considerations such as shock state presence, injury grade, operative versus nonoperative management, concomitant injuries, and medication pharmacokinetics should be weighed when initiating chemoprophylaxis. Hemoglobin stabilization for a specified period of time (e.g., 24 hours) may provide a balanced approach when considering VTE prophylaxis in the setting of blunt solid-organ injuries (Van 2016). A spine fracture with intraspinal hematoma risk, SCI, and TBI presents a clinical challenge because hematoma expansion at the anatomical site can be devastating given that new or complete spinal cord injury can result in para- or quadriplegia. Wide practice variability exists for chemoprophylaxis timing in spine and head traumas. Small studies suggest that chemoprophylaxis initiation at 24 hours after stable head CT had similar hemorrhage progression than did later initiation (Farooqui 2013, Saadeh 2012). The BTF Guidelines cite insufficient evidence regarding preferred agent, dose, and timing of chemoprophylaxis, whereas the Society of Critical Care Medicine and the Neurocritical Care Society recommend chemoprophylaxis within 24–48

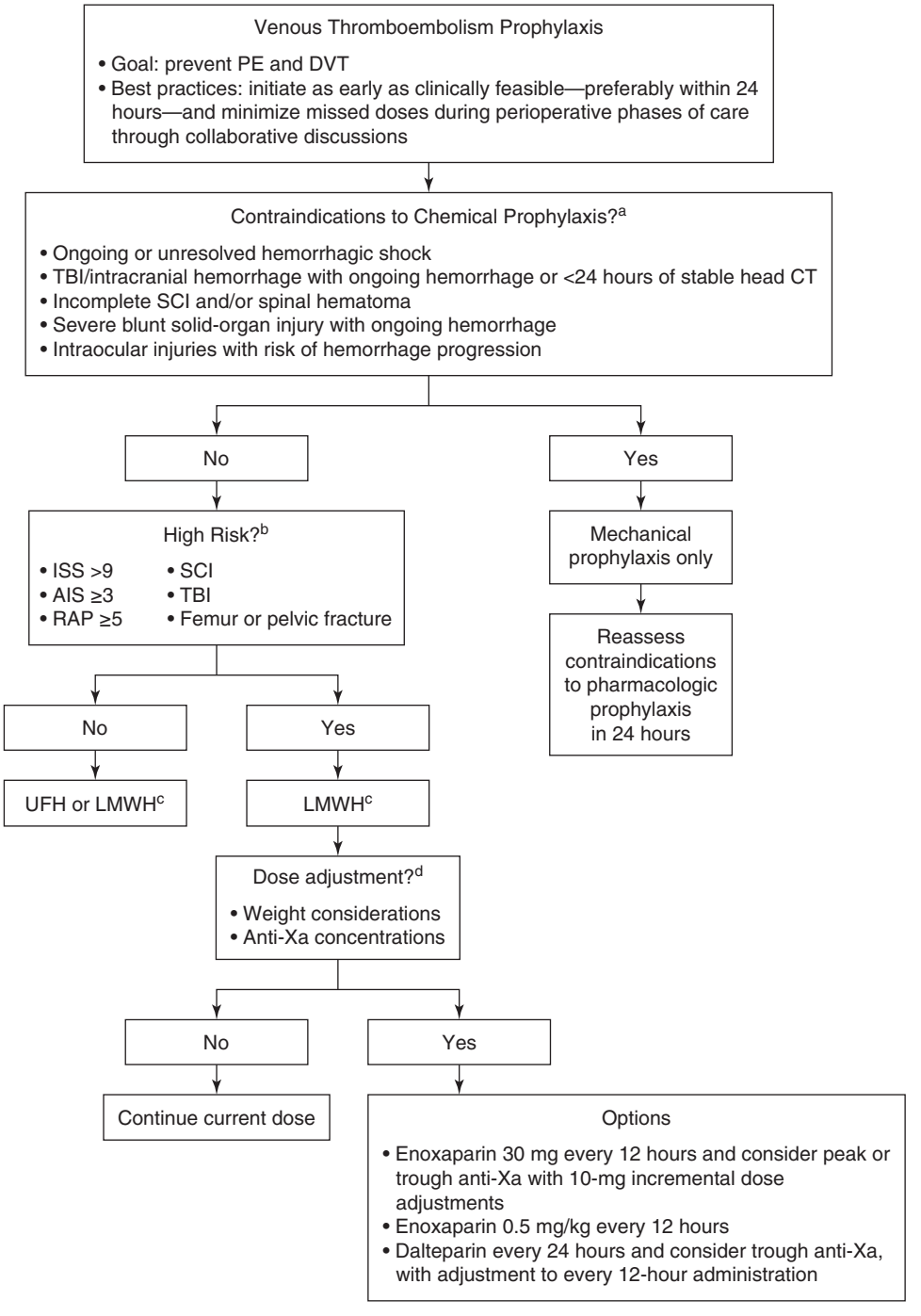


Figure 5. Venous thromboembolism prophylaxis algorithm.

[a]Contraindications listed are not all-inclusive and should not take the place of clinical judgment.

[b]Additional high-risk features have been described in the literature, including ED systolic blood pressure less than 90 mm Hg, obesity, and high-energy blunt mechanism. Use of duplex screening in high-risk patients is mixed and may be considered in a multimodal protocol for VTE prevention.

[c]Patients with allergies to heparin products should not be prescribed UFH or LMWH. Patients with creatinine clearances less than 30 mL/min or with spinal epidural placements should receive UFH or have the LMWH dose adjusted. Patients at extremes of weight may require empiric dose adjustments.

[d]Anti-Xa assessment has been performed on all patients who are receiving LMWH, who have Greenfield RAP scores of 5 or greater, or who are admitted to an ICU. Empiric weight-based adjustments are heterogeneous, and no studies exist to recommend one strategy over another.

AIS = Abbreviated Injury Scale; CT = computed tomography; DVT = deep vein thrombosis; ISS = Injury Severity Score; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RAP = Greenfield Risk Assessment Profile; SCI = spinal cord injury; TBI = traumatic brain injury; UFH = unfractionated heparin.

Information from Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381-453; Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis (9th Edition): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2)(Suppl):e227S-e277S. Kopelman TR, Walters JW, Bogert JN, et al. Goal directed enoxaparin dosing provides superior chemoprophylaxis against vein thrombosis. Injury 2017;48:1088-92.

hours in patients with TBIs and intracerebral hemorrhages—or 24 hours after craniotomy (Carney 2018, Nyquist 2017).

Chemoprophylaxis Agent Selection

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are used routinely in critically ill trauma patients. The EAST guidelines recommend LMWH over UFH for high-risk patients—defined as having an ISS of 9 or greater (Rogers 2002). The ACCP guidelines equivocally recommend UFH or LMWH over no prophylaxis but do not specify a preferential chemotherapeutic agent (Gould 2012). Despite mixed results from studies comparing the efficacy of UFH vs LMWH in trauma patients, most trauma centers preferentially select LMWH particularly in high-risk patients. The preferential use of LMWH is supported by a recently published retrospective, propensity-matched cohort study comparing the incidence of PE and DVT between LMWH (n=37,960) and UFH (n=37,960) using data from the American College of Surgeons Trauma Quality Improvement Program. The study suggested that LMWH use is associated with a 42% decreased risk of PE compared to UFH (1.4% vs. 2.4%) and a 28% decreased risk of DVT (3.9% vs. 5.4%) (Byrne 2017) (see Figure 5).

Dosing and Monitoring of LMWH

Dose optimization of LMWH chemoprophylaxis may improve outcomes while reducing adverse events. Pharmacists should be familiar with differences in pharmacodynamics and pharmacokinetics between agents to allow for patient-specific variability. Missed doses should be minimized because fivefold increased odds for VTE have been demonstrated in trauma and general surgery patients (Louis 2014).

Serum anti-factor-Xa concentrations (anti-Xa) have been proposed to monitor and dose adjust enoxaparin prophylaxis (i.e., standard-of-care dose is 30 mg every 12 hours) because of the high risk of thrombosis and bleeding in trauma patients. End points include a peak serum concentration of 0.2–0.5 IU/mL and/or a trough serum concentration of 0.1–0.2 IU/mL (Haas 2005, Malinoski 2010). One team monitored serum peak and trough anti-Xa after the third dose of enoxaparin 30 mg every 12 hours. Trough anti-Xa of less than 0.1 IU/mL occurred in half the study population, with a significantly higher DVT rate (37% vs. 11%, p=0.026) (Malinoski 2010). Subsequent studies evaluated enoxaparin dose adjustment by 10-mg increments up to 60 mg every 12 hours, using either peak or trough anti-Xa levels; however, the correlation between peak and trough has been variable (Costantini 2013). Some studies demonstrate a reduction in VTE with anti-Xa monitoring; others demonstrate no difference—likely because of heterogeneity in patient population, comparator groups, dose adjustment protocol, and statistical analysis. Risk stratification based on clinical features such as ICU admission or Greenfield RAP may provide construct for optimal anti-Xa use. Modeling, retrospective analyses, and literature reviews suggest a weight-based dose of 0.5 mg/kg (average dose range 0.43–0.55 mg/kg) every 12 hours to achieve a prophylactic anti-Xa concentration, but adequately powered studies are necessary to confirm impact on VTE rate versus bleeding incidence (Chapman 2016, Kopelman 2017). Although dalteparin is less commonly used in trauma patients, one study demonstrated that implementation of a protocol that adjusted dalteparin dosing from 5,000 units daily to twice daily in high-risk patients with low anti-Xa levels reduced the risk of VTE compared with the preintervention period (Droege 2014). Based on laboratory availability of anti-Xa, trauma institutions may consider implementation of anti-Xa monitoring in conjunction with a weight-adjusted dosing algorithm—particularly in high-risk patient populations (see Figure 5). For a discussion on dosing challenges, see the Online Appendix.

CONCLUSION

The management of severely injured trauma patients is complex and involves an understanding of how to manage hemorrhagic shock and specific injuries.

Initial resuscitation of trauma patients with hemorrhagic shock involves principles related to DCR. Pharmacists should recognize that resuscitation involves administration of blood products that mimic whole blood in addition to deployment of methods to control bleeding rather than crystalloid resuscitation. Excessive administration of crystalloids during the initial resuscitation of trauma patients contributes to increased mortality, ARDS, and MODS. Adjunctive medications such as tranexamic acid may improve mortality and reduce blood product use. Pharmacists balance reversing

Practice Points

There are many opportunities for pharmacists to be involved with the pharmacotherapy of patients with multisystem trauma. As the management of hemorrhagic shock in trauma patients continues to evolve, pharmacists will have to understand the role of adjunctive agents to control bleeding and reverse medication-induced coagulopathy. In addition, pharmacists must understand the treatment of specific injuries and complications related to trauma.

- **The management of hemorrhagic shock has shifted from fluid-based to a blood-based resuscitation.**
- **Damage control resuscitation principles emphasize (1) the use of blood products that mimic whole blood, (2) minimization of the use of crystalloids in acute resuscitation, and (3) permissive hypotension.**
- **Tranexamic acid may be used as an adjunctive agent to control bleeding in trauma patients receiving massive transfusions or with laboratory evidence of fibrinolysis.**
- **The use of four-factor PCC is preferred for reversal of warfarin in trauma patients with acute bleeding or bleeding in critical sites.**
- **Data published on the reversal of factor Xa inhibitors are limited to noncomparative studies, thereby making it difficult to determine the optimal agent. In addition, the majority of data evaluating adequate hemostasis as an end point looked at reversal of rivaroxaban and apixaban.**
- **Available data suggest that four-factor PCC and andexanet result in similar rates of hemostasis and thromboembolic complications for the reversal of rivaroxaban and apixaban.**
- **Adequate resuscitation, analgesia, and sedation can help prevent secondary injury in patients with severe TBI. Elevated ICP requires a stepwise approach, including selection, dosing, and monitoring of hyperosmolar therapies.**
- **Early diagnosis and treatment of BCVI with antithrombotic therapy require equipoise for bleeding at other injury sites and transition to antiplatelet therapy for patient ease.**
- **A patient with suspected hollow viscus injury should receive a single antibiotic dose with gram-negative and anaerobic coverage. If hollow viscus injuries are identified, antibiotics should not be continued for longer than 24 hours, provided source control is achieved.**
- **Pharmacists play an important role in antibiotic stewardship for patients with open fractures. Prophylaxis for type I and II fractures consists of treatment with cefazolin. The optimal treatment for type III fractures is unclear, but ceftriaxone may provide a good alternative in place of aminoglycoside- or fluoroquinolone-based regimens.**
- **Venous thromboembolism prophylaxis in trauma patients is challenging given controversy related to ideal time to initiate therapy, agent selection, dosing, and monitoring to avoid both unnecessary bleeding and clotting complications. Low-molecular-weight heparin is preferred by most trauma centers, with consideration of anti-Xa monitoring in critically ill, high-risk patients.**
- **Pharmacokinetic alterations—specifically, hypermetabolism and augmented clearance—may result in increased dosing requirements; however, more data are needed to provide therapy-specific guidance.**

the pharmacologic effects of anticoagulants and achieving hemostasis with limiting thromboembolic risk.

After initial stabilization of a trauma patient, the focus shifts to management of specific injuries and prevention of complications. Pharmacists provide recommendations regarding appropriate medications, dosing, and monitoring of medications to prevent and treat complications in trauma patients.

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Self-Assessment Questions

1. The trauma service is considering the formulary status of three new hemostatic agents as surgical adjuncts in hemorrhagic shock. A recent phase III study demonstrates adequate hemostasis is achieved at 12 hours by agent A in 28%, agent B in 35%, and agent C in 48% of patients. Standard of care control group achieved adequate hemostasis in 30% of patients. Which one of the following would be the best option based on the correct calculation of number needed to treat (NNT) and relative risk reduction (RRR)?

   A. Agent B; NNT 20, RRR 14%
   B. Agent B; NNT 17, RRR 7.1%
   C. Agent C; NNT 6, RRR 26%
   D. Agent C; NNT 18, RRR 60%

Questions 2 and 3 pertain to the following case.

A.H., a 26-year-old man with no contributory medical history, is admitted to the trauma service after being in a motocross crash. He was a helmeted driver. A.H.'s Glasgow Coma Scale (GCS) score at the scene is 12 and he is intubated for combativeness. Head CT demonstrates extensive, multifocal hemorrhagic shear injury; and small subdural, intraventricular, and subarachnoid hemorrhages. Upon arrival to the trauma ICU, A.H.'s blood pressure is 96/52 mm Hg, oxygen saturation is 98%, and GCS is 7. Neurosurgery is called for external ventricular drain (EVD) placement. A.H.'s initial intracranial pressure (ICP) is 20 mm Hg, and he is resuscitated with 0.9% sodium chloride. Six hours later, A.H. has a repeat head CT that reveals worsening subdural hematoma in the left frontal lobe and ICP is 26 mm Hg. Mannitol 20% 1 g/kg bolus is administered. One hour later, ICP is 28 mm Hg. Hemodynamic and laboratory analysis reveals a blood pressure of 108/62 mm Hg, sodium 140 mEq/L, potassium 3.8 mEq/L, chloride 110 mEq/L, BUN 10 mg/dL, SCr 0.98 mg/dL, glucose 89 mg/dL, and serum osmolality 300 mOsm/L.

2. Which one of the following is best to recommend for A.H.?

   A. Mannitol 20% 1g/kg bolus
   B. Sodium chloride 3% 1 mL/kg/hour continuous infusion
   C. Sodium chloride 23.4% 30 mL bolus
   D. No acute intervention is necessary as TBI parameters are at goal.

3. A.H.'s neurosurgery team would like to initiate early seizure prophylaxis. Which one of the following is best to recommend for A.H.?

   A. No seizure prophylaxis
   B. Phenytoin for 14 days
   C. Levetiracetam for 28 days
   D. Levetiracetam for 7 days

4. A 67-year-old man (weight 80 kg) presents to the ED after a motor vehicle collision (MVC); he was intubated in the field. The patient's medical history includes hypertension and hyperlipidemia, and his home drugs include lisinopril 20 mg daily and atorvastatin 40 mg nightly. Primary survey reveals a GCS score of 13, and focused assessment with sonography in trauma (FAST) is positive. Computed tomography imaging of the head, chest, abdomen, and pelvis reveals C6 burst fracture, mandibular fracture, right orbital wall fracture, right one through six rib fractures, hemopneumothorax, and grade IV liver injury. The patient is taken to interventional radiology because of concerns for bleeding from the liver injury, and selective embolization of bleeding vessels is accomplished. Subsequent CT angiography (CTA) of the cerebral vessels reveals right vertebral artery pseudoaneurysm measuring 0.8 cm. The pseudoaneurysm is not amenable to surgical intervention. The orthopedic spine team determines that the spine fracture is unstable and requires surgical fixation in the next 24–48 hours. The patient is admitted to the trauma ICU for further resuscitation. Which one of the following is best to recommend initiating for this patient's blunt cerebrovascular injury?

   A. Aspirin 325 mg via enteral tube daily on admission to the trauma ICU
   B. Aspirin 325 mg via enteral tube daily once hemoglobin is stable
   C. Enoxaparin 80 mg subcutaneously twice daily once hemoglobin is stable
   D. Low-dose intravenous heparin infusion once hemoglobin is stable

5. A 34-year-old woman (weight 105 kg, height 5'4", SCr 0.55 mg/dL) with no significant medical history was in a head-on MVC. Her injuries include a right clavicle fracture, grade II liver injury, grade IV spleen injury, right acetabular fracture, and left femur fracture. The patient is taken to the operating room for emergent exploratory laparotomy with splenectomy with abdominal closure. She is now post-operative day 1 and has undergone adequate resuscitation and stable hemoglobin. Orthopedic surgery is consulted and plans operative intervention on the femur and acetabular fracture in 3 days. Which one of the following is best to recommend for venous thromboembolism prevention in this patient?

   A. Insert IVC filter.
   B. Apply pneumatic compression devices.
   C. Start enoxaparin 30 mg every 12 hours.
   D. Start heparin 5000 units every 8 hours.

6. A 37-year-old man (weight 73 kg, height 5'9") is admitted to the ICU after multiple gunshot wounds to the abdomen and right upper extremity. His injuries include a through and through grade V liver injury with active bleeding; shattered spleen; multiple injuries to the stomach, small bowel, and transverse colon; and a left open humeral fracture. The patient's vitals include pulse 143 beats per minute, blood pressure 102/68 mm Hg, respiratory rate 26 breaths per minute, and oxygen saturation 98% on room air, diaphoretic and agitated. Emergent exploratory laparotomy is performed with complex hepatorrhaphy with packing, distal gastrectomy, distal duodenal resection, transverse colectomy, and temporary abdominal closure. The patient receives massive transfusion with five units of whole blood, one unit of packed red cells, and one unit of fresh frozen plasma. On hospital day 2 he is taken back to the OR for reexploration, removal of peri-hepatic packing, cholecystectomy, t-tube placement, repair of the duodenum, placement of duodenostomy tube, duodeno-jejunostomy, Roux-en-Y gastrojejunostomy, jejunostomy, and end colostomy. The patient is now hospital day 3; his current laboratory test results include Hgb 9.5 g/dL, Hct 27.3%, WBC 18.4 × 10^3 cells/mcL, and Plt 242 × 10^3 cells/mcL. The patient's vital signs are stable. His last transfusion was before the operating room on hospital day 2. Which one of the following is best to recommend for venous thromboembolism prophylaxis in this patient?

   A. IVC filter placement
   B. Heparin 5000 units every 8 hours
   C. Enoxaparin 30 mg every 12 hours
   D. Enoxaparin 30 mg every 12 hours, check anti-Xa

7. A 25-year-old man is transported to a level 1 trauma center after a gunshot wound to the chest. Initially, he is mentally intact and has a palpable radial pulse. The patient's vital signs include blood pressure 96/40 mm Hg and heart rate 108 beats per minute. He arrives at the trauma center and proceeds to decompensate. He is no longer answering questions and has no palpable radial pulse. The trauma surgeons take him emergently to surgery, but the patient continues to be hemodynamically unstable despite initiation of massive transfusion protocol and attempted operative control of bleeding. The trauma surgeons request a dose of recombinant factor VIIa to aid in hemostasis. Which one of the following outcomes is most likely with the use of recombinant factor VIIa in this patient?

   A. Reduced mortality and blood product use
   B. Reduced mortality risk but no significant reduction in blood product use
   C. Reduced blood product use but no significant reduction in risk of mortality
   D. No significant reduction in blood product use or risk of mortality

Questions 8 and 9 pertain to the following case.

T.J. is a 36-year-old man admitted to the trauma center after a MVC. On arrival to the hospital, he is hypotensive with a blood pressure of 70/30 mm Hg, heart rate of 148 beats per minute, and respiratory rate of 38 breaths per minute. T.J. is confused and is unable to answer questions about the details of his accident. An initial 1-L bolus of lactated Ringers results in no improvement in his hemodynamics. A focused assessment with sonography in trauma demonstrates free fluid in T.J.'s abdomen. He undergoes an exploratory laparotomy with splenectomy and colectomy with primary anastomosis for a perforated colon.

8. Which one of the following is best to recommend for antimicrobial prophylaxis in T.J.?

   A. Cefoxitin 1 g intravenous every 6 hours for 24 hours
   B. Piperacillin/tazobactam 3.375 g intravenous every 6 hours for 4 days
   C. Cefazolin 1 g intravenous every 8 hours for 24 hours
   D. Ampicillin/sulbactam 3 g intravenous every 6 hours for 48 hours

9. After stabilization, T.J. is returned to the ICU for continued monitoring and resuscitation. The nurse notes that his pupils are fixed and dilated. A stat CT scan of the head demonstrates a large epidural hematoma. On arrival back to the ICU, T.J. becomes hypotensive. Hemoglobin level is 10.6 mg/dL and stable from the previous measurement. The ICU resident requests albumin for resuscitation. Which one of the following is best to recommend regarding albumin for resuscitation in T.J.?

   A. Albumin and crystalloid resuscitation are associated with similar mortality and neurologic outcomes, however albumin is more expensive and should not be used.
   B. Albumin resuscitation reduced mortality but did not improve neurologic outcomes compared to patients who received normal saline and can be considered in patients with TBI.
   C. Albumin resuscitation compared with normal saline has been shown to increase mortality in patients with TBI and should not be used.
   D. Albumin resuscitation is associated with similar mortality rates but improved neurologic outcomes compared with normal saline and can be considered in patients with TBI.

10. A 24-year-old man is admitted to the hospital after being in a high-speed MVC. Chest radiography demonstrates a widened mediastinum. Because of concern for an aortic injury, a CT scan is ordered to determine the cause of the widened mediastinum. Preliminary results indicate that the patient has a large intimal flap aortic dissection and vascular surgery is consulted. The patient's vital signs reveal blood pressure 160/98 mm Hg and heart rate 115

beats per minute. Morphine is administered to treat pain; however, the patient's vital signs remain unchanged. Vascular surgery recommends delayed endovascular repair and immediate medical management for the patient's blunt traumatic aortic injury. Which one of the following is best to recommend initiating for this patient?

A. Nicardipine infusion titrated to maintain systolic blood pressure 100–120 mm Hg
B. Nitroprusside titrated to maintain systolic blood pressure less than 100 mm Hg
C. Metoprolol 25 mg orally twice daily
D. Esmolol infusion titrated to maintain systolic blood pressure 100–120 mm Hg

11. A 45-year-old man is admitted to the trauma center after a prolonged extrication from his vehicle after a MVC. He is hypotensive with a blood pressure of 90/40 mm Hg and urine that is dark brown. Because of concern for crush injury, the trauma team orders a creatine kinase level that returns a result of 6252 IU/L. Which one of the following is best to recommend for this patient's presumed rhabdomyolysis?

    A. Lactated ringer 2 L followed by an infusion at 400 mL/hr. Titrate urine output to at least 200 mL/hr.
    B. Sodium bicarbonate 150 meq/L in sterile water at 400 mL/hr. Titrate to urine output of at least 200 mL/hr
    C. Sodium bicarbonate 150 meq/L in sterile water at 400 mL/hr plus mannitol to maintain a urine output of at least 200 mL/hr
    D. Normal saline at 1 L/hr. Titrate to urine output of 1 mL/kg/hr.

12. A 85-year-old man (weight 70 kg) is admitted after a ground level fall caused by tripping on a curb while walking his dog. He reports hitting his head on the pavement but no loss of consciousness. Initial GCS is 15. His medical history is significant for atrial fibrillation on apixaban 5 mg orally twice daily. The patient reports talking his last dose of apixaban 9 hours before his fall. His SCr is 1.6 mg/dL, which is his baseline. A CT scan of the head reveals an 8-mm subdural hematoma. The neurosurgical team recommends neurologic checks and reversal of his apixaban. Which of the following is best to recommend for reversing this patient's apixaban?

    A. Four-factor PCC 5000 units intravenously
    B. Andexanet 800 mg bolus at 30 mg/min followed by 960 mg over 2 hours
    C. Andexanet 400 mg bolus at 30 mg/min followed by 480 mg over 2 hours
    D. Four-factor PCC 2500 units intravenously

Questions 13–15 pertain to the following case.

J.L is a 35-year-old woman (weight 80 kg) transported to the level 1 trauma center after an MVC. In the field she was hypotensive and tachycardic (systolic blood pressure 80/44 mm Hg, heart rate 147 beats per minute) and received 1 L of lactate ringers with minimal impact on her blood pressure. On arriving at the hospital J.L. has a FAST exam that demonstrates free fluid in her abdomen. She is taken emergently to the operating room and receives 12 units each of red blood cells and plasma plus 2 units of platelets to mimic whole blood transfusion. J.L. is found to have a ruptured spleen and perforated bowel and undergoes splenectomy and small bowel resection with repair. She is sent to the surgical ICU for further resuscitation but continues to have unstable hemoglobin levels.

13. In addition to identifying the source of bleeding, which one of the following is best to recommend to control bleeding in J.L.?

    A. Three-factor PCC 50 units/kg
    B. Tranexamic acid 1 g intravenous over 10 minutes followed by 1 g over 8 hours
    C. Recombinant factor VIIa 90 mcg/kg
    D. Tranexamic acid 1 g intravenous over 10 minutes

14. During resuscitation, it is noted that J.L. has a type III open fracture of her tibia. Her SCr is 1.5 mg/dL and she has no drug allergies. Which one of the following is best to recommend for J.L.?

    A. Ceftriaxone 2 g intravenous every 24 hours
    B. Cefazolin 2 g intravenous every 8 hours
    C. Clindamycin 900 mg intravenous every 8 hours
    D. Ciprofloxacin 400 mg intravenous every 8 hours

15. Twenty-four hours after admission, J.L. is taken to surgery for repair of her open tibia fracture and wound closure is achieved. What duration of antibiotics would be best to recommend for J.L.'s open fracture?

    A. Total of 72 hours of antibiotic coverage
    B. Discontinue antibiotics after wound closure
    C. 24 hours after surgery for her open tibia fracture
    D. 48 hours after surgery for her open tibia fracture