

SRGS[®] SELECTED READINGS in GENERAL SURGERY

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Vascular Surgery, Part III	V43N1	Published
Critical Care of Surgical Patients, Part I	V43N2	Published
Critical Care of Surgical Patients, Part II	V43N3	Published
Trauma, Part I	V43N4	Summer
Trauma, Part II	V43N5	Summer
Surgical Infection	V43N6	Fall
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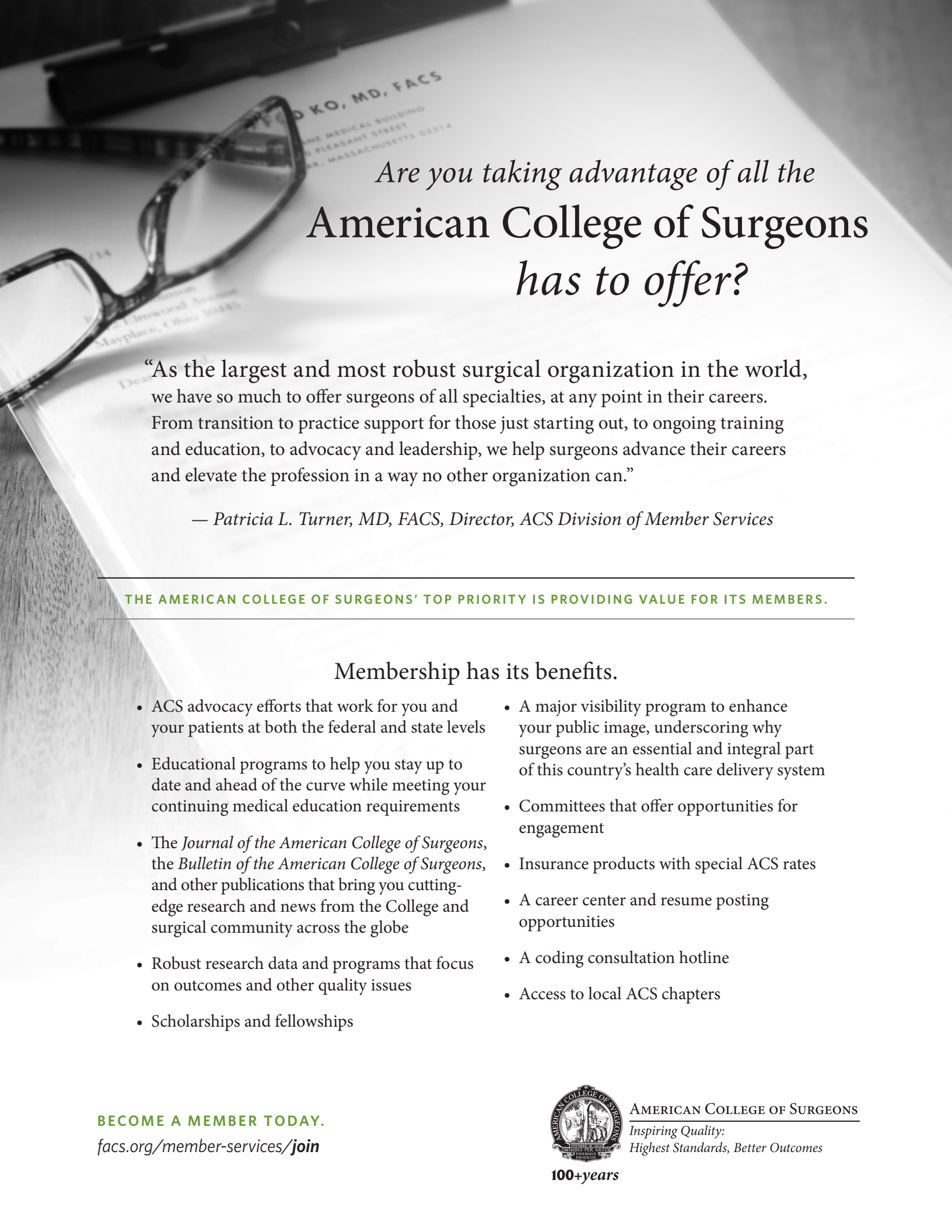
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Introduction | **CRITICAL CARE OF
SURGICAL PATIENTS, PART II**
VOLUME 43 | 3 | 2017

Welcome to *Selected Readings in General Surgery (SRGS)*. In the second part of our two-issue series focusing on critical care of the surgical patient, we will begin by reviewing articles relevant to the use of blood and blood products in surgical practice. Emphasis on safe transfusion practices has increased over the past decade and the articles reviewed will provide information on recognizing and managing transfusion reactions, evidence-based guidance for choosing the optimum hemoglobin trigger for transfusion, and the controversy regarding the potential risks of transfusing blood that is approaching the end of its storage cycle vs. using fresh blood.

Following the transfusion discussion, we will review articles on managing shock in surgical patients. We will also explore the mechanisms and management of hemorrhage-associated coagulopathy as well as the management of sepsis, septic shock, and cardiogenic shock.

Nicholas Namias, MD, FACS, provided valuable editorial assistance for this critical care series and I am grateful for his help.

Transfusion in Surgical Patients

Red blood cell transfusion is a valuable clinical tool that can be a lifesaving intervention. To transfuse effectively, an understanding of the risks associated with transfusion is important; common risks include transfusion reactions and disease transmission. Similarly, knowledge of data supporting current transfusion practices is necessary to use blood and blood products as safely and effectively as possible.

Risks of Transfusion

Transfusion reactions are the most common type of complication of blood product administration. Delaney and coauthors¹ discussed this topic in *The Lancet*, 2016. The authors noted that transfusions are an essential element of health care but are associated with significant risks and costs. Recognition of the feasibility and safety of restricted transfusion protocols has helped reduce the frequency of transfusions and transfusion reactions as well as reduce associated costs. Transfusion reactions occur in up to one

Figure 1

Symptoms and suggested interventions based on type of transfusion reaction, part one. Reproduced from Delaney and coauthors¹ with permission.

All transfusions must be stopped when a patient is experiencing a reaction and assessed by a provider Provide supportive therapy to support vital organ function (cardiac, pulmonary, renal) For questions regarding transfusion reaction diagnosis or management, call the transfusion service, or other appropriate physician		
Reaction	Symptoms	Interventions
Increase in temperature		
Possible febrile non-haemolytic reaction	Incremental increase <1°C above baseline and no other new symptoms	<ul style="list-style-type: none"> • Close observation, frequent vital signs • If stable and no other new symptoms then continue with transfusion
Possible bacterial contamination	Incremental increase ≥1°C above baseline, or incremental increase <1°C with any other new symptoms (chills or rigors, hypotension, nausea or vomiting)	<ul style="list-style-type: none"> • Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antipyretic drug • Consider blood cultures (patient); empirical antibiotics if neutropenic • Do not resume transfusion • Strongly consider culturing blood product if ≥2°C increase in temperature or if high clinical suspicion of sepsis • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
Possible haemolysis		
<p>For consistently febrile patient due to underlying disease or treatment, when possible:</p> <ul style="list-style-type: none"> • Avoid starting transfusion if patient's temperature is increasing • Treat fever with antipyretic drug before starting transfusion • If incremental increase in temperature ≥1°C above baseline treat as per above (stop and do not resume transfusion, cultures if indicated) • Notify blood transfusion laboratory, return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory 		
Allergic symptoms		
Urticaria	Mild hives, rash, or skin itching only	<ul style="list-style-type: none"> • Stop transfusion, keep intravenous line open, and assess patient • Antihistamines • Notify patient clinician and blood transfusion laboratory; sample not required • If symptoms resolve, then can resume transfusion • If symptoms do not improve or worsen or recur then discontinue transfusion; return unit (with administration set) to blood transfusion laboratory
Possible allergic reaction	Hives, rash, itching, and or any other new symptoms (throat, eye, and tongue swelling, etc)	<ul style="list-style-type: none"> • Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antihistamines • Do not resume transfusion • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory

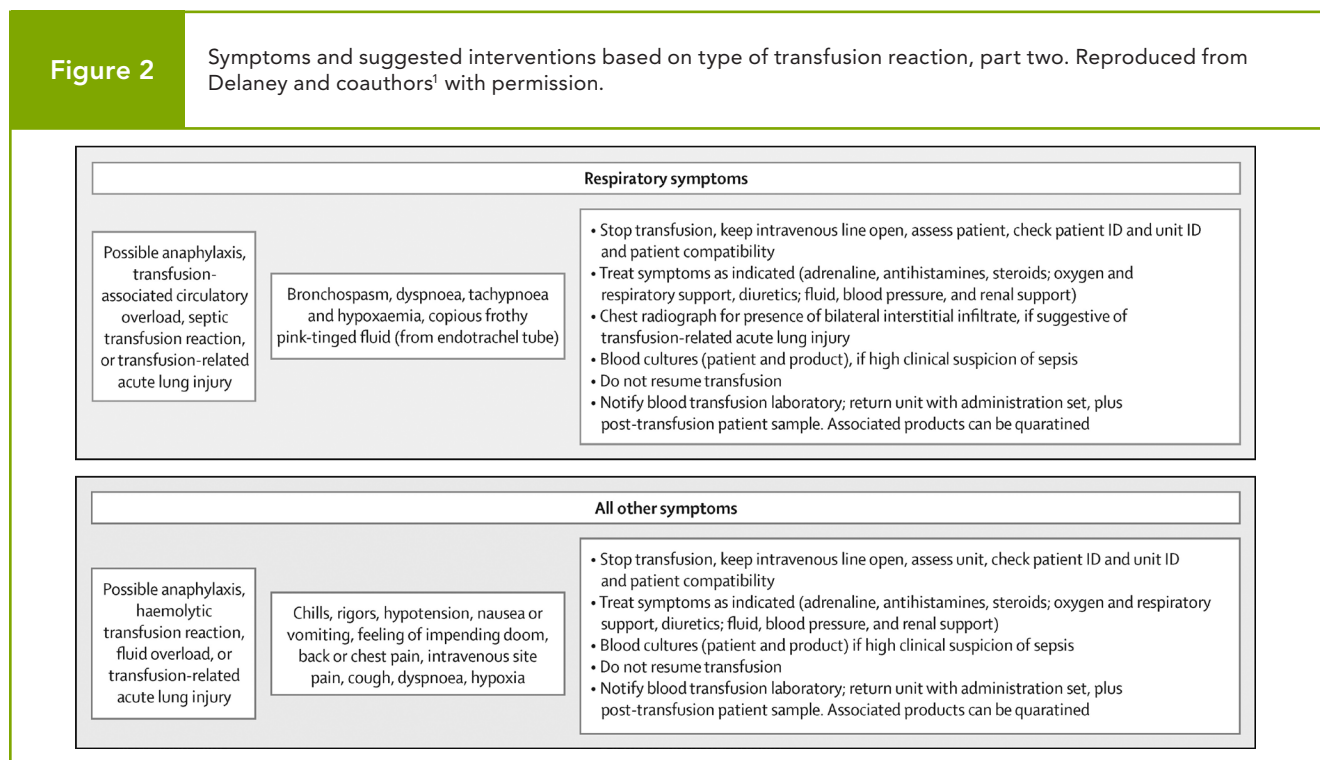
out of every 100 transfusions; fatal transfusion reactions are rare, occurring in one out of every 200,000–400,000 units transfused.

Managing transfusion reactions depends on the type and severity of the reaction. General principles include stopping the transfusion, maintaining venous access by keeping the line open with saline infusion, instituting supportive care to preserve organ function, reporting the reaction to the blood bank, and having the transfused unit checked to ensure that the patient received the intended product and that the red cells or other transfused product(s) were not infected or contaminated. The authors presented a series of charts with interventions categorized based on the symptoms encountered (Figure 1 and Figure 2).

reactions represent the most severe subgroup of allergic reactions. These can be life-threatening and frequently present with bronchospasm, respiratory distress, and hypotension. Mild allergic reactions are initially treated with transfusion cessation and an antihistamine such as diphenhydramine. If symptoms resolve quickly, the transfusion can safely restart. Severe allergic or anaphylactic reactions require epinephrine (intramuscular); second-line interventions include antihistamines, bronchodilators, and corticosteroids. The authors emphasized that there is insufficient evidence to support routine prophylaxis with antihistamines or glucocorticoids in patients with a history of mild allergic reactions. For more severe reactions, the authors recommended patient counseling regarding future transfusions, premedication with antihistamines,

Figure 2

Symptoms and suggested interventions based on type of transfusion reaction, part two. Reproduced from Delaney and coauthors' with permission.



Delaney and coauthors first discussed allergic and anaphylactic reactions; symptoms of these reactions usually occur during or within four hours of transfusion and are more common in platelet transfusions than in transfusions of packed red blood cells. Most allergic reactions are mild, with rash, pruritus urticaria, and localized angioedema being the most common manifestations. Anaphylactic

and minimizing the plasma content of the transfusion.

The next section of the article discussed immune and nonimmune hemolytic transfusion reactions. Immune reactions are most commonly caused by administering incompatible blood because of either failing to properly identify the correct recipient of the transfusion or mislabeling the blood. Treatment consists of stopping the

transfusion and using supportive care as necessary. The authors stated that evidence is insufficient to recommend interventions such as red cell or plasma exchange, intravenous immunoglobulin, or complement-inhibiting drugs. The authors added that delayed hemolytic transfusion reactions are most common in patients with sickle cell disease.

Acute hypotensive reactions are encountered mostly in patients who are taking angiotensin-converting enzyme inhibitors for hypertension. The mechanism of these reactions is through the production of bradykinin caused by activation of the coagulation cascade. Hypotensive reactions have occurred during cardiopulmonary bypass and radical prostatectomy procedures; transfusion cessation and supportive care are the mainstays of management.

Prolonged storage of blood may cause febrile acute transfusion reactions, which may be mediated by leukocytes and platelets. Prolonged storage is also associated with changes such as increased plasma iron levels, increased cell-free DNA, and increased cellular vesicles. The duration of storage is related to the degree of these changes. The topic of possible harm due to transfusing older blood was the focus of an article by Heddle and coauthors² in the *New England Journal of Medicine*, 2016. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors indicated that the transfusion of older units of banked red blood cells in patients with few risk factors for infection has been associated, in observational studies, with an increased risk of infection and mortality. They reported a randomized, prospective trial conducted in six hospitals. Outcomes data were available from more than 20,000 patients. Overall, in-hospital mortality was 9% and did not differ in patients transfused with older blood compared with those who received blood stored for short intervals (13 days or less). The authors concluded that in-hospital postoperative mortality was not influenced by the age of transfused blood. In an editorial that accompanied this article, Tobiasian and Ness³ pointed out that current available data do not indicate an association between the age of transfused blood and an increased in-hospital mortality risk. They stressed, however, that the available data do not provide guidance on the possible harm of blood transfusions using blood products during the last week of storage. Recent

clinical practice guidelines promulgated by the AABB⁴ state that blood at any point within the licensed storage interval can be utilized for transfusions.

The immunomodulatory actions of stored blood are thought to affect postoperative outcomes. Aside from the influences of the underlying disease (malignancy, cirrhosis) that create the need for operation, both the technical difficulty of the operation that influences the need for and volume of transfusion and the specific effects of transfusion have been challenging to researchers seeking to quantify the immunomodulatory effects and possible harms of perioperative transfusions. Associations of transfusion and adverse outcomes have been published frequently in the surgical literature but establishing causation has not been achieved.

Smilowitz and coauthors⁵ evaluated the association of transfusion with adverse postoperative outcomes in the *American Journal of Medicine*, 2016. They obtained long-term follow-up data (5–7 years) on more than 3,000 patients who underwent orthopedic procedures. They found that transfusion was associated with an increased risk of long-term mortality, but this risk was attenuated when adjustments for preoperative anemia and volume of blood loss (perhaps indicative of the operation's difficulty) were made. The authors concluded that reducing perioperative transfusion is indicated, but measures to reduce perioperative blood loss and preoperative anemia are equally or perhaps more important.

The association of blood transfusion and operative outcomes for one major surgical procedure, liver transplantation, was the focus of an article by Rana and coauthors⁶ in the *Journal of the American College of Surgeons*, 2013. The authors conducted a single-center retrospective review of liver transplantation performed for a variety of disease processes. Disease severity varied widely in the patients reviewed. The analysis included outcomes data on 233 patients seen over an interval of three years. All operations were performed by a single surgical team. The authors identified the preoperative diagnosis of hepatocellular carcinoma and intraoperative blood transfusion volumes as discrete risk factors for increased mortality. Hepatocellular carcinoma was a risk factor for medium- and long-term mortality because of recurrence of disease during follow-up. Blood transfusion was a risk factor for short-term mortality and the mortality risk increased by

1% for each unit of blood administered. Interestingly, an elevated serum bilirubin, a history of prior operation, and prolonged recipient hepatectomy time were significant risk factors for the need for intraoperative transfusion. This observation suggests that the severity of the underlying liver disease and the technical difficulty of the operation contribute significantly to the need for transfusion. It is possible, therefore, that the worse outcomes observed in patients who received larger transfusion volumes are markers of disease severity.

Blood transfusions' immunomodulatory effects have been thought to contribute to early recurrence and/or the development of metastatic disease after cancer resections. Harlaar and coauthors⁷ reported long-term outcomes data on patients who received a banked blood transfusion or an autologous blood transfusion during operations for colorectal cancer resection in *Annals of Surgery*, 2012. The authors reported 20-year outcomes data on 423 patients from a randomized, prospective trial comparing outcomes after curative colorectal cancer resection in patients who received autologous blood transfusion. Follow-up data were available for 94% of the patients originally enrolled in the prospective trial. The analysis showed that outcomes at four years after operation were worse for patients who received any type of blood transfusion compared with patients who received no transfusion. At 20 years of follow-up, patients with donated autologous blood transfusion had reduced overall and cancer-specific survival compared with patients who received no transfusions or banked blood transfusions. The authors hypothesized that the anemia produced by autologous blood donation may have contributed to tissue hypoxia that could have produced accelerated growth of residual tumor cells, resulting in metastatic disease occurring more in the anemic patients. While the reported data are insufficient to settle the question of the impact of blood transfusion on the risk of adverse outcomes, the authors suggested an effect of blood loss and blood replacement on short-term outcomes. The reason for the increased mortality risk for patients who donated autologous blood was not completely elucidated.

Transfusion-Related Disease Transmission

Delaney and coauthors¹ cited data suggesting that up to 75,000 septic blood transfusion reactions occur, worldwide, every year. Presenting symptoms included fever, rigors, and hypotension. They recommended evaluating all recently transfused units if a patient develops signs of sepsis. After obtaining cultures of blood and intravenous lines, broad-spectrum antimicrobials with efficacy against *Pseudomonas sp.* are indicated.

An older article that presented data on disease transmission from transfusion was by Goodnough⁸ in *Critical Care Medicine*, 2003. The author began by explaining that the rarity of serious transfusion reactions and transfusion-related disease transmission has made it difficult to estimate transfusion risks. Mathematical models have been developed to predict transfusion risks and these models assume that disease transmission is most likely to occur when blood from infected donors is collected in the "window period" when the donor is infectious, but donor-screening tests are not positive. This assumption may lead to underestimating disease transmission risk. Another potentially hazardous assumption is related to the fact that patients who receive blood have 1- and 10-year mortality rates ranging from 24% to 52%; these patients may not survive long enough for the disease transmission to be diagnosed. Despite these limitations, Goodnough emphasized that the risk of transmitting viral diseases (mainly hepatitis B and C and human immunodeficiency virus) are lower than at any time in the history of transfusion. The author cited data indicating a risk of hepatitis transmission of 1 out of 220,000 transfusions to 1 out of 800,000 transfusions; the risk of human immunodeficiency virus transmission is 1 out of 1.4 million transfusions. Available data show that these risks continue to decline with improved donor screening practices, particularly the recently implemented practice of nucleic acid testing.

Goodnough next discussed specific aspects of viral disease transmission. He cited the first documented instance of human immunodeficiency virus transmission through banked blood as occurring in 1982, before screening blood tests were available. Following documentation of disease transmission caused by infected blood products, blood banks began screening donors for specific characteristics and allowing donors to self-exclude their blood

after donation. This practice resulted in an immediate decline in disease transmission. With the implementation of antibody testing in March 1985, the rate of reported transmissions of human immunodeficiency virus decreased from more than 700 per year to five per year. Additional small increments of progress occurred after the introduction of screening for p24 antigen.

Hepatitis B virus transmission declined markedly after the introduction of third-generation tests for the hepatitis B surface antigen. Hepatitis B currently accounts for only 10% of the instances of hepatitis transmission in transfused blood products.

Hepatitis C is an important viral disease that can be transmitted via transfusion. Transfusion-related hepatitis C leads to chronic disease in more than 80% of cases and 20% of infections progress to cirrhosis; 1%–5% of infections lead to hepatocellular carcinoma. The mortality risk for hepatitis C over 25–30 years after transfusion-related infection is nearly 15%.

Screening for human immunodeficiency and hepatitis viral disease is very effective. Goodnough cited data indicating that worldwide, since 1999, only two cases of human immune deficiency virus infection and one case of hepatitis C have been reported to be caused by transfusion-related transmission.

Cytomegalovirus infection, related to transfusion of blood products, is an important cause of mortality and morbidity in patients immunocompromised from treatment for malignant disease. The largest risk is observed in patients undergoing stem cell or bone marrow transplantation. The prevalence of cytomegalovirus infection in these patient groups is 60% and overt viral disease develops in up to one-half of the infected patients. Risk for disease can be reduced, but not eliminated, by using transfusions of blood cells from donors with negative serum tests of cytomegalovirus infection. The author cited data to show that granulocyte transfusions from serum-negative donors resulted in seroconversion in 1%–4% of patients.

Other data cited by the author indicated that the risk of infection is not different with cells originating from donors who are positive for cytomegalovirus infection compared with negative; however, the risk of clinically overt viral disease seems to be less when negative donor cells are used. Cytomegalovirus infection is much less common in patients who undergo autologous stem cell or

bone marrow transplantation. This protection is observed despite equivalent rates of serum assay conversion and urinary excretion of viral products in patients undergoing allogeneic or autologous bone marrow transplantation. Goodnough disclosed that 10%–50% of blood donors test negative for cytomegalovirus infection. Leuco-reduction also seems to reduce the risk of cytomegalovirus infection. Current recommendations state that patients receiving allogeneic or autologous bone marrow transplants should receive blood products donated by serum-negative patients; these products should also undergo leuco-reduction.

Bacterial infection of banked blood products can cause rare but often fatal sepsis in patients who receive a transfusion. *Yersinia enterocolitica* is the most common pathogen infecting red blood cell units. The contamination rate is less than 1 per million donated units, but clinical infection may become manifest during the transfusion and the mortality rate for clinical infection is 60%. Platelets carry the greatest risk for bacterial infection because these units are stored, for up to five days, at temperatures of 20–24°C. This means that stored platelets are an excellent culture medium for bacteria. Goodnough cited surveillance data indicating that bacterial contamination occurs in 1 of every 1,000–2,000 units. Because 4 million platelet units are transmitted annually in the United States (25% of these are apheresis platelets), estimates are that 300–1,000 cases of bacterial sepsis may be expected each year. Pooled platelets carry a higher risk than apheresis platelet transfusions. Liquid medium culturing of platelets has been implemented in an effort to reduce the risk of infection.

Other infectious diseases that can potentially be transmitted by blood products include leukemia caused by human T-lymphotropic viruses, type I (HTLV-I) or type II (HTLV-II). Only a single case had been reported at the time of publication of Goodnough's article. Blood products can potentially transmit Epstein-Barr virus disease, leishmaniasis, babesiosis, toxoplasmosis, brucellosis, malaria, Chagas disease, West Nile virus, and prion disease, but such instances are extremely rare.

Current Transfusion Practices

The most recent practice guidelines for the use of blood and blood products in the perioperative period were developed and promulgated by the American Society of Anesthesiologists in 2006. A summary of the practice guidelines was presented in a report published in *Anesthesiology* in 2006.⁹ The guidelines reviewed practical measures for detecting patients who might require blood or blood products. The initial evaluation should include, at a minimum, a review of medical records, a detailed history focusing on historical evidence of congenital disorders of coagulation, hemoglobinopathy, and other blood disorders. Additional findings in the history should provide information on the risk of ischemic cardiac disease, history of prior transfusion, and any history of use of prescription drugs, over-the-counter drugs, or herbal remedies that alter coagulation. The history should also include evidence of prior exposure to drugs (aprotinin) that could precipitate an allergic reaction on repeat administration. Recommended laboratory assessments include hemoglobin and hematocrit determinations and a coagulation profile. Both the patient and their family's willingness, or lack of willingness, to accept blood transfusions should be documented. Managing patients who refuse blood products will be discussed in a later section of this issue.

The guidelines state that specific evidence to support use of drugs such as aprotinin, epsilon-amino caproic acid, and tranexamic acid (which is a synthetic modification of the amino acid lysine that blocks the interaction of plasminogen and fibrin and, therefore, prevents clot lysis) is lacking except for certain cardiac or orthopaedic procedures associated with a significant risk of bleeding, such as repeat open cardiac procedures and reoperation for joint replacement. According to the guidelines, anti-fibrinolytic drugs have been implicated in vascular graft thrombosis and severe allergic reactions have resulted from aprotinin use. Later in this review, we will discuss the use of tranexamic acid as a component of resuscitation strategies for patients at risk for shock-associated coagulopathy.

Documentation of the value of preoperative erythropoietin treatment of anemia is not available, although certain patient groups, such as patients with renal disease, anemia of chronic disease, and patients who refuse transfusion, may benefit. Several weeks of treatment are required for correction of anemia using erythropoietin. The

guidelines state that preoperative collection of autologous blood has been associated with reduced transfusion risks. The guidelines document emphasizes, however, that programs using preoperative collection of autologous blood have reported severe transfusion reactions (associated with misidentification of patients) and bacterial infections.

The guidelines recommend cessation of drugs such as warfarin, aspirin, and clopidogrel before elective operations. Intervals of one to three weeks are required to reverse the effects of clopidogrel and aspirin on platelets. The method chosen for preoperative restoration of clotting function depends on a careful assessment of the type, urgency, and risk of the surgical procedure chosen. The guidelines also assess the thromboembolic complication risk that might occur soon after the chronic warfarin dose is decreased or eliminated. Modules that deal with the perioperative management of patients who are taking drugs that interfere with coagulation and patients with indwelling coronary stents are available for review on the American College of Surgeons Evidence-based Decisions in Surgery website at ebds.facs.org.

The decision to transfuse before, during, and after an operation is based on clinical assessments of the volume of blood loss and the physiologic effects of blood loss. Monitoring of ongoing blood loss requires clear and frequent communication between the surgical team and the anesthesiology team. The use of assessments of blood pressure, heart rate, arterial oxygen saturation, central venous pressure, pulmonary artery occlusion pressure, central venous (or mixed venous) oxygen saturation, and lactate levels depend on the type of operation and the patient risk. For patients with a history of cardiac dysfunction, intraoperative echocardiography may be indicated.

The practice guidelines state that assessing blood pressure, heart rate, and arterial oxygen saturation is routine during surgical procedures, but the literature is unclear about the specific contributions these assessments make regarding the need for transfusion. A synthesis of various information points will usually be required to support clinical decisions. Intraoperative measurement of hemoglobin and hematocrit is common, but these values may not reflect end-organ perfusion status. The guidelines state that transfusion is not needed in stable patients who do not have cardiac disease until the hemoglobin level is below 6 g/dL. Transfusion is definitely not needed when the hemoglobin level is above 10 g/dL.

The decision to transfuse patients whose hemoglobin levels are between 6 g/dL and 10 g/dL is made based on the assessment of each patient's cardiovascular reserve, the risk of ongoing blood loss, and the status of end-organ perfusion. Hebert and coauthors¹⁰ documented the safety of lower hemoglobin levels in stable, critically ill patients in a 1999 report. An appreciation of the risks of transfusion and an understanding of the limitations of the blood supply has stimulated caution and overall conservatism about using banked blood and blood products. The benefits of a conservative approach to transfusion are most obvious in patients under the age of 55 who have no clinical evidence of cardiovascular disease. The clinical practice guidelines promulgated by the AABB⁴ recommend careful clinical evaluation of the patient and determination of the appropriate hemoglobin level for transfusion based on the evaluation of each individual patient. For stable patients, a hemoglobin level of 7 g/dL is recommended and a level of 8 g/dL is recommended for patients with comorbid conditions or patients undergoing procedures associated with significant blood loss.

We will highlight coagulopathy from massive transfusion later in this review. The practice guidelines supported the use of blood, platelets, and fresh frozen plasma for this condition as well as cryoprecipitate for the support of fibrinogen levels. Recombinant activated factor VII may be useful as “rescue therapy” for patients with microvascular bleeding. The American Society of Anesthesiologists guidelines⁹ stated that measures such as normovolemic hemodilution and deliberately lowered venous pressures may be helpful in selected patients undergoing cardiac, hepatic, and orthopedic procedures.

Techniques of Perioperative Blood Salvage

Blood recovery and reinfusion during and/or after an operation is potentially a means of reducing the use of blood and blood products in surgical patients. Collection and reinfusion of blood after tube thoracostomy for traumatic hemothorax has been shown to be safe, but blood salvaged from thoracostomy tube drainage has been shown to be deficient in platelets and clotting factors.

The recovery of postoperative blood drainage from the operative site is possible using closed drainage systems that collect blood through a filtration system into a blood ad-

ministration bag. This approach has been used in Europe and is especially well suited for patients undergoing orthopedic procedures. An article that described the potential value of postoperative blood salvage was by Mirza and coauthors¹¹ in the *Annals of the Royal College of Surgeons*, 2007. The authors reported results in 109 patients undergoing total hip replacement. The amount of perioperative blood loss (as indicated by the change in hemoglobin level) in these patients was compared with a group of historical control patients. Patients who had blood salvage had a smaller perioperative hemoglobin drop. Nine percent of the salvage patients required perioperative transfusion of banked blood compared with 30 percent of the historical control group. The authors concluded that this approach may reduce the use of banked blood in patients undergoing operations associated with predictable postoperative drainage of uncontaminated blood.

Management of Patients Who Refuse Blood & Blood Products

Surgeons inevitably will encounter patients who decline all or some parts of proposed strategies for care of surgical conditions. The use of blood and blood products is unacceptable to some patients. Typically, this patient group includes, but is not limited to, Jehovah's Witnesses. A significant body of knowledge has accumulated that has permitted safe surgical care for Jehovah's Witnesses and this knowledge can be used to optimize the care of any patient who declines the use of blood and blood products. In this section, we will discuss two articles that focus on the elements of care for Jehovah's Witnesses.

Hughes and coauthors¹² discussed this topic in the *Journal of Trauma*, 2008. The authors began by providing background on the origins and development of Jehovah's Witnesses. Hughes and coauthors explained that the group evolved from a Bible study group formed by Charles Taze Russell in Alleghany, Pennsylvania, in 1869. Based on extensive study, the group identified what they perceived as fundamental errors in interpretations of biblical text. This group's interpretation led to the belief that there were philosophical errors in the practice of Christian doctrine. The literal interpretations of scripture by the group evolved into commands. Obedience to these commands, in the eyes of the adherents to this doctrine,

was required for any chance of life after death. In 1879, the group was known as “Bible Students” and the group produced a religious magazine later called *The Watchtower*. In 1931, the group adopted the name “Jehovah’s Witnesses.” Currently, this is the fastest growing religion in the Western world, with nearly 7 million members; in the United States, more than 1 million members are enrolled. The organization is based on a person-to-person ministry and is recognized for their work promoting literacy and disaster relief. Each member must commit a certain amount of time each month to the ministry. Fundamental to their beliefs is the recognition that God’s kingdom is the only legitimate government. Thus, members do not join service organizations or serve in the military; they remain politically neutral.

The rejection of blood transfusion was codified in the belief system of Jehovah’s Witnesses in 1945. The belief is based on the literal interpretation of several Old Testament passages that prohibit the eating of food that contains blood. In 1951, an article in *The Watchtower* cited the use of intravenous fluids in hospitals as “intravenous feeding” and declared that the intravenous administration of blood was equivalent to the “feeding” of blood and was, therefore, unacceptable based on the interpretation of Old Testament text. Hughes and coauthors noted that this prohibition has been interpreted to extend to the use of banked blood, blood cells, plasma, and platelets. Pre-operative autologous blood donation is prohibited because the blood is separated from the body. This interpretation permits the use of intraoperative blood salvage as long as the collection circuit is continuous with the administration device so that the separation of the blood from the patient’s body does not occur.

In 2000, the Watch Tower Society issued a statement that Jehovah’s Witnesses would no longer excommunicate members who accepted transfusion. Instead, the member would be judged to have voluntarily given up membership based on having accepted a blood transfusion. Hughes and colleagues also emphasized that there is variability among Jehovah’s Witnesses about the acceptability of blood derivatives. Some adherents will accept albumin, immunoglobulins, and factor concentrates. Recombinant erythropoietin may also be accepted. In addition, some Jehovah’s Witnesses do not believe they have committed

an act requiring them to leave the organization if the agreement to accept a transfusion is made privately with the treating physician or surgeon. In such circumstances, patient confidentiality is obviously critical. Against this approach is the frequent physical presence of a Jehovah’s Witnesses member, who is in the care area to ensure that the treated member does not receive a transfusion or any unacceptable blood product.

It is important that surgeons decide, ahead of time, whether they will be able to accept the fact that the patient may not accept a transfusion. The surgeon will need to reconcile the patient’s wishes with the possibility that a “preventable” death may occur if a transfusion is withheld. Acceptable arrangements for transferring the patient’s care to an alternate surgeon may become necessary. Hospital resources are available for both patients and treating surgeons: ethics committees, risk management groups, and transfusion medicine specialists are potentially valuable. In many cities, Jehovah’s Witnesses groups offer consultative advice for patients and treating surgeons.

Legal aspects of the care of Jehovah’s Witnesses are grounded in the 1914 legal decision that established the right of patients to refuse treatment. The patient should confirm, in writing, their decision to exercise this right, particularly a Jehovah’s Witnesses member. Many Jehovah’s Witnesses carry an advance directive document with them at all times and Hughes and associates stressed the importance of making this knowledge known to all caregivers; thus, the medical record should display, predominantly, the wishes of the patient. It is worth mentioning that many court decisions have determined that parents do not have the right to refuse transfusions for their children. The ability of adolescents, or mature minors, to refuse a transfusion is less clear and rulings have varied depending on the jurisdiction. Surgeons will need to consult hospital risk management and counsel for assistance in dealing with these issues.

Where time permits a full discussion of the risks and benefits of an operation, formal informed consent will be possible. The decision to proceed with treatment when the informed consent discussion has not occurred is challenging and evidence-based guidelines to support the decision process are not available. The presence of an advance directive card does not preclude the necessities of obtaining informed consent or proceeding with needed

treatment in emergencies where informed consent cannot be obtained. This means that the decision to transfuse, or to withhold a transfusion for a Jehovah's Witnesses patient, in an emergency may be viewed, in retrospect, as a basis for legal action against the surgeon and/or hospital. To manage Jehovah's Witnesses patients in emergencies, early knowledge of the patient's religious beliefs is necessary. This information should be actively sought and made available to all caregivers; Hughes and colleagues cited data from a Level I trauma center indicating that this necessary knowledge was frequently not obtained. In this analysis, 5% of the Jehovah's Witnesses patients received transfusion, but in only one case was this reasonably preventable.

Data about outcomes of injured Jehovah's Witnesses patients have not shown an increased risk of death from injury in this group. Earlier decisions for an operation have been consistently observed in studies of the management of injured Jehovah's Witnesses patients. In elective surgery patients, measures to prevent bleeding and evidence-based operative approaches have resulted in improved outcomes for Jehovah's Witnesses as indicated in data cited by these authors. Additional data have shown that postoperative anemia (hemoglobin level of 6 g/dL) did not predict mortality or morbidity. While data indicating an increased risk of mortality have been reported for patients with chronic severe anemia, anemia, in this setting, has been interpreted as evidence of increased overall risk.

Hughes and colleagues explained that the surgical management of Jehovah's Witnesses should include measures to minimize iatrogenic blood loss (phlebotomy), minimize intraoperative blood loss (hemodilution, intraoperative blood salvage), enhance red blood cell production, ensure hemostasis, and maintain blood volume with electrolyte and/or colloid solutions. Protocols for the elective management of Jehovah's Witnesses have avoided transfusion without increasing operative risk. In *Archives of Surgery*, 2006, Jabbour and coauthors¹³ reported on the effectiveness of a transfusion-free program for the conduct of orthotopic liver transplantation in Jehovah's Witnesses. The authors compared patients treated by a formal protocol approach to transfusion avoidance to a group of historic controls. The protocol stressed the maintenance of low venous pressure, use of acute normo-

volemic hemodilution, and intraoperative blood salvage. These authors acknowledged that their protocol group was sicker, as judged by MELD scores, than the nonprotocol historic controls. Despite this, there was no operative mortality increase in the transfusion-free patients. These data indicate that avoidance of transfusion in complex elective surgery is safe when a protocol approach is used.

Shock Due to Hemorrhage & Trauma

Hemorrhagic shock is encountered in most types of surgical practice. This section will focus on the pathophysiology and management of this condition as well as derangements in homeostasis that are unique to traumatic/hemorrhagic shock.

The basic features of the pathophysiology of shock were described in an article by Cestero and Dent¹⁴ in *Surgical Clinics of North America*, 2015. The authors stressed that the physiologic state that defines all forms of shock is a failure of oxygen supply to meet tissue demand. This leads to a series of compensatory changes that vary depending on the etiology of the shock state (hemorrhage/trauma, sepsis, cardiogenic). Failure of compensatory mechanisms will predictably occur if necessary interventions to remedy the abnormalities that are causing the shock state are not available or are inadequate; decompensated shock follows with loss of vascular tone and cardiac contractility, increasing severity of acidosis, development of hypothermia, and death.

Traditionally, shock from hemorrhage and trauma has been thought to proceed sequentially through stages of compensation that include a phase of catecholamine-mediated vasoconstriction and redistribution of blood volume toward the brain and heart and away from skeletal muscle, kidneys, and splanchnic circulation. During this phase, movement of proteins, water, and ions from the extracellular fluid space into the intravascular space provides partial refilling of the volume lost to bleeding. This response, coupled with catecholamine-mediated vasoconstriction, serves to support blood pressure. Vasoconstriction

tion in small- and medium-sized vessels may limit blood loss. If there is a large area of retained nonviable tissue (mangled extremity) or if large arteries and/or veins are injured, bleeding will continue, albeit at a slower rate.

The patient will then enter a subsequent phase of partial compensation where they are mildly to moderately hypotensive; this is followed, within a variable interval, by a final decompensatory phase characterized by systemic vasodilation, bradycardia, and death. The duration of these two phases is determined mainly by the rate and volume of continued bleeding. The phase of partial compensation has been envisioned as a phase wherein autoregulation of vascular beds fails and tissue blood flow becomes pressure dependent. During this phase, cellular hypoxia is thought to lead to disordered mitochondrial function and a shift to anaerobic metabolism. Accumulation of acid metabolites and lactate are evidence of these phenomena. As partial compensation proceeds to decompensation, cell membrane function fails with movement of water and ions from the extracellular space into the intracellular space. During these final two phases, consumption of clotting factors at sites of vascular injury, dilution of clotting factors as a result of resuscitation with fluids deficient in clotting factors, activation of the inflammatory cascade, and the creation of diffuse microvascular thrombosis contribute to the development of shock-related coagulopathy. This state is characterized by emergence of the “lethal triad” of acidosis, hypothermia, and diffuse microvascular bleeding.

Beginning in the Korean War and continuing into the current conflicts in Iraq and Afghanistan, lessons learned from combat casualty care experiences have stimulated research into injury care. An early understanding emerged from these experiences: unless bleeding was controlled and oxygen delivery to tissues restored, decompensation could not be reversed. Spinella and coauthors¹⁵ summarized the recent lessons learned in combat casualty care that have led to efforts to control bleeding and reverse elements of the decompensatory phases of shock (mainly hypothermia and coagulopathy) in the prehospital phase of care; this article was published in the *United States Army Medical Department Journal*, 2016. Data cited by the authors show that 90% of deaths from combat injuries occur in the prehospital phase of care and that 25%

of these deaths are potentially preventable. Hemorrhage is the most common cause of death in the preventable death group. These observations have stimulated efforts to apply interventions to stop bleeding and to begin resuscitation with blood, plasma, and platelets during the prehospital phase of care in order to avoid decompensation and shock-related coagulopathy. The authors observed that hypotensive resuscitation (see later discussion) can potentially avoid adverse effects that occur when infusion of large volumes of crystalloid is used to support “normal” arterial pressure. Systolic arterial pressure targets of 80–90 mm Hg were used and data cited by the authors showed that patients with penetrating torso trauma and evacuation times of less than 30 minutes had improved survival with hypotensive resuscitation compared with patient managed with resuscitation protocols that used normalized arterial pressure as a treatment target. The authors emphasized, however, that data to support the use of hypotensive resuscitation when evacuation times are longer are not available. Potential risks of hypotensive resuscitation when evacuation times are longer include reduced cardiac output and decreased blood oxygen content. The authors recommended using this approach cautiously when longer evacuation times are unavoidable. Prehospital use of hemostatic resuscitation (whole blood, platelets, and plasma) is possible in combat injury care due to the development of universal donor (low anti-A, anti-B Group O) blood stored at 4°C, freeze-dried plasma, and platelets obtained by apheresis and stored at 4°C.

The concept of “damage control” for patients with severe injuries associated with massive blood loss was developed to manage patients with torso injuries and severe hemorrhaging. As combat casualty care has developed, this concept has been extended to include patients with severe lower extremity, pelvic, and perineal injuries that result from encounters with improvised explosive devices (IED). The objectives of damage control approaches are to achieve hemostasis and control contamination using preoperative interventions such as tourniquet application and hemostatic dressing application. In the in-hospital phase of care, resuscitation is combined with an abbreviated operation to avoid the “lethal triad” and improve the chances of patient survival. The physiologic construct described above has, over an extended period of time be-

ginning with the Vietnam War, driven the development of treatment protocols for shock based on early identification of bleeding sites and control of hemorrhage, replacement of red blood cells, and replacement of volumes of electrolyte solution calculated based on expected losses from the extracellular fluid. Among the major features of the current understanding of shock and resuscitation that have recently undergone modification include the concept that shock and trauma-related coagulopathy begins early after injury, therefore, early resuscitation may need to include both red blood cell replacement and replacement of clotting factors. Based on research conducted during the care of combat casualties, use of “hemostatic” resuscitation and massive transfusion protocols has progressed and these approaches are currently used to care for civilian trauma center patients who present with severe injuries, shock, and ongoing bleeding.

In addition, basic and clinical research has led to an understanding that patients with compensated and partially compensated shock have expected losses of extracellular fluid smaller than those calculated on the basis of experimental evidence from models of severe, decompensated shock. It is also now clear that restoring effective tissue perfusion pressure and oxygen delivery are the most important resuscitation targets—and that restoration of arterial pressure to “normal” is not necessary.

Finally, abundant clinical and experimental research has confirmed that severe injury and hemorrhagic shock may predispose susceptible patients to multiple organ failure. The traditional understanding of postshock multiple organ failure was that the original injury/shock insult set the stage for multiple organ failure and a “second hit,” usually an infection, precipitated organ failure. Advanced prehospital care, trauma systems, and advanced resuscitation techniques have led to new understandings of the sequence of events leading to multiple organ failure. This topic was discussed in an article by Minei and coauthors¹⁶ in *Critical Care Medicine*, 2012. The authors used patient data from the prospectively collected multi-institutional database associated with the Inflammation and the Host Response to Injury collaborative research program. Strict definitions of organ failure and infection were used and standard care protocols were employed in all participating centers. The authors used standard multiple organ failure scoring systems to detect the onset and course of organ

failure. The analysis showed that multiple organ failure became evident within the first 48 hours after injury. Organ failure was more likely to occur in older patients, patients with severe injury, and patients with comorbid conditions, especially liver disease. The evidence of organ failure declined over the first week after admission. If evidence of multiple organ failure persisted, as determined by cumulative organ failure scores, mortality risk increased. The authors hypothesized that stricter definitions of infections such as pneumonia and adherence to standard diagnostic and treatment protocols contributed to the changed pattern of multiple organ failure observed in their patients. They also emphasized the influence of newer approaches to resuscitation that aim to minimize the risk of coagulopathy and restrict the volume of electrolyte solutions used during resuscitation.

Additional research on cellular mechanisms that contribute to the pathophysiology of shock has focused on the role of the endothelium in the development of shock-related coagulopathy. Chang and coauthors¹⁷ reviewed this topic in *Blood*, 2016. Early observations of the relationship between prolonged uncontrolled bleeding and coagulopathy were recorded during the Vietnam War. Subsequent studies have shown that most traumatic hemorrhage can be controlled with compression, angioembolization, and/or vascular repair. When early control of bleeding is not accomplished, coagulopathy becomes a major cause of continued hemorrhage and clinical deterioration.

Activated protein C is a contributor to hemorrhage-related coagulopathy. Protein C is activated by binding to endothelial receptors; the activated form inactivates factors Va and VIIIa in the coagulation cascade. This factor also contributes to fibrinolysis. Activated protein C is cytoprotective by virtue of activation of anti-inflammatory and antiapoptotic cell signaling. Data cited in the article show that patients with prolonged hypoperfusion and high injury severity scores are most likely to develop coagulopathy due to activated protein C. The authors emphasized that mechanisms of coagulopathy that develop after injury are complex. Certain forms of injury (traumatic brain injury, pulmonary contusion) can result in coagulopathy in the absence of hypoperfusion. Recent research has disclosed evidence of a major role of the endothelium in the development of injury-related coagulopathy. Activation of endothelial cells can be caused by the cells' exposure

to catecholamines and inflammatory mediators such as tumor necrosis factor. Activation of the endothelial cell glycocalyx layer contributes to a procoagulant state. One possible hypothesis is that coagulopathy develops as mechanisms are activated to counter the procoagulant state in an effort to preserve microvessel patency and maintain tissue perfusion. The authors found that “shedding” of components of the glycocalyx layer results in increases in two anticoagulant factors, chondroitin sulfate and heparan sulfate. As these components increase due to shedding, a coagulopathic environment is created.

Frith and coauthors¹⁸ presented additional data suggesting that coagulopathic changes can be detected early after injury before prolonged bleeding leads to hypoperfusion in *Current Opinion in Anesthesiology*, 2012. Data cited by the authors indicate that abnormalities of coagulation can be detected in the prehospital phase of care and that these are more common in severely injured patients and in patients with hypotension and increased lactate levels. The authors hypothesized that early onset coagulopathy contributes to ongoing bleeding in injured patients. They reviewed a number of studies that have shown improved outcomes with early administration of red blood cells, plasma, and platelets. Data from these studies provide evidence of hyperfibrinolysis and endothelial disruption as major mechanisms of trauma-related coagulopathy. The authors indicated that data to support a critical deficiency of platelets and plasma factors are not available. They proposed the interesting hypothesis that the effectiveness of platelet and plasma infusion may not be due to replacement of depleted factors, but factors that have been deactivated by the coagulopathic process. Data presented in the article confirm the value of point-of-care thromboelastography for the early diagnosis of coagulopathy. These tests can detect coagulation abnormalities that arise from hyperfibrinolysis as well as dysfunction of plasma and platelets. Early diagnosis can guide the implementation of massive transfusion protocols and the use of antifibrinolytic agents such as tranexamic acid.

The contribution of genomic changes to outcomes in patients with injury and shock was the focus of an article by Cuenca and coauthors¹⁹ in *Critical Care Medicine*, 2013. The authors performed rapid genomic analysis on blood samples of 167 injured patients. The genomic patterns were used to construct a score to predict a com-

plicated vs. a noncomplicated clinical course. A complicated clinical course was defined as a multiple organ failure score >6 and a recovery time of >14 days. The analysis showed that the genomic score was a moderately strong predictor of a complicated course (area under the receiver operating characteristic [ROC] curve of 0.811). The authors concluded that genomic scoring may be useful for predicting outcomes in severely injured patients. The authors hypothesized that these data could be used to define populations that would be candidates for prospective clinical trials of therapies for injury and multiple organ failure. In an editorial that accompanied this article, Abraham²⁰ stressed the potential value of this approach but urged caution, since the scoring system was developed and tested in the same group of patients. He added that the altered genomic patterns could be a reflection of either altered genetic patterns or altered cell populations in the samples used. Further research will be needed to refine these observations and develop clinically useful approaches based on genomic patterns.

Current understandings hold that splanchnic ischemia leads to the movement of substances into intestinal lymph and that these substances contribute to the creation of a proinflammatory state and progression to multiple organ failure in patients who are genetically susceptible to the development of dysfunctional systemic inflammatory responses. In this section, we will review some of the research and clinical data that have contributed to the current understanding of the mechanisms of the proinflammatory state following shock from hemorrhage and trauma.

Peltz and coauthors²¹ used a murine shock model and examined the pattern of proteins present in lymph draining from the intestine in *Surgery*, 2009. There were significant alterations in the patterns of proteins present in lymph from shocked animals. Low levels of haptoglobin recovered in lymph from shocked animals suggest the activation of a hemolytic process. There was an increase in the number of intracellular proteins, suggesting that significant cell damage occurred in the intestines of shocked animals; the increase in alpha-enolase and actin possibly indicated the activation of the coagulation mechanism and simultaneous endothelial damage. Of interest is that several androgen-related proteins were also increased. The authors concluded that evaluating the protein pattern

of intestinal lymph may illuminate the mechanisms of remote organ damage and identify possible therapeutic targets.

A potential means of reducing shock-induced damage to the intestine is with direct peritoneal resuscitation using peritoneal dialysis fluid. Matheson and coauthors²² presented research on the flow and composition of mesenteric lymph in a study of rodent hemorrhagic shock in *Archives of Surgery*, 2009. Earlier work by these authors had demonstrated endothelial swelling leading to reductions in intestinal microvascular flow. Conventional resuscitation did not prevent this phenomenon, but reductions of cell swelling with direct peritoneal resuscitation combined with conventional resuscitation preserved intestinal microcirculatory flow. In this experiment, the authors hypothesized that preservation of intestinal microvascular flow would alter intestinal lymph flow and composition. They were able to demonstrate increased mesenteric lymph flow with shock and resuscitation. Increased levels of lymph hyaluronic acid and proinflammatory cytokines were observed, with shock treated by conventional resuscitation. Direct peritoneal resuscitation added to conventional resuscitation preserved intestinal microvascular flow and function. Mesenteric lymph flow was restored to normal and cytokine levels were returned to control levels by treating rodent hemorrhagic shock with the combination of conventional and direct peritoneal resuscitation.

Matheson and coauthors documented a logical mechanism for cellular dysfunction and reduced intestinal blood flow; they have also explained the mechanisms of cellular swelling, reduced tissue blood flow, and elaboration of proinflammatory cytokines from the gut. In other experiments, the authors showed that skeletal muscle cell swelling and fluid sequestration occur. These experiments confirm the existence and the magnitude of fluid shifts in profound shock and the authors proposed a plausible link between mesenteric ischemia and postshock inflammation. This same group of investigators showed that direct peritoneal resuscitation improves hepatic inflammation produced by hemorrhagic shock in a rodent model.²³ Matheson and coauthors also extended this line of research into the clinical arena and showed that direct peritoneal resuscitation shortens the interval required for complete abdominal wall closure after damage control

laparotomy.²⁴ In another report,²⁵ they confirmed that direct peritoneal resuscitation improves hepatic dysfunction in obese injured patients. A recent clinical study from this group showed that direct peritoneal resuscitation improved function in livers obtained from deceased organ donors.²⁶

The question of whether lymph draining from other tissues rendered ischemic during shock would also cause cellular changes consistent with multiple organ failure was the topic of several reports by Diebel and coauthors.²⁷⁻²⁹ These authors showed that lymph gathered from a skeletal muscle bed two hours after shock in a canine model led to acute lung cell injury and neutrophil priming. Taken together with the research described earlier, it seems likely that lymph from tissue rendered ischemic during shock can cause transfer of cytotoxic substances into the general circulation. These toxic molecules are capable of producing tissue damage in remote sites that could lead to multiple organ failure. Whether these mechanisms are active in human shock requires further clarification.

Additional data from a study by Morishita and coauthors³⁰ in the *Journal of Trauma and Acute Care Surgery*, 2012, indicated that toxic lipid substances are also present in lymph draining the intestines in a rodent model of hemorrhagic shock. The results of this study showed that phosphatidylcholine, phosphatidylethanolamine, and metabolites of these lipids, as well as sphingomyelin, were increased in intestinal lymph. The authors cited data indicating that these substances can cause damage to the pulmonary endothelium and produce changes in lung tissue that mimic those seen in acute respiratory distress syndrome (ARDS).

Microvascular flow abnormalities associated with shock and injury may be produced by alterations in circulating blood cells as well as anatomic and functional abnormalities in the small vessels of the microcirculation. This topic was addressed in an article by Machiedo and coauthors³¹ in the *Journal of Trauma*, 2009. The authors evaluated the effects of blood infusion from animals subjected to trauma and shock on organ blood flow in a rodent model. Organ blood flow was measured using radioactive microspheres. The authors were able to document increased sequestration of red blood cells from animals subjected to trauma and shock and subsequently infused into normal animals in organs such as the liver

and spleen. Organ blood flows were reduced. The authors concluded that red blood cell changes induced by trauma and shock predispose these cells to lodge in organ microcirculations, obstructing blood flow. These data and the studies discussed earlier suggest a diverse group of changes in organ microcirculation resulting from trauma and shock. Detailed studies of the human microcirculation are needed to provide clinical evidence of outcome improvement measures.

Protection against cellular death is another avenue that could improve outcomes in severely injured patients suffering from shock. One measure leading to improved cell survival is the inhibition of histone deacetylation. Inhibiting this process was the topic of an older but still relevant report by Gonzales and coauthors³² in the *Journal of Trauma*, 2008. According to the authors, hemorrhagic shock-induced changes in the liver produce aberrations in gene-regulatory programs; one important pathway for these changes is the recruitment of histone deacetylases in liver tissue. Valproic acid, a regularly prescribed antiepileptic drug, was recently shown to produce neuroprotective effects through the inhibition of histone deacetylation. Pretreatment with valproic acid in a rodent model of severe hemorrhagic shock produced favorable changes leading to liver cell survival and these changes were directly related to hyper-acetylation of hepatic histones.

Alam and coauthors³³ evaluated the cell protective activity of valproic acid in a porcine model of severe hemorrhage, trauma, and shock in *Surgery*, 2009. The authors treated animals with valproic acid after hemorrhage and liver injury in contrast to the pretreatment model examined in the article by Gonzales.³² Alam and coauthors³³ examined outcomes in animals untreated, animals treated with fresh whole blood, and animals treated with intravenous valproic acid. Survival was 100% and 86% in animals treated with fresh whole blood and valproic acid, respectively, compared with 25% in the control group. The authors examined liver tissue and found that survival was associated with the preservation of the AKT cell survival pathway. Normal function of this pathway depends on prevention of histone deacetylation. These two studies indicate that interventions at the cellular level hold promise as therapeutic pathways to manage trauma and shock.

Monitoring Patients in Shock

The clinical hallmark of shock in the critically ill surgical patient is arterial hypotension. The American College of Surgeons (ACS) Committee on Trauma's (COT) Advanced Trauma Life Support® (ATLS®) course defines shock as an arterial blood pressure <90 mm Hg confirmed before patient arrival at the hospital and/or present during initial assessment. The review article by Cestero and Dent¹⁴ indicated that measurements that help determine the adequate resuscitation of a patient in shock can be divided into two categories, hemodynamic measurements and perfusion measurements. The latter category contains measurements that provide insight into oxygen availability at the cellular level. The following sections of this issue will provide relevant information on various monitoring approaches.

Hemodynamic Monitoring

Basic features of hemodynamic monitoring include intermittent or continuous measurements of arterial pressure, heart rate, arterial oxygen saturation and, in selected patients, central venous oxygen saturation. Arterial pressure can be measured with blood pressure cuffs (automatic or manual) and with indwelling arterial catheters attached to continuous monitoring transducers. Automatic blood pressure cuffs produce blood pressure values consistently higher than actual pressures. This feature is particularly noticeable in lower pressure ranges. Manual blood pressure cuffs require personnel and the measurement process is cumbersome in critically ill patients. Placement of arterial catheters in peripheral arteries may be challenging in vasoconstricted patients. Arterial pressure measurements can be supplemented with serial measurements of central venous pressure, but utilization of venous pressure has limitations. In the intensive care unit or the operating room, additional variables such as central venous oxygen saturation, right heart pressures, mixed venous oxygen saturation, and cardiac output can be measured. Transthoracic or transesophageal echocardiography can be used to determine the presence and degree of cardiac dysfunction.

Cestero and Dent confirmed that mean arterial pressure (MAP) is a frequently cited measurement that clinicians utilize to determine endpoints of resuscitation. The

formula for calculating MAP is $MAP = \text{diastolic pressure} + 1/3(\text{systolic pressure} - \text{diastolic pressure})$. Despite the fact that this assessment is widely used, there is no universally accepted value of MAP that can be used as a target for defining shock or adequacy of resuscitation. Additional data cited in the article support the use of hypotensive resuscitation based on a systolic pressure goal of 80–90 mm Hg or a MAP goal of 65 mm Hg as a means of improving outcomes in injured patients. One classic study has shown improved outcomes in patients sustaining torso trauma when resuscitation was delayed until arrival in the operating room— as long as patients maintained a systolic pressure in the 80–90 mm Hg range. The authors also asserted that hypotensive resuscitation is recommended for combat casualty care as long as there is no evidence of traumatic brain injury; hypotension in traumatic brain injury patients is associated with a greater risk of adverse outcomes. Guidelines for sepsis management recommend resuscitation of patients diagnosed with septic shock using a MAP target of 65 mm Hg. Guidelines updated in 2016 by the Surviving Sepsis Campaign³⁴ continue to use this target.

Additional hemodynamic variables that can be assessed include measurements of central venous pressure, mixed venous oxygen saturation, and central venous oxygen saturation. Cestero and Dent¹⁴ stated that central venous pressure measurements have been shown to correlate poorly with other markers of fluid volume status and assessments of tissue perfusion. Administration of blood and/or intravenous fluid to achieve a certain central venous pressure target has been used to determine “fluid responsiveness”; when the patient is fluid responsive, additional administration of volume is indicated to achieve normalization of hemodynamics and tissue perfusion. A meta-analysis by Marik and Cavallazzi³⁵ in *Critical Care Medicine*, 2013, challenged the effectiveness of central venous pressure monitoring during resuscitation. Using standard analysis methods, the authors identified 43 acceptable studies. Use of central venous pressure to guide fluid therapy in the intensive care unit and in the operating room was analyzed. The study outcomes showed that no evidence supported the use of static central venous pressure measurements to assess fluid volume status and to provide guidance when resuscitating patients in shock.

Marik³⁶ evaluated the various methods of determining fluid responsiveness in critically ill patients in *Critical Care Medicine*, 2016. The author emphasized that hemodynamic measurements need to be available, relatively easy to use, and accurate. These measurements should also be sensitive to the changes that patient characteristics (e.g., obesity and cardiac arrhythmias) and therapeutic measures (e.g., ventilator therapy) impose on the assessments chosen by caregivers. Based on an extensive review of the literature, Marik recommended using the passive leg-raising maneuver or administering a 200–500 mL fluid bolus over 15 minutes, with the response determined by direct measurement of stroke volume using a non-invasive cardiac output monitor. Marik³⁷ also reviewed the capabilities of the various noninvasive cardiac output devices in the *Journal of Cardiothoracic and Vascular Anesthesia*, 2013. Readers are encouraged to review this article as needed.

Cestero and Dent¹⁴ cited additional data that show a good correlation of stroke volume and stroke volume variation (variation of stroke volume at different phases of the ventilation cycle) measured with a noninvasive cardiac output monitor with fluid responsiveness. The main limitation of this form of measurement is the inaccuracies that occur in patients with cardiac arrhythmias, aortic valvular disease, and peripheral vascular disease. Because some of the recommended measurements can only be performed when the patient is on a ventilator, the passive leg-raising test or the fluid bolus response test recommended in the article by Marik³⁶ may be more suited for use in nonventilated patients.

Cestero and Dent¹⁴ stated that echocardiographic evaluation of stroke volume and volume status using indices such as the inferior vena cava diameter can accurately determine fluid volume status and fluid responsiveness. They pointed out that the main limitation is the need for specialized training to assess some of the desirable variables. The use of echocardiographic monitoring in the initial assessment and resuscitation of injured patients was the focus of an article by Tchorz and coauthors³⁸ in the *Journal of Trauma and Acute Care Surgery*, 2012. The authors measured sequential cardiac output and stroke volume using standard pulmonary artery catheter measurements and compared these to the same variables mea-

sured with transthoracic echocardiography. They evaluated 29 patients for 48 hours (at 12-hour intervals) after admission to the intensive care unit. Twenty-five of the 29 patients were critically ill trauma patients. The overall mortality for the group was 22%. The analysis showed that measurements of cardiac output were strongly correlated using the two techniques. Stroke volume showed a weaker but still significant correlation. Of interest is that echocardiography showed tricuspid regurgitation in 80% of patients and mitral regurgitation in 50% of patients. The significance of these mitral and tricuspid valve regurgitation findings is unknown; however, it suggests that variability in the response of patients to fluid volume resuscitation using central venous pressure as a guide may be due to unrecognized tricuspid regurgitation. Tricuspid regurgitation in these patients tended to cluster in the early phases of resuscitation and, theoretically, this could explain some of the variability of responses to fluid therapy based on central venous pressure measurements in hemodynamically unstable patients. The authors concluded that transthoracic echocardiography has promise as a means of monitoring hemodynamic status in injured patients. This paper was presented at a plenary session of the annual meeting of the American Association for the Surgery of Trauma in September 2009. The discussion that occurred after the presentation is included with the article. Discussants noted the limitations to using transthoracic echocardiography in obese patients and in patients with subcutaneous emphysema. Despite these concerns, echocardiography probably has value for surgeons providing care for critically ill patients.

Murthi and coauthors³⁹ provided additional data on the use of echocardiography in critically ill and injured patients in the *Journal of Trauma and Acute Care Surgery*, 2012. The authors compared surgeon-performed echocardiography with measurements of cardiac function using the pulmonary artery catheter in 115 critically ill patients. The analysis showed a strong concurrence between echocardiography and pulmonary artery catheter measurements. This association was especially strong for patients with depressed cardiac function. Of interest is that depressed cardiac function detected by echocardiography was confirmed by the presence of reduced cardiac index on pulmonary artery catheter measurements in only

27% of patients. This suggests that echocardiography has a significantly better ability to detect cardiac dysfunction. The authors concluded that surgeon-performed echocardiography has significant potential value when caring for critically ill surgical patients. A recent article from this group⁴⁰ used transthoracic echocardiography to determine fluid responsiveness in a mixed population of injured and acute care surgery patients in a single-institution intensive care unit. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. Similar to the findings in the article by Marik,³⁶ stroke volume change, as determined by the combination of the velocity time integral and the change in diameter of the internal jugular vein with a positional change were the most dependable measures of fluid responsiveness.

Additional data on the use of ultrasound to define the hemodynamic status of critically ill trauma patients were in an article by Prekker and coauthors⁴¹ in *Critical Care Medicine*, 2013. These authors used ultrasonography to measure the dimensions of the internal jugular vein and inferior vena cava. The collapsibility of the inferior vena cava during inspiration was assessed. These measurements were then compared to venous pressure measurements obtained with an indwelling central venous catheter. The ability of inferior vena cava diameter to predict changes in central venous pressure was very strong (area under the ROC curve of 0.91). The authors concluded that point-of-care ultrasound has potential value as a means of determining central venous pressure in critically ill patients. These data are limited by the fact that the measurements were made on critically ill medical patients rather than surgical patients and sequential measurements in patients undergoing acute fluid resuscitation during episodes of clinically significant bleeding were not reported.

Monitoring Oxygenation & Perfusion

Cestero and Dent¹⁴ reviewed data on the use of mixed venous oxygen saturation as a means of diagnosing shock and as a measure of resuscitation effectiveness. Normal values for mixed venous oxygen saturation are 65%–75%, with values below 50% indicating inadequate tissue oxygenation. The authors stated that determining mixed venous oxygen saturation requires pulmonary artery

catheter placement. They cited data from several studies that showed no improvement in outcomes of critically ill patients when mixed venous oxygen saturation was used to determine the adequacy of resuscitation. The authors emphasized that failure to achieve the target goal of mixed venous oxygen saturation was associated with in-hospital mortality and this suggests that the value of mixed venous oxygen saturation might be more accurate as a predictor of mortality than as a goal for resuscitation. According to Cestero and Dent, a central venous oxygen saturation determination does not require pulmonary artery catheter placement. They reviewed data that showed a good correlation of central venous oxygen saturation and mixed venous oxygen saturation if the central venous catheter tip was located near the entrance to the right atrium.

Giraud and coauthors⁴² presented data on the usefulness of central venous oxygen saturation as an indicator of fluid responsiveness in the *Journal of Trauma*, 2011. The authors measured central venous oxygen saturation and a variety of pulmonary artery catheter variables in 30 critically ill surgical patients who required acute volume expansion. The authors found that an increase in central venous oxygen saturation in response to volume expansion was moderately predictive of a positive response to fluid therapy (with a sensitivity and specificity of 80%–84%). Giraud and coauthors recommended that this variable be included as one of several indices of fluid responsiveness. As a general statement, combining arterial pressure and heart rate with central venous oxygen saturation will provide adequate estimates of hemodynamic function to guide the clinician dealing with most forms of shock encountered in surgical patients.

A fundamental concept of shock is that circulation inadequacy leads to a cellular shift from aerobic to anaerobic metabolism. Anaerobic metabolism leads to the accumulation of acid metabolites in tissue. The main form of acidic metabolic product measured in critically ill patients has been serum lactate and this has been used to diagnose the presence of lactic acidosis. A review article focusing on the pathophysiology of lactic acidosis was by Kraut and Madias⁴³ in the *New England Journal of Medicine*, 2014. The authors stated that lactate accumulates because of the generation of pyruvate by anaerobic glycolysis and the subsequent conversion of pyruvate to lactate in the cytosol through a reaction catalyzed by lac-

tate dehydrogenase. When tissue hypoxia occurs during a shock state, lactate is overproduced and underutilized. In the hyperdynamic phase of sepsis, stimulation of beta receptors by epinephrine augments glycolytic flux and contributes to lactate accumulation.

Cestero and Dent¹⁴ confirmed that measurements of lactate indicate the balance between lactate production and clearance. Clearance of lactate occurs mostly in the liver, with a small amount occurring in the kidneys. Because of this, patients with liver or kidney disease may have elevated lactate levels in the absence of hypoperfusion. Elevated lactate levels and abnormal base deficit (calculated from pH and pCO₂) are associated with mortality in patients diagnosed with hemorrhagic or septic shock. Data cited in the article show that the times to lactate normalization or base deficit correction are accurate markers of the degree of physiologic derangement caused by the shock state. The main limitations of these markers in determining resuscitation adequacy are elevations of the markers that may be encountered in patients with liver disease, kidney disease, and in patients with seizures. Additional data indicated that lactate levels may be falsely low in patients with mesenteric ischemia.

Cestero and Dent cited data that outlined the limitations of base deficit calculations in diagnosing the severity of shock and determining the adequacy of resuscitation. They emphasized that hypothermia, administration of sodium bicarbonate, and alcohol intoxication can affect base deficit calculations. Diabetic ketoacidosis and administration of saline solution can also alter base deficit. For these reasons, base deficit should be used cautiously as an indicator of the shock state and response to therapy.

Traditionally, assessments of acid base status have been routine in the management of shock. Assessment of global acid base status has usually been achieved by calculating base deficit from values for pH, bicarbonate, and PCO₂ obtained from arterial blood gas analysis or from assessments of bicarbonate levels obtained from venous blood samples. The potential usefulness of the base deficit as a guide to resuscitation of injured patients was analyzed in a study by Mutschler and coauthors⁴⁴ in *Critical Care*, 2013. The authors queried a national trauma database used in Europe and recovered data on more than 16,000 patients seen over eight years. The authors classified four categories of patient injury severity based on the admission

base deficit measurement. The categories progressed from an admission base deficit of <2 mmol/L (class 1) to >10 mmol/L (class 4). The authors found a linear correlation when base deficit class was related to mortality, need for transfusion, and risk of coagulopathy. The use of base deficit class predicted the presence of hypovolemic shock more accurately than the shock classification system used by the ACS COT ATLS course. The authors concluded that admission base deficit has value for establishing a diagnosis of hypovolemic shock.

For surgeons managing critically ill patients, measuring lactate is most useful when the elevated lactate level occurs in the setting of metabolic acidosis; acidosis is independently confirmed by measurements of serum bicarbonate and/or base deficit. The presence of elevated lactate with metabolic acidosis is predictive of mortality and resolution of hyperlactatemia suggests successful reversal of anaerobic metabolism.

Monitoring at the Tissue Level

Global markers of inadequate oxygen delivery such as central venous oxygen saturation, base deficit, and lactate levels represent the resultant vector of all vascular beds. There has been wide recognition that some vascular beds (especially the splanchnic bed) are persistently underperfused and hypoxic, even though global indices of oxygen supply and consumption have been corrected to normal levels. Studies in humans and experimental animals have demonstrated significant variability in blood flow and recovery of normal cellular metabolism in resuscitated hemorrhagic shock. Accessible microvascular beds evaluated in clinical studies include skin, skeletal muscle, the sublingual bed, and the gastric mucosa. Mucosal pH and PCO_2 , tissue oxygen saturation, and tissue oxygen tension have been studied as possible indices of successful resuscitation. Data from these evaluations will be discussed in this section.

Values for pH and PCO_2 can be measured in the gastric and sublingual mucosa using saline-filled latex chambers applied to the mucosal surface. Because the chamber is permeable to CO_2 , the carbon dioxide tension of the mucosa is equivalent to the carbon dioxide tension of the saline within the chamber after equilibration, and this can be measured in a standard blood gas

analyzer. Simultaneous measures of blood bicarbonate permit calculation of the mucosal pH. An important assumption included in these measurements is that mucosal and blood bicarbonate levels are equivalent. This assumption is controversial.

A classic clinical study by Ivatury and coauthors⁴⁵ in the *Journal of the American College of Surgeons*, 1996, was a randomized, prospective trial in which 57 severely injured patients were resuscitated from shock using global indicators of oxygen delivery and consumption. Consistent with the practice at the time, resuscitation to “supranormal” levels of oxygen delivery and consumption was performed. Gastric mucosal pH was assessed using the tonometry technique described above. Elevation of the gastric mucosal pH to a level >7.3 was defined as adequate tissue-level resuscitation. Forty-four patients reached target levels of gastric mucosal pH and three of these developed multiple organ failure; fifty-four percent of the patients who did not reach target levels for gastric mucosal pH developed multiple organ failure. Low levels of gastric mucosal pH were observed in the hours before a serious complication, such as abdominal compartment syndrome, was diagnosed. The authors concluded that patients who reach target levels of gastric mucosal pH are less likely to develop organ failure and low gastric mucosal pH may be a warning signal of an impending serious complication. Unfortunately, this study did not show that resuscitation to a target level of gastric mucosal pH was superior to resuscitation using global indicators of oxygen delivery and consumption. In fact, the frequency of complications such as organ failure and abdominal compartment syndrome were equivalent in the group resuscitated to a target mucosal pH compared with the group resuscitated using global markers.

Per Cestero and Dent,¹⁴ the initial enthusiasm for monitoring gastric mucosal pH has waned because of the recognition that multiple confounders (enteral feeding, buffering of gastric acid, and inaccurate measurement of gastric PCO_2) render the measurements undependable.

The sublingual mucosa has a microcirculatory anatomy and physiology similar to the gastric mucosa. An available probe will rapidly measure sublingual mucosal carbon dioxide tension and this might be helpful in establishing prognosis and in defining adequate resuscitation.

tion. Cestero and Dent stated that studies of sublingual capnometry have not shown better predictive value than measures such as serum lactate and base deficit.

Editorial Comment

Additional investigation should clarify the complex interrelationships between vascular beds and permit the development of more precise approaches to resuscitation in the future. Routine use of tissue oxygen measurements, though theoretically attractive, is not supported by sufficient data at this time. The difficulty in using tissue tonometry as a continuous monitoring methodology has limited its use. Global indices of oxygen delivery and consumption such as central venous oxygen saturation, base deficit, and lactate levels are valuable indices when used as supplements to sequential clinical assessments during resuscitation. It is likely that practical, easy-to-use instruments for assessing microcirculation (see earlier discussion) will soon be available and these assessments will provide potentially useful information for guiding therapy of shock as well as identifying new avenues for research.

Shock & Resuscitation-Related Coagulopathy

In earlier sections of this issue, the general principles and effective application of “damage control” techniques for managing critically injured patients were discussed. Recognition of the lethal triad of acidosis, hypothermia, and coagulopathy leading to death in patients with prolonged bleeding and hypovolemic shock motivated the development of these techniques. The critically important contribution of “damage control” leading to improved survival in this patient group was to document methods for rapid control of hemorrhage, followed by restoration of tissue perfusion, body temperature, and coagulation system function in the controlled environment of the intensive care unit. The concept of hemostatic resuscitation grew out of the application of damage control techniques used to manage combat injuries and civilian trauma.

Experience with combat casualties in Iraq and Afghanistan has shown that persistent microvascular hemorrhage from coagulopathy is a component of severe injury that may have its onset early in the management of the trauma victim. These observations have led to the development of “massive transfusion” protocols that stress the replacement of clotting factors along with blood. Combat resuscitation protocols using fresh whole blood are an outgrowth of the understanding that clotting factor replacement along with restoration of volume and oxygen-carrying capacity ideally should occur simultaneously with hemorrhage control in the severely injured patient. As research into the mechanisms of trauma-related coagulopathy has progressed, understanding of the roles of various parts of the coagulation cascade in the development of coagulopathy has increased.

Historically, trauma-related coagulopathy has been thought to be the result of loss of coagulation factors due to hemorrhage, dilution of clotting factors with electrolyte fluid resuscitation, and consumption of clotting factors as the intrinsic defense mechanisms seek to achieve hemostasis at the site(s) of injury. Evidence is increasing that the cellular and microcirculatory events (discussed earlier) that damage the endothelium contribute to the proinflammatory environment that is characteristic of the early response to injury and shock. Endothelial damage and the proinflammatory responses activate coagulation within the small vessels of the microcirculation and contribute to the consumption of coagulation factors. Hyperfibrinolysis may occur in response to microvascular thrombosis. This section will cover the diagnosis, management, and outcomes of treatment for coagulopathy associated with severe injury.

Although trauma-related coagulopathy is frequently a complication of hemorrhagic shock and tissue destruction, it can occur without evidence of shock. Research into the pathophysiology of traumatic brain injury (TBI) has disclosed that coagulopathy can be diagnosed in patients with this type of trauma. The article by Chang and coauthors¹⁷ indicated that mechanisms other than endothelial damage and activation of the coagulation cascade contribute to coagulopathy associated with TBI. Possible mechanisms might include elaboration of tissue factor from the injured brain and interactions of plasma

proteins with brain tissue that is normally isolated from contact with circulating blood. Data cited in the article show that microparticles released from the injured brain tissue increase in the circulation after TBI and these may play a role in the development of coagulopathy. Other research referred to in the article has identified microparticles in cerebrospinal fluid following TBI. Animal studies have confirmed a hypercoagulable state after TBI that is associated with increased levels of brain-derived microparticles. The final studies described by Chang and colleagues showed that TBI produced in animals was associated with a hyperfibrinolytic state.

Another article that presented useful information regarding TBI-associated coagulopathy was by Laroche and coauthors⁴⁶ in *Neurosurgery*, 2012. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors explained that thromboelastography can confirm dysfunction of the enzymatic coagulation cascade, platelet function abnormalities, and activation of the fibrinolytic system in patients with TBI. Additional data cited by the authors associated coagulopathy with an increased risk of secondary brain injury due to delayed intracranial hemorrhage and an increased mortality risk. The data cited documented the presence of coagulopathy in 23% of patients with significant TBI. When coagulopathy was present, mortality was 50.4% compared to 17.3% in patients without coagulopathy. Risk factors for coagulopathy were Glasgow Coma Score <8, age >75 years, and hypotension prior to initial in-hospital evaluation.

Diagnosis of Trauma-Related Coagulopathy

Early trauma-related coagulopathy has typically been identified by documenting abnormalities of prothrombin time (expressed as INR [international normalized ratio]) and activated partial thromboplastin time. The availability of these two assays and the fact that results can generally be obtained during the initial assessment and resuscitation phase of trauma management has been the main driver of this practice. The facts that these two tests do not sufficiently characterize the coagulopathy to predict, accurately, the risk of persistent microvascular bleeding or to guide therapy have been widely recog-

nized; thromboelastography has emerged as a useful test for predicting coagulopathy. A rapid version of this assay has significantly reduced the time required to obtain the test results.

An article describing the value of early thromboelastography in diagnosing postinjury coagulopathy was by Cotton and coauthors⁴⁷ in the *Journal of Trauma*, 2011. These authors reported the results of early rapid thromboelastography in 272 patients from a single trauma center. Rapid thromboelastography uses different activator substances than conventional thromboelastography and test results are available within minutes and can be displayed graphically in the trauma resuscitation area so that decisions regarding implementation of a massive transfusion protocol can be made. In this study, the authors compared results of thromboelastography to conventional clotting tests such as INR and partial thromboplastin time. The analysis showed that results of rapid thromboelastography were available with 15 minutes of patient arrival. Conventional clotting tests were available, on average, at 48 minutes after patient arrival. A comparison of rapid thromboelastography results with conventional clotting test results showed that rapid thromboelastography provided accurate results, with no changes in management made after reviewing the results of standard clotting studies. The most important component of rapid thromboelastography for coagulopathy prediction and the need for massive transfusion was the activated clotting time.

Holcomb and coauthors⁴⁸ evaluated using rapid thromboelastography results to activate a massive transfusion protocol in *Annals of Surgery*, 2012. The authors reviewed data from 1,974 admissions to a single trauma center. Rapid thromboelastography was performed at admission on all patients and the accuracy of this test in predicting coagulopathy and the need for massive transfusion was compared to the predictive accuracy of conventional clotting studies. The analysis showed that rapid thromboelastography was very accurate in predicting coagulopathy and the need for massive transfusion. Massive transfusion protocol implementation based on the results of rapid thromboelastography was also accurate and permitted the development of a protocol for red blood cell transfusion and clotting factor replacement based on the rapid thromboelastography results. The data in this

article were presented to the plenary session of the 2012 annual meeting of the American Surgical Association. Presentation discussants pointed out that rapid thromboelastography does not provide information to support the use of fibrinogen. Discussants also affirmed that rapid thromboelastography results can be used to detect the effects of the newer antithrombotic drugs that may be used on a chronic basis by patients who are admitted for injury.

Resuscitation Strategies

The objective of resuscitation from shock is to restore tissue blood flow and oxygen delivery by manipulating systemic arterial pressure, cardiac preload, intravascular volume, and blood-oxygen-carrying capacity. Traditionally, resuscitation from shock because of injury and shock due to hemorrhage, septic shock, and cardiogenic shock have shared several common features, namely, an initial fluid bolus using electrolyte solutions followed by red blood cell transfusion to improve oxygen carrying capacity. If cardiac dysfunction is present, vasopressor and/or inotropic drug therapies are added. It is clear that factors other than fluid and blood therapy contribute significantly to the success of resuscitation.

For shock from hemorrhage, the central factors that lead to successful resuscitation are identifying the bleeding sites and rapidly controlling the bleeding. Septic shock patients require identification of the source of infection and control of that source, if possible, to ensure successful resuscitation. Patients with cardiogenic shock may benefit from early percutaneous coronary artery stenting. Patients with “obstructive” shock (pulmonary embolus, tension hemothorax or pneumothorax, pericardial tamponade) require relief of the obstruction to circulation for resuscitation to be successful.

The success of trauma-related coagulopathy management requires an accurate early diagnosis, timely use of operation or angioembolization to control bleeding, and early use of “hemostatic resuscitation” strategies. “Damage control” resuscitation and operative management in this patient group (with early termination of operation before the development of acidosis and hypothermia and continued supportive management in the intensive care unit) is a major contributing factor to the success of hemostatic resuscitation. Hemostatic resuscitation strategies

emphasize red blood cell transfusion along with clotting factor replacement, usually with thawed or never-frozen plasma and platelets. Recently, hemostatic resuscitation has been guided by point-of-care, rapid thromboelastography. There is an increasing recognition that some patients with injury and shock have hyperfibrinolysis (confirmed by rapid thromboelastography); because of this, antifibrinolytic agents such as tranexamic acid have been investigated.

Recent research has focused on massive transfusion protocols that aim to replace clotting factors and red blood cells while reducing the volume of electrolyte solution administered. Because it is now known that large volumes of plasma can contribute to complications such as ARDS, current protocols emphasize the need to avoid an aggressive administration of clotting factors in patients who are not at risk for hemorrhage-related coagulopathy. While massive transfusion protocols and hypotensive resuscitation strategies were originally developed for trauma patient care, these strategies have been shown to be useful in elective and emergency surgical procedures as well.

Regarding massive transfusions, current management protocols recommend that red blood cells, plasma, and platelets be administered in a 1:1:1 ratio. The effectiveness of this approach was evaluated in a randomized control trial (the PROPPR trial). Holcomb and coauthors⁴⁹ published the results in *JAMA*, 2015. The study randomized patients to receive the components in a 1:1:1 ratio (N=338) or in a 1:1:2 ratio (N=342). Results of the trial showed that overall mortality at 24 hours and 30 days was equivalent in the two groups. Risk of death from exsanguination was significantly reduced in the 1:1:1 group and the rate of achieving hemostasis was significantly higher in this group. The authors observed that potential complications of plasma infusion, such as ARDS, multiple organ failure, and venous thromboembolism, did not increase in the 1:1:1 group. The authors concluded that massive transfusion protocols using the 1:1:1 approach are safe and effective.

Chang and Holcomb⁵⁰ presented data to guide the use of hemostatic resuscitation in *Critical Care Clinics*, 2017. The authors found that available data support the effectiveness of the 1:1:1 ratio of red cells, plasma, and platelets. They stressed that reductions in the volume of crystalloid administered to injured patients has been as-

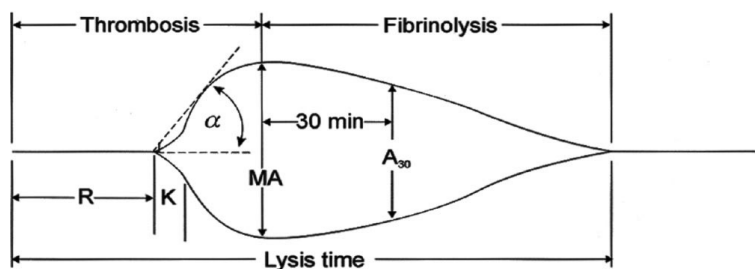
sociated with lower mortality and coagulopathic bleeding risks. Data cited in the article support early thromboelastography to identify patients at risk of coagulopathy. The authors also recommended hypotensive resuscitation for this high-risk patient group if TBI is not present and the hypotensive interval is relatively short. In the concluding sections of their article, the authors emphasized that fibrinogen and cryoprecipitate use cannot be strongly recommended until data from ongoing prospective randomized trials become available. The authors also recommended the current ACS COT guidelines (use of cryoprecipitate to maintain fibrinogen levels of 180 mg/dL or greater).

Available data have supported adjusting components of hemostatic resuscitation protocols based on findings of early thromboelastography; Bogert and coauthors⁵¹ reviewed this topic in the *Journal of Intensive Care Medicine*, 2016. An illustration in the article revealed how the measuring device shows thromboelastography results and offered suggestions for component use based on the report (Figure 3).

Gruen and coauthors⁵² reviewed various hemorrhage control approaches in injured patients in *Lancet*, 2012. The authors stated that early (coagulopathy) and late (multiple organ failure) complications from hemorrhage are mediated by a pattern of genomic alterations that affect up to 75% of the human genome. These abnormalities contribute to a “genomic storm” characterized by the simultaneous activation and suppression of the innate and adaptive immune systems and the production of proinflammatory mediators from damaged portions of the microcirculation. Current resuscitation approaches that aim to replace red blood cells and coagulation factors while reducing electrolyte solution volumes are thought to facilitate recovery from the genomic abnormalities if bleeding is controlled with early operative approaches. The authors explained that procoagulant dressings and topical hemostatic agents could improve bleeding control outcomes; the authors

Figure 3

Adjustment of hemostatic resuscitation components based on results of early thromboelastography. Reproduced from Bogert and coauthors⁵¹ with permission.



<i>r</i> -TEG value	Coagulation issue	Management
ACT > 128 sec	Factor deficiency or severe hemodilution	Transfuse plasma
k-time > 2.5 min	Hypofibrinogenemia	Transfuse plasma Cryoprecipitate if angle also abnormal
α -angle < 60 deg	Hypofibrinogenemia and/or platelet dysfunction	Transfuse cryoprecipitate Add platelets if mA is also abnormal
MA < 55 mm	Platelet dysfunction and/or hypofibrinogenemia	Transfuse platelets Add cryoprecipitate if angle also abnormal
LY-30 > 3%	Accelerated fibrinolysis	Tranexamic acid (TXA) or amino-caproic acid

provided a table listing available agents (Figure 4). The authors also confirmed the effectiveness of angioembolization techniques for patients with acute or persistent bleeding from solid organ injuries and pelvic fractures.

Our earlier discussion of the mechanisms of trauma-related coagulopathy confirmed that some patients have a component of hyperfibrinolysis that contributes to the coagulopathic state. Evidence from a very large randomized prospective trial conducted in European trauma centers documented a significant, albeit small (14.5% vs. 16%), improvement in mortality in patients injured primarily by blunt mechanisms when tranexamic acid was added to a hemostatic resuscitation protocol.⁵³ A later study analyzing the same data in a time-dependent fashion confirmed a reduction in deaths from bleeding with the use of tranexamic acid during the first hour after injury.⁵⁴

Figure 4

Available hemostatic adjuncts for use during the primary operative procedure. Reproduced from Gruen and coauthors⁵² with permission.

Mode of delivery (commercial examples)	
Factor concentrators*	
Mineral zeolite	Granules (QuikClot); mesh bags (QuikClot Sport Advanced Clotting Sponge); gauze (QuikClot Combat Gauze)
Biological polymers	Powder (TraumaDex); nylon bags (self-expanding haemostatic polymer)
Mucoat adhesives†	
Chitosan	Granules (TraumaStat); gauze (Chitogauze PRO, Celox, Hemogrip)
Chitin	Gauze (Modified Rapid Deployment Hemostat)
Mineral-based	Granules (WoundStat, WoundSeal Powder)
Synthetic peptides	Powder (InstaClot)
Polyethylene glycol	Gel (Coseal)
Oxidised cellulose	Gauze (BloodSTOP, Surgicel Fibrillar, Surgicel Nu-Knit)
Gelatin	Foam (Sugifoam, Gelfoam, Gelfilm)
Microfibrillar collagen	Powder (Avitene Flour, Helitene, Instat); rolled sheet (Avitene Sheets, EndoAvitene); sponge (Avitene Ultrafoam, Avitene Ultrawrap, Helistat); gel (Vitagel)
Procoagulant supplementors‡	
Human-derived factors§	Dry: oxidised cellulose and polyglactin matrix with thrombin and fibrinogen coating (Fibrin Pad); gauze imbedded with lyophilised fibrinogen and thrombin (Dry Fibrin Sealant Dressings); equine collagen patch with fibrinogen and thrombin (TachoSil) Liquid or aerosol: fibrin sealants (Tisseel, Evicel, Crosseal); gelatin–thrombin suspension (Flo seal)
Bovine-derived factors¶	Gauze (FastAct); glue (BioGlue); sponge (TachoComb)
Plant-derived factors	Powder (HemoStase MPH, Arista)
Synthetic factors¶¶	Solution (Recothrom)

Vascular occlusive events (a potential complication of the use of tranexamic acid) were observed in less than 0.5% of patients and the risk of a vascular occlusive event (myocardial infarction, stroke, etc.) was the same in both the treatment and control groups.

Experience from care of patients injured in combat operations in Afghanistan reported by Morrison and coauthors⁵⁵ in *JAMA-Surgery*, 2013, suggested that mortality risk is lower with the use of supplemental fibrinogen (in the form of cryoprecipitate) combined with a specific antifibrinolytic agent, tranexamic acid. The authors queried the trauma registries of U.S. and British combat injury care facilities in Afghanistan and reviewed outcomes data

on 1,332 patients. The authors identified groups of patients resuscitated with approaches using cryoprecipitate, tranexamic acid, a combination of cryoprecipitate and tranexamic acid, and neither agent. The mortality rates for patients who received cryoprecipitate or neither agent exceeded 21%, while the mortality for patients receiving both agents was 11%; for patients receiving tranexamic acid alone, the mortality was 18%. The authors concluded that a hemostatic resuscitation protocol that includes fibrinogen replacement and a specific antifibrinolytic agent is associated with improved outcomes.

Cotton and coauthors⁵⁶ assessed the association of hyperfibrinolysis with trauma mortality in the *Journal of Trauma and Acute Care Surgery*, 2012. The authors tested 1,996 consecutive patients for evidence of hyperfibrinolysis on rapid thromboelastography performed immediately upon arrival at a single trauma center over a one-year interval. Hyperfibrinolysis was diagnosed in 2% of patients. This group was older, had higher injury severity scores, was more often in shock, and had received larger volumes of crystalloid fluid in the prehospital phase of care. The authors observed a significantly higher mortality (76% vs. 10%) in patients with evidence of hyperfibrinolysis. Surgeons from this same trauma center also analyzed their trauma registry over a four-year interval and reported a mortality comparison of patients who had hyperfibrinolysis and received tranexamic acid compared with patients who did not receive the drug. Hyperfibrinolysis was diagnosed based on findings from early thromboelastography. The authors recorded outcomes from 1,032 patients with evidence of hyperfibrinolysis. Ten percent of the patients received tranexamic acid. After multiple logistic regressions, no mortality benefit from tranexamic acid could be identified. This study was presented to a plenary session of the annual meeting of the American Association for the Surgery of Trauma in 2014. During the discussion portion of this meeting, it was revealed that making comparisons from a retrospective review of trauma registry data can result in selection bias because of factors not captured in the registry data and because precise causes of mortality may not be accurately recorded. Despite these limitations, discussants agreed that these outcomes challenged the conclusions of the European study referred to earlier.

An article by Napolitano and coauthors⁵⁷ in the *Journal of Trauma and Acute Care Surgery*, 2013, reviewed data on the use of tranexamic acid and made recommendations for the use of this agent in injured patients. The authors conducted a comprehensive review of available literature dealing with tranexamic acid. They found that several studies have documented the presence of hyperfibrinolysis in 10%–20% of severely injured patients. Evidence of hyperfibrinolysis may be present in up to 35% of patients who have massive bleeding due to injury and coagulopathy. The authors then examined the data supporting the use of tranexamic acid in trauma patients and acknowl-

edged a significant risk of selection bias in the large randomized trial referred to earlier⁵³ because surgeons were given significant latitude in selecting patients for enrollment. Nonetheless, tranexamic acid seemed to provide a small mortality benefit, especially when given within the first hour of injury to patients with an admitting systolic blood pressure of 70 mm Hg or less. The authors stressed that tranexamic acid given more than three hours after injury was actually associated with an increased mortality risk, with a significant increase in deaths from bleeding.

Napolitano and colleagues⁵⁷ confirmed the observation of a small risk increase of pulmonary embolus and deep venous thrombosis in several studies of tranexamic acid treatment and an increased risk of postoperative seizures in cardiac surgery patients receiving tranexamic acid. Based on this comprehensive literature review, the authors concluded that tranexamic acid has not been adequately studied in patient populations who are treated with contemporary hemostatic resuscitation protocols. Based on the present state of knowledge, the authors recommended consideration of tranexamic acid use in patients with an admitting systolic blood pressure of 75 mm Hg or less if the drug can be given within the first hour after injury. Early use (within the first hour) of the drug may also be considered in patients with early evidence of hyperfibrinolysis based on results of point-of-care thromboelastography.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an intervention designed to occlude the aorta just above the bleeding source, thus helping to achieve hemostasis in patients bleeding from sites in the thorax, abdomen, and pelvis. Morrison and coauthors⁵⁸ conducted a systematic review of the literature to assess evidence of this device's ability to achieve early control of life-threatening bleeding in the *Journal of Trauma and Acute Care Surgery*, 2016. The authors found 41 acceptable studies that reported outcomes data on 857 patients. The studies focused on bleeding from obstetric complications, pelvic oncologic surgery, gastrointestinal bleeding, ruptured abdominal aortic aneurysm, and torso injuries. The device was placed, in most instances, via the femoral artery. The authors noted that fluoroscopy guided placement in more than half of the reports. Fluoroscopy-free placement was successful overall, with only one placement-

related complication reported (aortic injury). The studies disclosed a rise in systolic blood pressure averaging 53 mm Hg following inflation of the occluding balloon. Only two studies compared outcomes in a REBOA group with outcomes in a group of similar patients not treated with REBOA. There was no report of improved mortality risk. The authors concluded that the device may possibly be beneficial, but additional prospective studies are needed.

Hypotensive resuscitation is potentially useful in reducing the rate of blood loss during the surgical control of bleeding sites. Morrison and coauthors⁵⁹ presented results of this approach in injured patients in the *Journal of Trauma*, 2011. These authors presented the results of a randomized prospective trial comparing hypotensive resuscitation (target mean arterial pressure of 50 mm Hg) with standard intraoperative management (target mean arterial pressure of 65 mm Hg). All patients had at least one documented preoperative hypotensive episode and all patients underwent either laparotomy or thoracotomy for ongoing bleeding. The authors emphasized that patients with spontaneous blood pressures above the target range did not receive drugs to reduce blood pressure.

The results showed that early (seven-day) mortality was lower in the hypotensive resuscitation group. At 30 days, there was no mortality difference. The authors concluded that hypotensive resuscitation is a safe method of facilitating intraoperative bleeding control. The authors observed that evidence of early coagulopathy was significantly lower in the hypotensive resuscitation group. This group received significantly lower volumes of blood, clotting factors, and electrolyte fluids. The authors emphasized that this report was an interim analysis of 90 patients and the target enrollment of patients was 271. They concluded from this early analysis that hypotensive resuscitation is safe and a potentially beneficial means of facilitating operative hemostasis and preventing hemorrhage-related coagulopathy.

Outcomes of Hemostatic Resuscitation Protocols

According to retrospective studies, patients treated with massive transfusion protocols have a survival advantage. The increased identification of coagulopathy early after trauma has resulted in an increased availability of red blood cells and clotting factors in the trauma resuscitation area. Other changes in trauma center protocols include hypotensive resuscitation and damage control operative techniques. Whether massive transfusion protocols alone improve results remains controversial.

Cap and coauthors⁶⁰ documented improved survival in severely injured patients treated with the early implementation of a massive transfusion protocol in the *Journal of Trauma and Acute Care Surgery*, 2012. These authors reviewed outcomes in more than 8,000 patients injured during combat operations and treated in a single hospital in Iraq. A massive transfusion protocol targeting a blood to plasma ratio of 1:1, along with platelet infusion, was employed within the first six hours of injury in 274 patients. Twenty-four-hour mortality was 10% in patients who received the massive transfusion protocol compared with 21% in patients with massive bleeding who did not receive the protocol. Thirty-day mortality rates were the same in both groups. The authors concluded that rapidly identifying patients at risk for coagulopathy and implementing a protocol to replace lost red blood cells along with clotting factors and platelets leads to improved outcomes at 24 hours after injury.

The success of massive transfusion protocols is dependent on recognizing patients at risk for massive bleeding as early as possible and immediately administering blood and clotting factors. Cotton and coauthors⁶¹ discussed a predictive score for identifying candidates for massive transfusion protocols in the *Journal of Trauma*, 2010. The authors described a multicenter prospective use of a massive transfusion predictive score. The score was developed in a cohort of 571 patients at a single trauma center and validated in a prospective cohort of nearly 1,100 patients seen at three other centers. The score awarded one point for penetrating trauma mechanism, presence of fluid on abdominal ultrasound, one or more episodes of hypotension (systolic pressure <90 mm Hg), and a heart rate

of 120 beats per minute or more on admission to the resuscitation area. A score of 2 or more was the trigger for instituting the massive transfusion protocol. The analysis showed that the score was a moderately strong (area under the ROC curve of 0.73–0.81) predictor of the need for massive transfusion. The authors concluded that the predictive score could facilitate the massive transfusion decision-making process.

Callcut and coauthors⁶² presented additional data on predicting the need for massive transfusion in the *Journal of Trauma and Acute Care Surgery*, 2013. The authors evaluated the massive transfusion predictive score reported by Cotton and coauthors⁶¹ and added an assessment of INR levels from blood samples obtained soon after arrival in the trauma resuscitation area. The data were gathered from records of patients enrolled in a prospective multicenter trial of trauma resuscitation. The analysis showed that abnormally high INR levels in the resuscitation area and a massive transfusion score of 2 or higher were predictive of massive transfusion. A massive transfusion score of less than 2 had a negative predictive value of 89% for massive transfusion. The prediction sensitivity of a massive transfusion score of 2 or greater was 85%. The authors concluded that a massive transfusion score of less than 2 is an accurate indicator that massive transfusion will not be needed. The predictive accuracy of early point-of-care thromboelastography in patients at risk for massive bleeding will be presented in a later section of this issue.

Refining the definition of a massive transfusion protocol has been challenging. Retrospective data suggest a survival benefit for patients at risk for massive bleeding and coagulopathy with a ratio of red blood cells to fresh frozen plasma to platelets of 1:1:1. During resuscitation using this approach, electrolyte fluid infusion is minimized and adjusted to a target of 100–200 mL per hour. Prompt surgical and angiographic approaches to hemorrhage control are applied, as appropriate. De Biasi and coauthors⁶³ attempted to clearly define the optimum ratio of transfusion components in *Transfusion*, 2011. These authors retrospectively reviewed outcomes data in 438 patients from a single center. Patients were included in the study if they received a red blood cell transfusion of three or more units in the first 24 hours after injury. The

authors analyzed mortality on an hourly basis following admission. Mortality was then related to red blood cell to plasma ratio and plasma deficit (defined as the volume of red blood cells transfused minus the volume of plasma administered) using linear regression statistical techniques. The analysis related mortality to the volume of plasma deficit—but not to the ratio of red blood cells to plasma administered. The benefits of a massive transfusion protocol were realized within the first six hours after injury and resuscitation was complete in more than half of the patients by the end of the third hour and in nearly 80% of patients by the end of the sixth hour. Early recognition and implementation of the massive transfusion protocol was very efficient at the authors' center and patients whose plasma deficit was corrected within the first 6–12 hours had a survival advantage. The authors emphasized the need for an approach that seeks to implement a massive transfusion protocol early that prevents a plasma deficit, improves outcomes, and reduces the volumes of blood and clotting factors. Protocol effectiveness is probably due to more efficient early hemorrhage control using the combined effects of prompt operative or nonoperative control of bleeding and clotting factor replacement.

As mentioned earlier, quickly recognizing at-risk patients and administering blood and clotting factors are key to the success of a massive transfusion protocol; therefore, the protocol is dependent on having blood and clotting factors immediately available. Many trauma centers now keep universal donor red blood cells and thawed fresh plasma in the trauma resuscitation area. It is well known that red blood cells undergo changes in physical function (deformability) and oxygen-carrying capacity during storage. In aggregate, these changes are known as the “storage lesion.” An approach to optimum blood availability would be to preserve red blood cells in a solution that led to a longer “shelf life” for the blood while maintaining oxygen-carrying capacity and transfusion safety. Fabricant and coauthors⁶⁴ described one approach to this in the *Journal of Trauma and Acute Care Surgery*, 2013. These authors conducted a randomized prospective study comparing the administration of deglycerolized cryopreserved red blood cells to conventional refrigerated red blood cells. Tissue oxygenation was monitored during and after transfusion. The analysis showed that the risk of transfusion reaction and changes in hematocrit and

thromboelastography were equivalent in both groups. Tissue oxygenation was preserved at a significantly higher level in the patients receiving deglycerolized cryopreserved red blood cells.

Accumulating data have confirmed that documenting the benefits of massive transfusion protocols depends on time-dependent analysis. This is because the benefits of clotting factor replacement are realized only when administered early and bleeding cessation efforts are successful. In the *Journal of Trauma*, 2011, Brakenridge and coauthors⁶⁵ confirmed that it is important to institute clotting factor replacement early in order to prevent mortality and postinjury complications. These authors reported data on the risk of postinjury multiple organ failure in a group of 1,366 patients drawn from a prospective study database. The authors found that the risk of multiple organ failure was related to the volume of blood transfused in the first 12 hours after injury. Total volumes of blood, electrolyte solutions, and clotting factors administered over the first three days after injury were not related to multiple organ failure.

Savage and coauthors⁶⁶ also confirmed the importance of the time-dependent administration of clotting factors in the *Journal of Trauma and Acute Care Surgery*, 2013. The authors retrospectively analyzed outcomes data on 167 patients from a single trauma center. The definition of massive transfusion as arbitrary numbers of units transfused over the first 24 hours after injury may provide misleading data because the analyses are subject to survivor bias—only patients surviving long enough to receive the massive transfusion protocol fluids are included in the outcomes analysis. The authors proposed a “critical administration threshold” (CAT) of three units of blood transfusion per hour. The authors analyzed the outcomes in this patient group in a time-dependent manner, beginning with the trauma center admission time. The analysis showed the CAT was reached once in 21% of patients, twice in 14% of patients, and three times in 11% of patients. The documentation of a CAT predicted 77% of deaths from massive bleeding. The conventional definition of massive transfusion identified only 33% of the deaths. The authors concluded that identifying early massive bleeding using the CAT is an effective means of choosing patients who may benefit from a massive transfusion protocol.

A later study by Moren and coauthors⁶⁷ in the *Journal of Trauma and Acute Care Surgery*, 2015, utilized a refined statistical analysis (recursive partitioning) to evaluate patient data from a prospective trial (PROMMTT trial) that assayed patients based on rates of transfusion to define massive transfusion. These investigators reanalyzed the data, adjusting for other features such as Glasgow Coma Score, findings of fluid on abdominal ultrasound, hemoglobin less than 11, and base deficit greater than five. When they adjusted the data, the authors confirmed that a very accurate definition of massive transfusion is the receipt of four units of blood per hour or more. The authors also verified the ability to use this definition with thromboelastography to initiate a massive transfusion protocol.

Holcomb and coauthors⁴⁸ also supported the importance of a time-dependent analysis of massive bleeding and the use of massive transfusion protocols; in *Archives of Surgery*, 2012, the authors reported data from a multi-institutional prospective trial of trauma resuscitation involving 10 trauma centers. The authors reported outcomes data from 905 patients. The data related mortality to the volume of blood transfusion and clotting factor replacement in the first six hours after injury. Patients receiving ratios of blood and clotting factors of 1:1 or 1:2 had lower mortality from hemorrhaging in this early time interval. The authors concluded that early recognition and treatment of trauma-related bleeding and coagulopathy is critical for reducing mortality from bleeding.

It is important to consider the relative risks of using massive transfusion protocols when patients do not meet the criteria for the protocol’s implementation. An article that evaluated outcomes of injured patients who received plasma transfusions despite not fulfilling the criteria for massive transfusion was by Inaba and coauthors⁶⁸ in the *Journal of the American College of Surgeons*, 2010. Using the propensity score technique, 284 patients who received plasma were matched to a similar number of patients who did not. The authors documented a significantly higher overall complication rate in patients who received plasma. The most common complication was ARDS. Although articles reviewed earlier have documented no increased risk of complications such as ARDS in massively trans-

fused patients who receive plasma, caution is obviously required to minimize plasma use in patients who do not meet the requirements for it.

Potential Complications of Hemostatic Resuscitation

Trauma patients are known to be at an increased risk for thromboembolic complications. As hemostatic resuscitation protocols increase in usage, it is important for surgeons to acknowledge the hypercoagulable state that accompanies injury and hemostatic resuscitation's potential contribution to this problem. Park and coauthors⁶⁹ described the value of admission thromboelastography to predict a hypercoagulable state in injured patients in the *Journal of Trauma*, 2009. Fifty-eight patients injured by burns or other mechanisms were admitted to the intensive care unit of a single trauma center. Thromboelastography was performed on admission and then daily for seven days. Conventional coagulation studies were also performed and all patients received recommended doses of enoxaparin for thromboembolism prevention. Regardless of thromboembolism prevention attempts, pulmonary embolus occurred in 6% of patients. Thromboelastography results, particularly maximal clot strength and rate of clot formation, were diagnostic of a hypercoagulable state—despite the use of recommended doses of enoxaparin. The authors recommended that sequential thromboelastography be used to detect a persistent hypercoagulable state and provide data for enoxaparin dosage adjustment.

In the *Journal of Trauma and Acute Care Surgery*, 2012, Cotton and coauthors⁷⁰ confirmed the value of admission thromboelastography in predicting thromboembolic complications. The authors reported a single-center retrospective medical record review of 2,070 patients who had rapid thromboelastography done on admission. Pulmonary embolism was diagnosed in 2.5% of the patients. Review of thromboelastography results showed evidence of a hypercoagulable state reflected by elevated maximum clot strength in these patients. The hypercoagulable patients were injured by blunt mechanisms, were older, and had additional comorbid conditions. Patients with pulmonary embolism were more likely to be Caucasian. The authors concluded that patients found to be hyperco-

agulable based on admission thromboelastography might be candidates for adjusted-dose thromboembolism prevention protocols.

Effective thromboembolism prevention with enoxaparin is associated with elevated trough levels of anti-factor Xa >0.1 IU/mL. Malinoski and coauthors⁷¹ determined the relationship of depressed levels of anti-factor Xa and venous thromboembolism in the *Journal of Trauma*, 2010. The authors obtained anti-factor Xa levels on 54 patients admitted to a single surgical intensive care unit. Most of the patients were admitted for traumatic injury. Anti-factor Xa levels were drawn after the third dose of thromboembolism prevention anticoagulant. Fifty percent of patients had low anti-factor Xa levels. Deep venous thrombosis developed in 37% of patients with low anti-factor Xa levels vs. 11% of those with normal levels. The authors concluded that the standard dosing of preventive anticoagulants is inadequate in 50% of critically ill surgical patients. This same group of investigators examined the use of adjusted enoxaparin doses in patients with low anti-factor Xa levels. Costantini and coauthors⁷² reported the results of this study in the *Journal of Trauma and Acute Care Surgery*, 2013. The authors detected low levels of anti-factor Xa in 70.5% of 61 trauma patients evaluated. These patients had their enoxaparin dosage adjusted upward by 10 mg twice daily until adequate anti-factor Xa levels were achieved. All patients underwent screening Doppler ultrasound examinations of the lower extremities. Deep venous thrombosis occurred in less than 5% of this patient group. There were no bleeding complications observed in the patients who had an upward adjustment of their enoxaparin dosage. The authors recommended prospective study evaluations of dose adjustment protocols.

Hypertonic Saline Resuscitation

Hypertonic saline resuscitation has been proposed as a means of maintaining cerebral perfusion in patients with traumatic brain injury. Bulger and coauthors⁷³ conducted a prospective randomized study of prehospital hypertonic saline administration to patients with traumatic brain injury and reported their findings in *JAMA*, 2010. The authors compared mortality and six-month neurologic outcomes in 1,087 patients randomized to receive 250 mL

of 7.5% saline plus dextran, 7.5% saline, or 0.9% saline during ambulance transport. Patients were enrolled if they were not hypotensive on initial evaluation by ambulance personnel and if they had a Glasgow coma score of 8 or less. The analysis showed no benefits from hypertonic saline use.

The authors revealed that the data monitoring board terminated their study early because the definition of futility had been met. The authors also acknowledged that data interpretation was limited because postadmission management of brain injury was not standardized and that the data on six-month outcomes was incomplete in a significant proportion of patients. Nonetheless, the prospective randomized design of the study is strong and the data suggest that prehospital use of hypertonic saline does not improve outcomes in patients with traumatic brain injury.

Vasopressor Agents

There is a focus on early and aggressive maintenance of cerebral perfusion pressure in patients with traumatic brain injury. This fact, combined with concern over possible adverse consequences of aggressive electrolyte fluid resuscitation, has led to increasing use of vasopressor drugs in early shock resuscitation. This approach was the topic of a report by Sperry and coauthors⁷⁴ in the *Journal of Trauma*, 2008. The authors reviewed data from a large multicenter trial of treatment for injured patients in hemorrhagic shock. They performed a Cox proportional hazards analysis to determine the influence on patient outcomes from using norepinephrine, phenylephrine, dopamine, and/or vasopressin within the first 24 hours after injury.

The authors' analysis disclosed an almost 80% increase in the risk of death for patients who were administered these drugs. After adjustment for several confounding factors, the authors showed that early vasopressor use was an independent driver of mortality risk. Additional data reported in an article by Plurad and coauthors⁷⁵ in the *Journal of Trauma*, 2011, assessed outcomes in patients entered into a prospective database at a single trauma center. The authors excluded patients with spinal cord injuries and severe brain injuries. Patients who received any vasopressor drug within the first 24 hours after admis-

sion were included. The analysis associated vasopressor use with a mortality rate of 43% compared to a mortality rate of less than 5% in patients who did not receive vasopressors. The authors concluded that vasopressor use in patients at risk for hypovolemia is associated with an increased mortality risk.

Editorial Comment

Available data disclose an association between vasopressor use and an increased mortality risk in injured patients. Data confirming a causal relationship is not yet available. Given that available information supports the safety of "hypotensive resuscitation" strategies, it is likely that a reexamination of blood pressure targets for vasopressor use in trauma patients needs to occur.

Use of Trauma Resuscitation Strategies in Nontrauma Patient Care

Several data sources suggest the benefit of resuscitation protocols that stress the early use of blood products and clotting factors combined with reduced volumes of electrolyte solution. There are also reports of similar approaches in elective surgery patients. An article by McArdle and coauthors⁷⁶ in *Annals of Surgery*, 2009, reported data from a preliminary analysis of a randomized prospective trial comparing a standard fluid administration protocol to a restricted volume protocol in patients undergoing elective open repair of abdominal aortic aneurysms.

Major complications after abdominal aortic aneurysm repair are often associated with signs of pulmonary edema and the onset of a systemic inflammatory response. Data cited in the article related these clinical features to vigorous perioperative fluid replacement. The authors randomized 21 patients to receive a standard fluid replacement protocol (12 mL/kg preload with 12 mL/kg/hour intraoperatively) vs. a restricted volume protocol (no preload and 4 mL/kg/hr intraoperatively). Postoperatively, standard therapy patients received 3 liters a day of electrolyte solution, whereas restricted volume patients received 2 liters a day. A comparison of the groups revealed that fluid balance was significantly higher in the standard therapy group and the frequency of major postoperative complications was higher in this group as well. The authors

concluded that a restrictive perioperative fluid protocol is associated with a decreased risk of major complications following open abdominal aortic aneurysm repair.

Stewart and coauthors⁷⁷ reported additional data on the relationship between fluid volume management and complication risks in the *Journal of the American College of Surgeons*, 2009. These authors conducted a post hoc analysis of surgical patients entered into a prospective randomized trial sponsored by the ARDS Clinical Trials Network. The trial investigated a conservative fluid management protocol. Fluid management was determined according to central venous pressure or pulmonary artery pressure. Liberal fluid management targeted a central venous pressure of >18 mm Hg, while restricted management targeted a central venous pressure of 13 mm Hg. Surgical patients were defined as patients admitted to surgical, cardiac surgical, burn, or trauma intensive care units. The analysis showed that major complications such as ARDS and multiple organ failure were observed significantly less often in patients randomized to the conservative fluid management group.

Recombinant Factor VIIa

Although a number of agents are available to assist in hemorrhage control during the initial resuscitation and operative care of bleeding patients, few of these are effective in managing life-threatening diffuse microvascular bleeding. Agents such as fibrin glue and recombinant thrombin-saturated gelatin sponges are helpful with small areas of bleeding. Data supporting the use of desmopressin and aprotinin are limited; these agents are most successful when given before the bleeding event. Recent reports have emphasized the potential benefit of recombinant factor VIIa as an adjunctive measure to control persistent, diffuse, microvascular bleeding.

Dutton and coauthors⁷⁸ discussed recombinant factor VIIa use in the *Journal of Trauma*, 2004. The authors began by pointing out that this agent was originally developed to manage hemophilia patients who had developed neutralizing antibodies to factor VIII. Recombinant factor VIIa acts by binding tissue factor at the site of vascular disruption. Coagulation is initiated and a “thrombin burst” is produced on the surface of platelets. According to the authors, prospective trials have documented the

usefulness of this agent in reducing blood loss during major elective surgery and in managing coagulopathy resulting from warfarin. The authors stated that no standard dose exists for using this agent in injured patients and that they chose to use a dose of 100 mcg/kg in injured patients with bleeding; a dose of 50 mcg/kg was chosen for patients who were coagulopathic secondary to warfarin use. Patients received repeat dosing as needed, with up to three total doses applied. The authors reported the data regarding efficacy separately for patients with acute traumatic injury, congenital or pharmacologic coagulopathy, and traumatic brain injury. Patients with bleeding due to acute injuries were more likely to be treated within the first 24 hours of injury. The authors observed reductions in bleeding in most instances. Thirteen of the 46 patients with acute traumatic bleeding died within the first 24 hours after admission; all of these patients received relatively large doses of recombinant factor VIIa, raising the possibility that these patients represented failures of treatment. Overall, the authors felt the treatment successfully achieved hemostasis in 75% of patients treated. Most of the treatment failures were deemed unsalvageable because of nonsurvivable injuries or severe brain damage. Dutton and coauthors noted the main advantage of recombinant factor VIIa is the immediate nature of the drug effect. The authors stressed the gaps in knowledge regarding safety. For example, it is not clear whether the agent will accelerate microvascular thrombosis in injured tissue such as the brain. It is also not known whether or not this agent enhances the hypercoagulable state seen in patients surviving shock.

Additional data from case series of combat injuries have supported the use of early recombinant factor VIIa in patients with diffuse microvascular bleeding from injury and shock.^{79,80} Patients identified as “massive transfusion” patients were treated with doses of recombinant factor VIIa equivalent to 120 mcg/kg, with the dose repeated usually up to three times, as needed. These series have cited reductions in overall mortality with no notable increase in venous thromboembolism episodes; however, readers should heed the fact that a causal relationship between use of recombinant factor VIIa and improved survival cannot be established based on data provided. Similarly, with regard to thromboembolic complications, these articles did not provide the approach to thromboembolism detection and protocols for managing throm-

boembolism prophylaxis. Despite these limitations, the evidence suggests that recombinant factor VIIa is useful as an adjunctive means of hemorrhage control and that the drug has a satisfactory safety profile.

Horton and coauthors⁸¹ presented data about patterns of use of recombinant factor VIIa among trauma surgeons in *The American Surgeon*, 2008. These authors surveyed surgeons, trauma program managers, and pharmacists who served in Level I or Level II trauma centers. The survey had a relatively low 36% response rate. According to the responses, nearly 90% of Level 1 trauma centers and just over half of the Level 2 centers used recombinant factor VIIa. There was an association between patient volume and usage, with increasing usage reported in high-volume centers. Wide variability of dosing was observed. Few centers used the 200 mcg/kg dose that was reported by Boffard and coauthors⁸²—the only reported prospective evaluation of the drug in trauma patients. Most centers used doses at or near the 90 mcg/kg dose recommended for hemophiliac patients.

Thrombotic complications are associated with the use of recombinant factor VIIa. Thomas and coauthors⁸³ addressed this topic in the *Journal of Trauma*, 2007. They reviewed data from 285 patients treated with this agent during a five-year interval, beginning with data on thrombotic complications associated with the use of recombinant factor VIIa in patients without traumatic bleeding. For example, in a reported trial consisting of patients with acute hemorrhagic stroke, 7% of the treated patients had documented thrombotic complications, compared with a frequency of 2% in patients receiving placebo. Reported trials and retrospective series dealing with injured patients have not observed an increase in thrombotic complications; Thomas and coauthors observed an overall incidence of thrombotic complications in 9.4% of the 285 patients analyzed. The most serious complications recorded included eight instances of mesenteric infarction, three instances of myocardial infarction, and five instances of cerebral infarction. The severity of injury in this patient group prevented definite attribution of the thrombotic complications to the use of recombinant factor VIIa, but the association of these events to the use of the drug suggests that additional surveillance to

document the actual risk is warranted. When planning to use recombinant factor VIIa in a patient with persistent microvascular bleeding, several clinical considerations are appropriate.

In their systematic review, Ranucci and coauthors⁸⁴ discussed using recombinant factor VIIa to assist hemostasis in major elective surgical procedures in *Archives of Surgery*, 2008. The authors reported data gleaned from seven randomized controlled trials. A consistent finding in all studies was a reduction in the number of allogeneic red cell transfusions in groups where recombinant factor VIIa was used as an adjunct to achieve hemostasis. Ranucci and coauthors reported an apparent variability of effectiveness depending on the dose of the agent used in the selected trials. The authors stressed the need for additional research so that the appropriate dose for varying indications can be determined. The cost of the drug is an important factor: where cost/benefit analyses have been performed, cost-effectiveness is only obtained in patients requiring massive transfusion (more than 10 units of red blood cells in 24 hours).

In an editorial comment by Dr. Margaret Knudson, data is cited supporting the use of recombinant factor VIIa in situations where major blood loss can be anticipated. Knudson stated that maximum benefit is obtained when the drug is used relatively early and is not relied on as a last resort. Another important point emphasized in the editorial is the need for additional assessments of the risk of thrombotic complications. According to Knudson, most reports have documented thrombotic events in 2%–4% of patients; this number is, however, smaller than the frequency reported by Thomas and coauthors.⁸³

Sepsis & Septic Shock: Pathophysiology & Management

Definitions of sepsis and septic shock were revised in 2016 because of a detailed meta-analysis conducted by an expert consensus panel convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Singer and coauthors⁸⁵ published the revised definitions in *JAMA*, 2016. The authors explained that prior definitions had been limited by an excessive focus on inflammation and a misleading model that proposed a continuum of sepsis to septic shock. In addition, there was insufficient sensitivity and specificity in the criteria to diagnose systemic inflammatory response syndrome (SIRS). Based on the meta-analysis and the expert opinion

of the panel, a new definition of sepsis was proposed: a life-threatening organ dysfunction caused by a dysregulated host response to infection. The panel recommended using the Sequential Organ Failure Assessment (SOFA) score to assist clinicians in defining sepsis in a patient admitted with signs of infection. The SOFA score assigns points to variables such as the PaO₂/FIO₂ ratio, Glasgow Coma Scale, MAP, type and rate of vasopressor administration, serum creatinine, bilirubin level, and platelet count (Figure 5). An increase in the SOFA score of 2 points or more supports a sepsis diagnosis; a score at this level is associated with an in-hospital mortality risk of 10%.

The panel recommended that septic shock be defined as patients with clinical signs of hypoperfusion who require vasopressors to maintain a MAP >65 mm Hg and who have serum lactate levels >2 mmol/L and no hypovolemia. Shankar-Hari and coauthors⁸⁶ confirmed this definition's validity in *JAMA*, 2016.

Figure 5

The SOFA scoring system for estimating risk of mortality from sepsis and septic shock. Reproduced from Vincent and coauthors³¹ with permission, as modified on the ASPR TRACIE website of the Department of Health and Human Services (HHS.gov).

Organ System, Measurement	SOFA Score				
	0	1	2	3	4
Respiration PaO ₂ /FIO ₂ , mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets x10 ³ /mm ³	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (μmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (μmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

The panel stressed that sepsis is shaped by factors related to the infecting agent and patient age, comorbid conditions, gender, race, and other genetic determinants. The panel indicated that sepsis-related organ dysfunction could be occult and that patients presenting with organ dysfunction should be evaluated for infection. The panel suggested that the quick SOFA score (qSOFA) could be used to document sepsis in patients being evaluated in the emergency department. The variables considered in the qSOFA score include respiratory rate, mental status, and systolic blood pressure.

Seymour and coauthors⁸⁷ evaluated the validity of the SOFA score in a study in *JAMA*, 2016. The authors compared the performance of the SOFA score, the qSOFA score, the Logistic Organ Dysfunction System (LODS), and the SIRS criteria in an analysis of nearly 150,000 patients admitted to the hospital with suspected infection. The analysis showed that the SOFA score and the LODS score both accurately predicted mortality risk, but the SOFA score was easier to use; both scores were superior to the SIRS criteria and the qSOFA score. The authors concluded that the SOFA score should be used for inpatients suspected of having sepsis.

Freund and coauthors⁸⁸ assessed the value of the qSOFA score as a valuable adjunctive measure with which to diagnosis sepsis in patients presenting to the emergency department with suspected infection; this prospective study of more than 1,000 patients was published in *JAMA*, 2017. The analysis showed that the qSOFA score accurately predicted risk in emergency department patients suspected of having infection and sepsis. The authors recommended using this score to improve risk calculation in these patients.

Lagu and coauthors⁸⁹ provided information on the epidemiology of sepsis and septic shock in *Critical Care Medicine*, 2012. The authors presented data on the health burden of severe sepsis (defined as end-organ dysfunction in a patient with a known infection). Data presented in the report confirmed that severe sepsis causes more than 700,000 hospital admissions annually in the United States. Hospital costs for these patients total more than \$24 billion. The analysis showed that all-cause hospital mortality for patients admitted with a diagnosis of severe

sepsis has declined at a rate of 2% per year over the interval from 2003 to 2007. The authors hypothesized that this reduction could be the result of improved care outcomes or the result of improved accuracy in diagnosis coding.

Moore and coauthors⁹⁰ provided data relevant to the epidemiology of sepsis in surgical patients in the *Journal of Trauma*, 2011. These authors used the definitions of sepsis, severe sepsis, and septic shock promulgated by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992.⁹¹ The authors classified patients admitted to a surgical intensive care unit using the following definitions:

Sepsis: Symptoms of SIRS with a focus of infection requiring operative intervention

Severe sepsis: Sepsis with evidence of organ dysfunction such as hypoxemia, central nervous system depression, renal insufficiency, or coagulopathy

Septic shock: Severe sepsis with hypotension and evidence of myocardial depression

The analysis showed that nearly 70% of surgical patients with sepsis had an abdominal source of infection. The data presented confirmed that evidence of coagulopathy (abnormal INR), evidence of renal insufficiency (elevated creatinine), evidence of myocardial damage (elevated beta natriuretic peptide), and evidence of liver dysfunction (elevated bilirubin and/or liver enzymes) were associated with increased mortality.

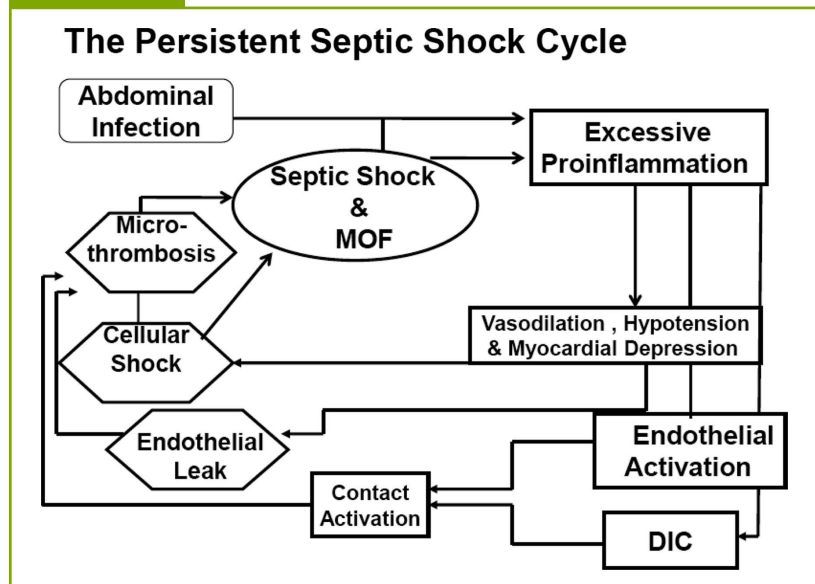
Turner and coauthors⁹² reported data on the possible value of monitoring levels of brain natriuretic peptide (BNP) in septic patients in the *Journal of the American College of Surgeons*, 2011. The analysis showed that BNP elevations were associated with sepsis severity and mortality. Patients with elevated BNP levels who had echocardiographic studies early in their course demonstrated depressed left ventricular ejection fraction. The degree of ventricular dysfunction was a strong predictor of mortality from sepsis. The authors concluded that it might be valuable to measure BNP levels early in the course of management when assessing cardiac dysfunction in septic patients and suggesting a need for additional diagnostic investigations such as echocardiography.

Moore and coauthors⁹⁰ stressed the importance of source control in surgical patients with sepsis. Early resuscitation of the septic surgical patient is challenging because of the need to reverse or at least improve organ function abnormalities while preparing the patient for the needed operation. If the patient is admitted with established coagulopathy, the efforts to restore clotting function take priority. The authors emphasized that epidemiologic data from their patients support the significance of an early proinflammatory environment, which then progresses to end-organ dysfunction characterized by renal insufficiency, activation of the coagulation system with diffuse microvascular thrombosis, endothelial dysfunction, and immune depression. A flow chart included in the Moore et al article illustrates this scenario (Figure 6).

Boomer and coauthors⁹³ presented direct evidence of immune system dysfunction in patients who die of sepsis and multiple organ failure in *JAMA*, 2011. The authors sampled spleen and lung tissue in 40 patients who had recently died from sepsis and multiple organ failure. An analysis of lung and spleen tissue for cytokine secretion and the expression of immune-suppressing ligands showed that cytokine expression was depressed to 10% of the levels seen in tissues obtained from recently deceased patients who did not die with sepsis and multiple organ failure. Compared to controls, there was also a significant up-regulation of the expression of immune-suppressing ligands in patients who died from sepsis. In an editorial that accompanied the article, Ward⁹⁴ affirmed that this study provides strong data associating evidence of immunosuppression with death from sepsis.

Figure 6

Diagram of the persistent septic shock cycle. Reproduced from Moore and coauthors⁹⁰ with permission.



Whether similar patterns of immune suppression are present in surviving patients is unclear. If further research identifies evidence of immune suppression in surviving patients, administration of agents such as interleukin-7 and interleukin-15 that target the restoration of immune function could help ameliorate immunosuppression, and perhaps, enhance survival.

Venet and coauthors⁹⁵ contributed additional data confirming evidence of immune suppression in septic patients in *Critical Care Medicine*, 2013. The authors assessed T lymphocyte receptor diversity across the entire genomic spectrum of this population of lymphocytes. Reduced receptor diversity has been documented in immune deficiency states such as those observed in post-bone marrow transplant patients, patients with HIV, and patients with chronic hepatitis C.

Encouragingly, the authors reported an overall mortality rate of 18% in their patients, which is significantly lower than mortality rates of >30% reported in other sources cited in the article. They attributed this improved outcome to the early application of evidence-based therapies for resuscitation and source control.

In this study, 41 patients admitted with septic shock had T-cell receptor diversity assessed on day one and day seven after admission. The analysis showed that T-cell diversity was abnormally low on day one and rapidly returned toward normal on day seven. Patients admitted with reduced T-cell receptor diversity had a higher risk of mortality and an increased risk of developing a nosocomial infection.

The authors concluded that analyses of lymphocyte function may contribute significantly to our understanding of the pathophysiology of sepsis.

Surgical patients with sepsis present with a variety of hemodynamic patterns. Signs of end-organ perfusion problems are frequently discovered early in the course of management. One possible mechanism of end-organ hypoperfusion is thought to be diffuse occlusion of the vessels in the microcirculation. De Backer and coauthors⁹⁶ provided data to support this interpretation in *Critical Care Medicine*, 2013. The authors assessed the sublingual microcirculation in 252 patients with severe sepsis admitted to a single-institution intensive care unit. The data reported confirmed an early reduction in the proportion of perfused microvessels, with a return toward normal by day seven. Interestingly, the proportion of nonperfused microvessels was predictive of mortality and the level of perfusion recovery was associated with an improved chance of survival. As sepsis persisted, the reduction in perfused microvessels continued to be a moderately strong (area under the ROC curve of 0.818) predictor of mortality. The authors concluded that an early and persistent depression of microvessel perfusion is a clinical indicator of sepsis severity and, if confirmed in other patient groups, could be used to determine both the adequacy of therapy and the risk of adverse outcomes. In an editorial accompanying the De Backer et al article, van Griensven⁹⁷ emphasized the discrepancy between most measures of global hemodynamics and tests that assess the adequacy of microcirculation and tissue oxygen delivery. Cited data indicated that the single global hemodynamic variable most closely associated with tissue oxygen delivery and microvessel perfusion adequacy is central venous oxygen saturation. Measures that would increase the recruitment of perfused microvessels may improve sepsis outcomes and these are worthy targets of future research.

The epidemiology and risk factors of sepsis in multiple trauma patients was the focus of an article by Wafaisade and coauthors⁹⁸ in *Critical Care Medicine*, 2011. The authors conducted a retrospective analysis of outcomes in patients entered into a national trauma registry in Germany between 1993 and 2008; nearly 30,000 patients with complete data were identified. The analysis showed that the incidence of sepsis declined over the study interval

but had become stable in recent years. Overall mortality declined from 17% to 12% over the study interval, but the mortality of patients who developed sepsis was stable (in the range of 20%). Risk factors for sepsis in this patient group were age, male gender, Glasgow Coma Score <8 in the prehospital phase of care, severity of injury, number of transfusions needed, number of operative procedures needed, and need for laparotomy. The authors concluded that knowledge of risk factors for sepsis could assist in developing sepsis prevention protocols for injured patients.

Critical Care of the Patient with Sepsis & Septic Shock

The earlier discussion of the pathophysiology of sepsis and septic shock emphasized the diversity of physiologic responses to inflammation and infection. Generalized vasodilation and a hyperdynamic circulation usually characterize the septic state. Arterial pressure may be within the low-normal range and cardiac index may be increased. Despite these observations, signs of end-organ hypoperfusion, manifested by elevated blood lactate levels, may be present. In patients with severe sepsis, evidence of end-organ hypoperfusion is clear-cut. Septic shock is present when patients exhibit hypotension resistant to intravascular and extracellular volume expansion. Faced with these combinations of clinical manifestations, surgeons caring for septic patients need to be familiar with the available means of assessing circulatory status (see the earlier section on monitoring patients in shock) and with the use of volume expanders, vasopressors, inotropic agents, and adjunctive drugs such as corticosteroids.

Goal-Directed Management of Suspected Sepsis & Septic Shock

Because sepsis and septic shock are associated with infection-induced inflammation, fluid exudation frequently occurs into the inflammation sites. In postoperative patients who become septic, recent or ongoing blood loss may also contribute to hypovolemia. Only when volume status is optimized will clear evidence of myocardial dysfunction become evident. Fluid therapy that is too aggressive contributes to sequestration of edema fluid in

inflamed tissues. In the lung, edema may contribute to alveolar instability, ventilation/perfusion mismatching, and hypoxemia. For these reasons, early and goal-directed fluid therapy of sepsis and septic shock is a consistent recommendation in practice guidelines.

In 2016, the Surviving Sepsis Campaign³⁴ updated its practice guidelines for managing sepsis, severe sepsis, and septic shock. The document is available free on the Society of Critical Care Medicine website at *sccm.org*. The guidelines strongly support a group of interventions, including early fluid therapy, early antimicrobial therapy, source control, and avoidance of hyperglycemia. The guidelines recommend an initial dose of balanced crystalloid fluid of 30 mL/kg, with additional fluid volumes guided by “dynamic” measurements such as the response of stroke volume to passive leg-raising (see articles reviewed in the section on monitoring patients in shock). Albumin in-

fusion is recommended as a useful addition for septic patients requiring large volumes of fluid for resuscitation. The guidelines do not recommend using hydroxyethyl starch solutions. Illustrations that summarize the recommendations for fluid resuscitation and vasopressor use in septic patients were provided in a summary article by Dellinger and coauthors⁹⁹ (Figure 7 and Figure 8). Each recommended intervention in the guidelines³⁴ was supported by evidence of sufficient strength to justify its inclusion as a performance measure (supported by evidence stronger than expert opinion).

Chang and Holcomb¹⁰⁰ reviewed evidence supporting fluid management approaches for patients with sepsis or septic shock in *Shock*, 2016. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors explained that balanced electrolyte resuscitation fluids are preferred over normal saline for initial fluid

Figure 7

Algorithm describing fluid resuscitation strategy for septic patients. Reproduced from Dellinger and coauthors⁹⁹ with permission.

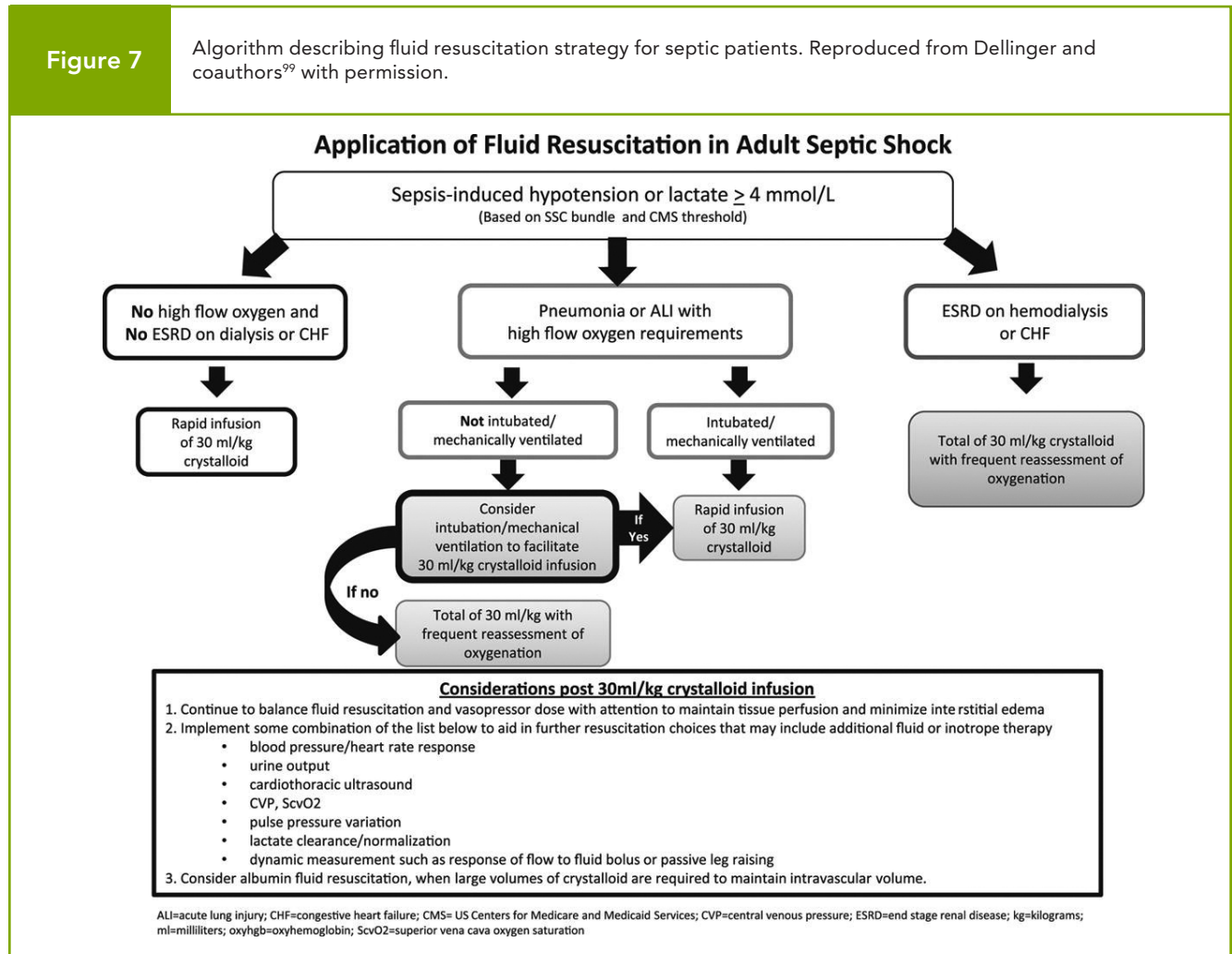
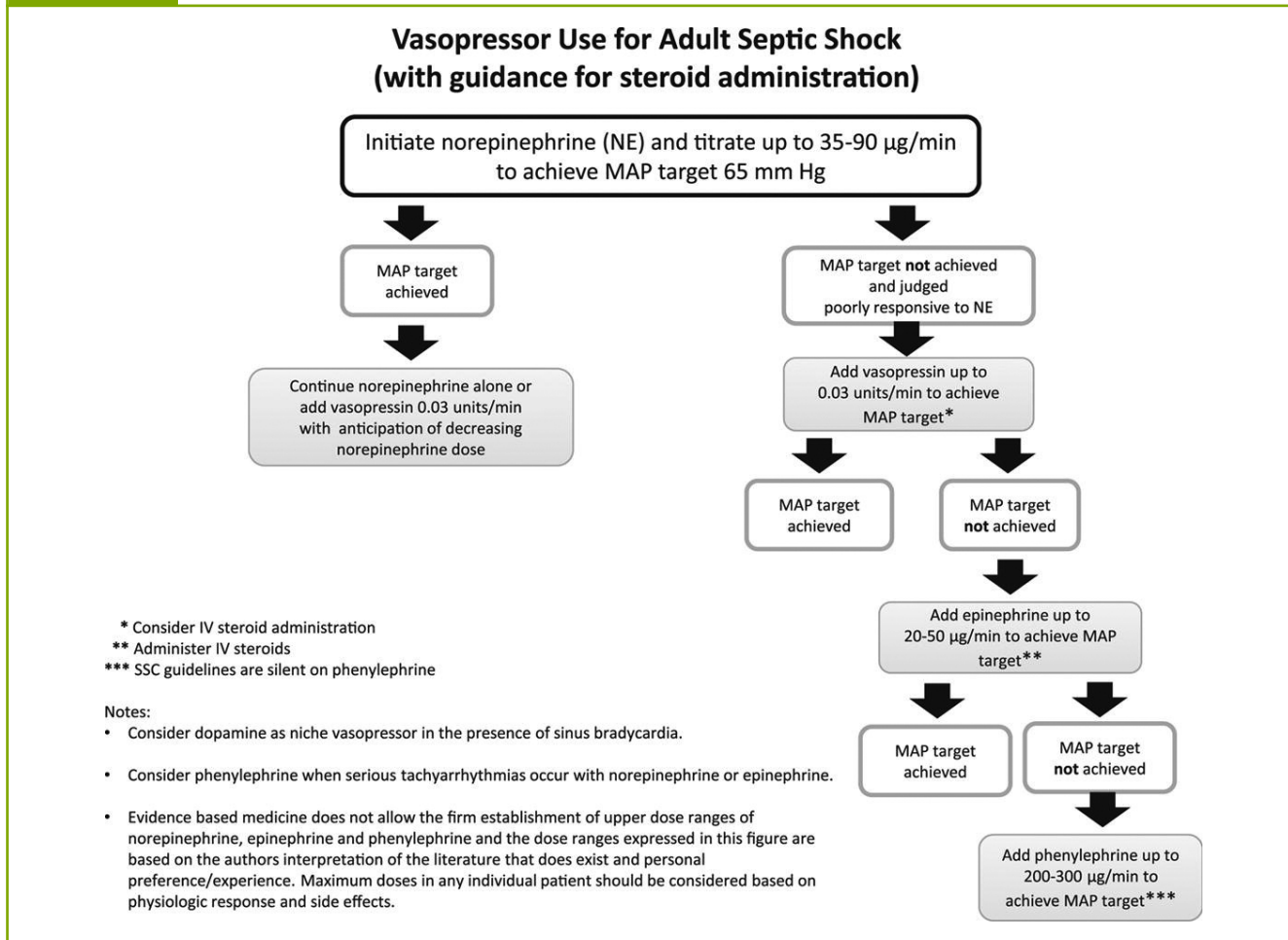


Figure 8

Algorithm describing a sequential approach to the use of vasopressors in septic shock patients. Reproduced from Dellinger and coauthors⁹⁹ with permission.



management of septic patients to prevent the hyperchloremia and acidosis that may result from saline infusion. Available evidence does not support superior outcomes in terms of reduced mortality in patients resuscitated with albumin, although albumin may be useful in supporting intravascular volume in patients requiring large volumes of crystalloid. Data cited by the authors confirmed the increased risk for harm associated with hydroxyethyl starch use.

Goal-directed therapy with intravenous fluids and vasopressor agents is a term that describes a therapeutic strategy designed to support perfusion and oxygen delivery to tissues during a septic episode. Cecconi and coauthors¹⁰¹ conducted a systematic review of the literature relevant to the effectiveness of goal-directed therapy in high-risk surgical patients in *Critical Care*, 2013.

The authors identified 32 acceptable trials that enrolled more than 2,800 patients. The analysis showed that goal-directed therapy reduced mortality significantly in the highest-risk subgroup of patients; high-risk was defined according to the calculated mortality risk. The best results were obtained in studies that reported using crystalloid fluids and vasopressor agents combined with measurements of stroke volume.

As noted in previous discussions, the heterogeneity of hemodynamic responses in patients with shock means that surgeons will need to consider the limitations of central venous pressure as a guide to fluid therapy (see earlier discussion on hemodynamic monitoring of patients in shock). Frequent bedside assessments will be necessary to determine the accuracy of the variable(s) chosen as goals for resuscitation; alternative variables will need to

be considered if resuscitation is not adequate. Jones and coauthors¹⁰² reported a randomized prospective trial of two approaches to goal-directed resuscitation of patients with sepsis and septic shock in *JAMA*, 2010. In this trial, the authors compared resuscitation outcomes when fluid volumes were guided by central venous oxygen saturation vs. lactate clearance. Per the authors, the generally accepted approaches to resuscitating patients with severe sepsis or septic shock include assessing cardiac preload using central venous pressure and estimating perfusion pressure using mean arterial pressure. More controversial are the various approaches to estimating the adequacy of tissue oxygen delivery. The 2013 Surviving Sepsis Campaign practice guidelines¹⁰³ recommend the use of central venous oxygen saturation of 70% or greater as a target indicating adequate tissue oxygen delivery. There are significant barriers to the use of central venous oxygen saturation, including the problems of appropriate sampling and technical challenges related to the measurement process. Jones and coauthors hypothesized that lactate clearance of at least 10% (based on two separate blood samples where lactate was measured) would be as accurate an estimate of tissue oxygen delivery as central venous oxygen saturation. Three hundred patients from several institutions were randomized to one of two comparison groups. The goals of resuscitation for both groups included normalization of systemic arterial pressure and central venous pressure of 8–10 mm Hg. Adequate tissue oxygen delivery was assumed present if lactate clearance was at least 10% when two peripheral blood samples for lactate were compared or if lactate was normal when two samples were drawn at least two hours apart. The analysis showed that short-term mortality rates were equivalent in the two groups, with the lactate clearance group having a 17% mortality compared with 23% in the central venous oxygen saturation group. The authors concluded that lactate clearance can be substituted for central venous oxygen saturation as a surrogate for tissue oxygen delivery.

In an editorial accompanying this article, Lewis¹⁰⁴ reviewed the data supporting the use of goal-directed fluid therapy and remarked that the data supporting this approach are not as strong as would be desired. Also noted was that randomized trials to determine the effectiveness of goal-directed therapy have been flawed. Nonetheless, the accumulated data suggest that improved survival is

associated with goal-directed therapy. The difficulty in obtaining accurate measurements of some variables included in goal-directed strategies (e.g., central venous oxygen saturation) has resulted in lower levels of usage of goal-directed strategies than envisioned by the guidelines-sponsoring organizations. Because of this, it is desirable to substitute an easier measurement technique. The editorialist pointed out a significant limitation to the study reported by Jones and colleagues: advanced resuscitation interventions, such as the use of vasopressors and red blood cell transfusions, were employed in fewer than 10% of the enrolled patients. This suggests that the enrolled patients were a sample drawn from a relatively good-risk cohort. Despite this limitation, the study does support the use of a more easily measured variable as a valid resuscitation goal.

Trof and coauthors¹⁰⁵ offered additional data on the use of monitored hemodynamic variables for goal-directed resuscitation in *Critical Care Medicine*, 2012. The authors conducted a randomized prospective multi-institutional trial comparing transpulmonary thermal dilution (assessment of extravascular lung water) with pulmonary artery catheter-guided resuscitation of patients in shock due to septic and nonseptic etiologies. The analysis equated the two strategies in septic shock patients in terms of hospital length of stay and ventilator-free days. The authors chose these endpoints as surrogates for lung damage risk during resuscitation. For patients with nonseptic shock, the thermal dilution strategy resulted in longer lengths of stay and more time on the ventilator. The authors concluded that the thermal dilution monitoring methodology is useful in patients with septic shock, but these results need to be interpreted with caution. As pointed out by Takala¹⁰⁶ in an editorial that accompanied the article, the authors failed to demonstrate a clear benefit of thermal dilution-guided fluid resuscitation in septic patients. This probably was the result of a significantly higher fluid volume delivery to this patient group when monitored by thermal dilution.

Boyd and coauthors¹⁰⁷ sought to confirm the potential harm of fluid overload during goal-directed resuscitation of patients with sepsis in *Critical Care Medicine*, 2011. The authors reported a retrospective review of data gathered during a randomized prospective trial of vasopressin as an adjunct to resuscitation of septic and septic shock patients. The reported data included 12-hour and four-day

fluid balance and central venous pressure measurements. The principle end point of the study was 28-day all-cause mortality. The authors found that patients with the highest quartile of positive fluid balance (17–24 liters positive balance by day four) had a significantly increased risk of death. The lowest risk of death was observed in patients who had a positive fluid balance of <3 liters after 12 hours of therapy. The authors also discovered that central venous pressure was reflective of fluid balance during the first 12 hours of resuscitation, but that after that time point, there was no correlation between central venous pressure and fluid balance. Patients with sustained central venous pressures of 12 mm Hg or higher were at increased risk of positive fluid balances in the higher mortality range. The authors concluded that there is a direct relationship between high positive fluid balance and mortality and that central venous pressure is an undependable guide for resuscitation after 12 hours of treatment. In an editorial, Ytrebo¹⁰⁸ observed that these data strongly confirm the lack of consistent benefit associated with using central venous pressure as a guide for fluid resuscitation. Instead, the editorialist recommended using a continuous measure of variables such as stroke volume and cardiac index combined with assessments of oxygen delivery and frequent bedside clinical examinations to optimize tissue oxygen delivery and avoid fluid overload.

The Surviving Sepsis Campaign practice guidelines³⁴ recommend red blood cell transfusions during the initial resuscitation of patients with sepsis and septic shock if the patient is anemic. In hemodynamically stable patients, transfusion is recommended for hemoglobin levels <7 g/dL. Parsons and coauthors¹⁰⁹ focused on the association of red blood cell transfusion and mortality at 28 and 90 days in patients with sepsis and septic shock in an article in *Critical Care*, 2011. The authors performed a secondary analysis of outcomes data in patients originally enrolled in a randomized prospective trial. The analysis showed that red blood cell transfusion was not a significant predictor of mortality at 28 and 90 days, even when septic patients met standard criteria for transfusion (hypotension, hemoglobin level <10 g/dL, and depressed central venous oxygen saturation). The authors emphasized that these data should be interpreted with caution because the included patients received transfusions more than 12

hours after a sepsis diagnosis. The authors also argued the possible benefit of red blood cell transfusions early in the management of sepsis patients.

Experts have suggested that critical care “bundles” may improve outcomes by increasing compliance with protocol-based fluid administration, antimicrobials, and monitoring approaches. Whether these techniques actually improve outcomes is unclear. Thompson and coauthors¹¹⁰ compared outcomes of protocol-based care with usual care in septic patients in *Critical Care Medicine*, 2016. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors compared outcomes from administrative data in nearly 50,000 patients treated in hospitals in a single state. The analysis showed that compliance with using the care bundle did not improve mortality risk compared with usual care in the entire patient group. The authors acknowledged variability in adherence to the protocol and that hospitals with very high adherence had improved outcomes compared to hospitals with low adherence. Their conclusion was that additional research is needed to determine the reasons for variability and the factors that might contribute to improved outcomes in high-adherence hospitals.

McKinley and coauthors¹¹¹ explored the effectiveness of evidence-based care using computer-generated protocols in a surgical intensive care unit in the *Journal of Trauma*, 2011. The authors assessed compliance with accepted practice guidelines using computer-generated protocols compared with a paper protocol in a group of historical control patients. The computer-generated protocol showed significant increases in compliance. Antimicrobial therapy was instituted sooner with the computer protocol and the volume of fluids given during resuscitation was not different. Of interest was that mortality decreased from 34% to 14% when the two intervals were compared. The authors concluded that care bundles applied with computer-generated protocols are associated with a significant improvement in patient outcomes.

Vasopressor Use

A considerable proportion of septic patients have mild arterial hypotension. By definition, patients with septic shock are hypotensive. The Surviving Sepsis Campaign³⁴ practice guidelines recommend a target MAP of 65 mm Hg for septic patients. If volume expansion fails to achieve this recommended pressure, the practice guidelines recommend using norepinephrine as the first-line vasopressor of choice. For patients failing to achieve the pressure target, the guidelines also recommend adding arginine vasopressin to the vasopressor therapy. Current practice guidelines recommend against the use of dopamine as either a low-dose therapy or standard-dose approach for sepsis-associated hypotension. Patients with persistent hypoperfusion may benefit from escalation of vasopressor therapy using epinephrine and phenylephrine in sequence.

De Backer and coauthors¹¹² confirmed the potential harm of dopamine use in the *New England Journal of Medicine*, 2010. The authors' randomized prospective trial compared norepinephrine to dopamine in 1,000 patients with septic shock. The trial results showed no significant difference between the dopamine and the norepinephrine groups in terms of mortality. A 95% confidence limit for the mortality difference was wide and the upper bound was a 42% mortality increase for patients treated with dopamine. The frequency of cardiac arrhythmia was significantly higher in patients randomized to receive dopamine. The authors concluded that patients with cardiogenic shock should not be treated with dopamine because of an increased risk of death. They also emphasized that the occurrence of cardiac arrhythmias in patients treated with dopamine suggests that this drug should not be used to manage hypotension in patients with shock.

A study by Jhanji and coauthors¹¹³ in *Critical Care Medicine* reported increases in cutaneous oxygen tension and microvascular flow with increasing norepinephrine doses in 16 patients with septic shock. These authors used transcutaneous oxygen measurements and Doppler laser flowmetry to assess microvascular oxygen availability and blood flow. Sublingual microvascular flow was assessed with Sidestream Dark Field imaging. The authors adjusted the dosing of norepinephrine to achieve mean arterial pressures of 60, 70, 80, and 90 mm Hg, sequentially. Global oxygen delivery as well as cutaneous oxygen ten-

sion and cutaneous microvascular flow increased in keeping with each MAP increase. Sublingual microcirculatory status did not change. The authors did not obtain outcome assessments in these patients. The authors concluded that additional research is desirable to refine definitions of optimum endpoints for vasopressor therapy in patients with septic shock.

An older randomized prospective double-blind trial compared norepinephrine treatment alone with norepinephrine combined with arginine vasopressin infusion.¹¹⁴ The outcomes of interest were 28-day and 90-day mortality. The authors did not confirm a mortality benefit in the group treated with norepinephrine plus vasopressin. In the subset of patients with less severe septic shock, there was a trend toward lowered mortality in the group treated with vasopressin, but the authors did not design the study to analyze patients based on shock severity. Overall mortality rates for both groups were low compared with prior experience and this may reflect an overall improvement in outcomes for patients with sepsis treated with modern protocol approaches. Because vasopressin, in the low doses recommended, has few, if any, adverse side effects, combining norepinephrine and vasopressin in selected patients may be beneficial. There is a need for additional data regarding this association.

There are provocative data that suggest a beneficial effect of heart rate control in patients with sepsis and septic shock to improve microcirculation and overall outcome. Morelli¹¹⁵ evaluated the potential benefits of heart rate control with the β -blocking agent esmolol in a prospective observational study in *Critical Care Medicine*, 2013. The author recorded changes in stroke volume and microcirculatory flow measured with sublingual capnometry. The study enrolled 25 patients and target heart rate range was 80–94 beats per minute. All patients achieved target heart rates, according to the analysis. Stroke volume was maintained at baseline levels during esmolol infusion and a significant increase in microcirculatory flow was observed. Norepinephrine requirements decreased during esmolol administration.

An article by Macchia and coauthors¹¹⁶ in *Critical Care Medicine*, 2012, examined outcomes recorded for patients with sepsis in a national database. They compared mortality rates in patients taking β -blocking agents

prior to admission with patients not taking these drugs. Chronic use of β -blocking agents was associated with a significantly reduced mortality rate (17% vs. 22%). Morelli and coauthors¹⁵ reported hemodynamic data obtained in patients with septic shock who were receiving corticosteroids (200 mg per day) and were being treated with norepinephrine to support arterial pressure (target MAP of 65 mm Hg). The authors administered esmolol intravenously to achieve a target heart rate of 80–94 beats per minute. Patients who achieved the target heart rates showed reduced cardiac index, but stroke volume remained unchanged. In treated patients, the study also reported:

- Improved microcirculatory flow, as measured in the sublingual vessels
- Reduced norepinephrine levels
- Preserved recommended target level of MAP and central venous oxygen saturation

The authors did not report overall mortality rates. Confirmation of these observations in larger prospective randomized trials may lead to heart rate control becoming a component of hemodynamic management for patients with sepsis and septic shock.

Corticosteroid Use

The Surviving Sepsis Campaign practice guidelines³⁴ do not recommend the routine use of corticosteroids when resuscitating patients with sepsis and septic shock. In patients with septic shock, the guidelines suggest 200 mg per day of cortisone if patients remain hypotensive with signs of end-organ hypoperfusion after maximal support with intravenous fluids and vasopressors. The guidelines also do not recommend using the ACTH stimulation test to detect relative adrenal insufficiency.

Recombinant Activated Protein C Use

Sepsis and septic shock trigger an inflammatory and procoagulant cascade that predisposes to microvascular thrombosis; this may be the etiology of organ failure leading to death in septic patients. A number of interventions designed to modulate these cascades have been evaluated

to target the underlying pathophysiology of sepsis. Success has been limited in these trials. An agent targeting the coagulation system is recombinant activated protein C. A randomized clinical trial comparing recombinant activated protein C to placebo in patients with sepsis and septic shock was by Ranieri and coauthors¹⁷ in the *New England Journal of Medicine*, 2012. The authors reported a trial that enrolled 1,697 patients. According to the authors, an earlier trial reported by Bernard and coauthors¹⁸ in the *New England Journal of Medicine*, 2001, documented a 6% absolute mortality reduction in patients with severe sepsis who were treated with recombinant activated protein C. This survival advantage was observed in patients who were severely ill only (APACHE II score >25). The main adverse effect of treatment with recombinant activated protein C was bleeding; there are reports of fatal intracranial hemorrhage in patients with use of the drug. Ranieri and colleagues¹⁷ found no improvement in 28-day or 90-day mortality in patients treated with recombinant activated protein C. There was no significant benefit of treatment, even with protein C level depression. The authors concluded that there is no evidence of benefit of recombinant activated protein C use in patients with sepsis or septic shock.

Antimicrobial Therapy

The Surviving Sepsis Campaign guidelines³⁴ recommend the early use of intravenous antimicrobial therapy designed to cover all expected organisms, with a subsequent de-escalation of therapy based on culture results. It is important that clinicians be aware of the frequencies of infecting organisms in the hospital environment. As mentioned previously, most episodes of sepsis in surgical patients are the result of intraabdominal infections. Enteric organisms will be the most frequent etiologic agents in these situations. For patients who develop intraabdominal sepsis while hospitalized, antimicrobial choices will need to include the multidrug-resistant organisms. Antimicrobial therapy is important but not the sole component of source control. Source control refers to eradicating the infection that is the cause of the episode of sepsis and/or septic shock. Over time, published research has suggested that sepsis and septic shock are the result of a

dysfunctional set of inflammatory, microcirculatory, and immune responses that proceed regardless of the outcome of the infection that stimulated the response.

An article that focused on infection as the main driver of the septic response was by Kumar¹¹⁹ in *Virulence*, 2014. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The author cited data supporting the concept that the microbial load drives the inflammatory response and that reducing the microbial load as quickly as possible following patient presentation would be the best method of limiting the systemic inflammatory, microcirculatory, and immunologic changes that produce the clinical and laboratory features of sepsis and septic shock. The natural conclusion from the data cited is that controlling the infection is the best way to reduce the mortality risk for patients with sepsis and septic shock. The data presented in the article support early antimicrobial therapy and surgical or percutaneous interventions to treat localized foci of infection. The author recommends choosing antimicrobials based on an understanding of the microbiologic patterns of infections occurring in the treating hospital, the location of the infection, and patient risk factors. Optimization of antimicrobial therapy using bactericidal agents, combination therapies, and monitoring of antimicrobial blood levels are measures supported by the data reviewed in the article.

Martinez and coauthors¹²⁰ analyzed the effects of source control on outcomes of care for patients with sepsis and septic shock in a study in *Critical Care Medicine*, 2017. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors performed a prospective observational study that included more than 3,600 patients with sepsis cared for in 99 intensive care units in a single country. Source control interventions for urinary, abdominal, and soft tissue infections were performed in 1,173 patients. The patient group undergoing source control were older, had a higher proportion of organ dysfunction, higher levels of serum lactate, and lower compliance with recommended resuscitation. Despite these factors, mortality was significantly lower in patients who underwent source control. The authors observed that time from admission to source control did not influence mortality. The authors proposed that delays might occur because of small foci of infection that might not be detected, because caregivers want to avoid

emergency intervention, or because of a desire by surgeons to wait until an area of necrosis had completely defined itself (in soft tissue infections, for example). The authors concluded that source control, whenever possible, has significant benefit for septic patients—supported by the finding of no adverse outcomes related to the time from source detection to the source control intervention. The authors confirmed that hospital stay was longer for patients undergoing source control. They hypothesized that this occurred because the majority of patients needing source control had abdominal infections and required one or more operative procedures.

An article that provided evidence confirming the importance of the infection source as the driver of the pathophysiologic patterns and outcomes of sepsis and septic shock was by Kalil and coauthors¹²¹ in *Critical Care Medicine*, 2017. The authors conducted a meta-analysis of prospective randomized trials and observational studies that focused on the effectiveness of early goal-directed fluid therapy for patients with sepsis and septic shock. The included studies reported on nearly 20,000 patients. The authors' analysis showed evidence of benefit for early goal-directed therapy in observational studies but not in randomized prospective trials. The consistent difference in the two types of studies was that early, appropriate antimicrobial therapy was used in the randomized prospective trials but was inconsistently used in the observational studies. The authors concluded that early control of the infection causing sepsis or septic shock was the main factor associated with successful outcomes of treatment of sepsis and septic shock.

Data supporting the use of early antimicrobial therapy were presented in an article by Ferrer and coauthors¹²² in *Critical Care Medicine*, 2014. The authors performed a retrospective study of prospectively gathered data used in the Surviving Sepsis Campaign; they reviewed outcomes from nearly 18,000 septic patients. Overall mortality in the group was 29.7%, reflecting the severity of illness in the included patients. The authors identified a statistically significant increase in risk of death with increasing time to administration of antimicrobial agents. This trend persisted after adjusting for risk factors such as intensive care unit admission.

Labelle and coauthors¹²³ reported outcomes of septic patients treated initially with appropriate antibiotic therapy in *Critical Care Medicine*, 2012. These authors analyzed medical record data on 436 consecutive, mixed medical and surgical patients with sepsis and septic shock treated in a single institution. Record review of antibiotic use and culture results identified patients who received appropriate initial antimicrobial therapy. More than half of the patients reviewed died during the hospitalization where sepsis treatment occurred. The analysis showed that determinants of mortality in patients treated with appropriate initial antimicrobial therapy were illness severity, as reflected in the APACHE II scores, and acquisition of infection in the intensive care unit. Of interest was that MRSA infection was a predictor of lower mortality risk. The authors concluded that future improvements in outcomes for this patient group could result from measures designed to prevent and aggressively treat intensive care unit-acquired infections.

Cardiogenic Shock Management

The clinical features of cardiogenic shock comprise arterial hypotension (systolic blood pressure <90 mm Hg) combined with signs of end-organ hypoperfusion (acidosis, elevated serum creatinine, abnormal sensorium), depressed cardiac index, and signs of ventricular dysfunction. Cardiogenic shock occurs in 7% of patients after myocardial infarction and this condition is the most common cause of early death after myocardial infarction. Other conditions that complicate myocardial infarction, such as papillary muscle rupture with acute mitral insufficiency and ventricular wall rupture with pericardial tamponade, are surgical emergencies that also cause cardiogenic shock.

Clinical practice guidelines for cardiogenic shock management were included in guidelines for managing ST-segment elevation myocardial infarction promulgated in 2013 by the American College of Cardiology and the American Heart Association.¹²⁴ These guidelines state that

cardiogenic shock following myocardial infarction occurs most often during the first 24 hours after the ischemic event.

Topalian and coauthors¹²⁵ discussed the epidemiology of cardiogenic shock in *Critical Care Medicine*, 2008. These authors cited three reports indicating that cardiogenic shock complicating myocardial infarction (defined as ST-segment elevation and/or new left bundle branch block on electrocardiogram) occurred in 7.1%–8.6% of patients after myocardial infarction. Once cardiogenic shock was diagnosed, subsequent mortality rates reported were 60%–80%. Mortality rates were higher in patients older than 75. Topalian and colleagues stressed recent data showing that aggressive attempts to provide complete revascularization of critical coronary stenoses and occlusions in patients with cardiogenic shock have resulted in lower mortality rates approaching 48%. The clinical practice guidelines¹²⁴ referred to earlier recommend revascularization using percutaneous interventions or coronary artery bypass as soon as possible after the shock diagnosis and delineation of the vascular anatomy. Fibrinolytic therapy is recommended for patients when revascularization is not feasible.

Patients at an increased risk of cardiogenic shock after myocardial infarction include older patients and patients with a history of hypertension, dyslipidemia, and previous coronary angioplasty. Cardiogenic shock has an average time of onset, after the appearance of clinical evidence of myocardial infarction, of seven hours. According to the Topalian et al review,¹²⁵ cardiogenic shock can occur after myocardial infarctions that result in ST-segment elevation and in those patients without ST-segment elevation accompanying the infarction. The etiology of infarction and cardiogenic shock is usually multivessel coronary atherosclerosis. In one report cited by the authors, more than half the patients with cardiogenic shock after myocardial infarction had triple vessel disease and more than 15% of patients had significant left main coronary artery stenosis. Anterior infarction is common, but multiple sites of infarction are diagnosed in more than half the patients who develop cardiogenic shock. Nearly 80% of patients who develop cardiogenic shock have left ventricular failure as the main pathogenesis of the shock event. Acute mitral insufficiency, septal rupture, right ventricular infarction, and ventricular wall rupture with pericardial tamponade

account for the remaining patients. Ventricular wall rupture is the least frequent etiology of cardiogenic shock, accounting for less than 1.5% of instances. Acute mitral insufficiency accounts for 7% of patients developing cardiogenic shock.

The pathophysiology of cardiogenic shock was the subject of an older review by Aymong and coauthors¹²⁶ in *Medical Clinics of North America*, 2007. The authors emphasized the critical importance of reduced coronary blood flow that results in a state of myocardial oxygen deprivation and disordered myocardial energy metabolism. They noted that heart muscle is very reliant on aerobic energy metabolism. Oxygen utilization in contracting heart muscle ranges from 8 mL to 15 mL of oxygen per 100 g tissue per minute. The noncontracting muscle uses only 1.5 mL of oxygen per 100 g tissue per minute. The heart, even in periods of low activity, extracts two to three times more oxygen than any other single organ. Myocardial oxygen demand is determined by ventricular tension, heart rate, and contractility. Oxygen delivery to the myocardium via the coronary arteries is primarily a diastolic phenomenon. Coronary perfusion pressure can be estimated from the difference in aortic diastolic pressure and mean left ventricular pressure. Coronary vascular resistance interacts with coronary perfusion pressure to determine net coronary flow.

Complicated interactions among various local and systemic mediators determine coronary vascular resistance. Endothelial dysfunction occurs because of coronary atherosclerosis and produces abnormal coronary responses to endogenous mediators of vasoconstriction and vasodilation. The net result is disordered autoregulation, with coronary flow becoming progressively more dependent on coronary perfusion pressure. Diastolic coronary perfusion can be reduced during conditions where cardiac output is decreased and when the diastolic interval is reduced (tachycardia). Myocardial infarction resulting from coronary thrombosis directly reduces coronary flow because of obstruction. With extensive involvement of the ventricular wall, cardiac output is reduced. Tachycardia results from the catecholamine response to reduced cardiac output and these factors combine to produce a self-perpetuating cycle of myocardial ischemia and infarction. Topalian and associates¹²⁵ emphasized that “ischemia begets ischemia” during this cycle.

Ventricular dysfunction leads to elevated end-diastolic pressures and pulmonary congestion. Elevated ventricular filling pressures increase myocardial wall stress. The authors of a series cited by Topalian et al observed restricted left ventricular filling in more than 60% of patients evaluated by echocardiography. This pathophysiologic process is complicated by the elaboration of inflammatory mediators. A report the authors referred to cited clinical evidence of systemic inflammatory response syndrome in 20% of patients. Aymong and colleagues¹²⁶ cited data indicating that elevated levels of interleukin-6 have been documented in patients with cardiogenic shock and that these levels are equivalent to the levels recorded in patients with sepsis and septic shock. Topalian and associates¹²⁵ and Aymong and colleagues¹²⁶ also found that the proinflammatory state observed in some patients with cardiogenic shock was associated with the stimulation of inducible nitric oxide. Unfortunately, a blockade of inducible nitric oxide synthesis did not produce a benefit in patients with cardiogenic shock. Aymong and coauthors stated that myocardial ischemia can result in myocyte necrosis. Other cells die because of apoptosis (programmed cell death). In addition, myocardial cells may be “stunned” from ischemia. Stunned cells do not recover full contractile function with early restoration of perfusion from revascularization procedures. Thus, normal contractile function might not be restored for several weeks after coronary artery thrombosis followed by revascularization.

The extensive multivessel coronary atherosclerosis seen in autopsy reports of patients dying of myocardial infarction and cardiogenic shock usually produces multiple myocardial infarctions of varying age rather than a single massive infarction. Low coronary flow and increased coagulation activity because of unstable coronary plaque can produce progressive coronary thromboses that extend to involve branches of the artery where the thrombosis originated. The authors explained that declining myocyte contractility can occur in areas remote from the infarction and this may be a consequence of hypoxia-inducible factor-1 production, which is stimulated when cardiac cell mitochondria sense hypoxia. This factor produces reduced cell metabolism and contractility. The resulting low metabolism state produced in areas remote from the infarction is termed “myocardial hibernation.” One of

the benefits of treating cardiogenic shock with intraaortic balloon counterpulsation may be restoration of coronary perfusion and myocyte oxygenation that serves to reverse myocyte hibernation and recover contractility.

Managing patients with suspected cardiogenic shock begins with a rapid assessment to determine adequacy of the airway, oxygenation, and circulation. Patients suspected to be hypovolemic may benefit from a fluid challenge and/or blood transfusion. Physical examination assisted by plain chest radiograph can disclose clinical evidence of pulmonary congestion. Electrocardiography and echocardiography are useful, early in patient management, to quantify the extent of ischemia and left ventricular dysfunction. Similarly, pulmonary artery catheter placement can supply sequential data on pulmonary artery pressures and cardiac index. Echocardiographic assessments of preload and ejection fraction (discussed in the section on diagnosing and monitoring patients in shock) may supply valuable data to guide the use of volume expansion strategies.

Topalian and colleagues¹²⁵ stressed that signs of hypoperfusion can occur without profound hypotension. For patients with arterial pressures consistently above 100 mm Hg, intravenous nitroglycerine in doses of 10–20 mcg per minute will produce coronary vasodilation and improve coronary flow. Dobutamine is used for hypotensive patients without signs of end-organ hypoperfusion to elevate arterial pressure. Doses of 2–20 mcg/kg/minute are indicated initially. If signs of hypoperfusion are present, the initial dose can be increased to 5–15 mcg/kg/minute. Failure to achieve improved blood pressure is an indication for using intravenous norepinephrine. Norepinephrine doses are titrated in the 0.5–30 mcg per minute range as a continuous intravenous infusion.

Epinephrine is another vasoactive agent that has been used to improve blood pressure and end-organ perfusion in patients with cardiogenic shock. A randomized prospective trial comparing the combination of dobutamine-norepinephrine to epinephrine in patients with cardiogenic shock not due to an acute ischemic event was by Levy and coauthors¹²⁷ in *Critical Care Medicine*, 2011. These authors randomized 30 patients to receive either epinephrine infusion or dobutamine-norepinephrine infusion. Patients were enrolled if standard definitions of

cardiogenic shock were fulfilled, a trial of dopamine had not improved blood pressure, and an acute myocardial ischemic event had been ruled out. The analysis showed that both agents raised MAP and improved end-organ perfusion, as reflected by improved urinary output. The epinephrine group had a higher frequency of new cardiac arrhythmias diagnosed and measurements of splanchnic perfusion (gastric mucosal perfusion) showed worse splanchnic perfusion in the epinephrine group.

The authors concluded that the combination of dobutamine-norepinephrine is preferable for vasopressor support in patients with cardiogenic shock who have not responded to dopamine infusion. In an editorial that accompanied the article, Krenn and Delle Karth¹²⁸ stressed that the increased rate-pressure product that resulted from epinephrine infusion may have reduced oxygen delivery to the myocardium and caused decreased splanchnic perfusion and a tendency toward new arrhythmia development in the patients receiving epinephrine. Despite the relatively small number of patients included in the trial, the editorialists agreed with the authors' conclusion that dobutamine-norepinephrine is preferable for managing cardiogenic shock that is not the result of an acute ischemic event.

Topalian and coauthors¹²⁵ also discussed intraaortic balloon counterpulsation. These devices, which can now be introduced percutaneously, can improve coronary flow and reduce left ventricular afterload. Currently, these devices are mainly used as “bridges” to revascularization interventions. Nearly one-third of the insertions of intraaortic balloon devices, in a report cited by these authors, were for cardiogenic shock. Practice guidelines list intraaortic balloon pump support as a useful intervention for managing patients with cardiogenic shock complicating a myocardial ischemic event.¹²⁴

Other data have called the perceived benefit of intraaortic balloon counterpulsation into question. A randomized, prospective trial by Thiele and coauthors¹²⁹ in the *New England Journal of Medicine*, 2012, reported data on 600 patients with cardiogenic shock (systolic blood pressure <90 mm Hg, need for vasopressor support, and/or signs of end-organ hypoperfusion) complicating a myocardial ischemic event. Patients were eligible for randomization if a myocardial revascularization procedure

was planned. The data analysis showed that intraaortic balloon counterpulsation did not reduce 30-day all-cause mortality (39% vs. 41% for control patients). Although there was a brief early improvement in laboratory markers of end-organ hypoperfusion, this benefit was not observed after day four of counterpulsation. The authors concluded that intraaortic balloon counterpulsation has no measurable benefit in terms of reduced mortality. In an editorial that accompanied the article, O'Connor and Rogers¹³⁰ pointed out that the patients included in this trial were moderate-risk patients and the results may not be generalizable to the highest-risk patient groups. They agreed that the data support the discontinuation of any routine use of intraaortic balloon counterpulsation for the majority of patients with cardiogenic shock complicating a myocardial ischemic event.

Topalian and coauthors¹²⁵ concluded their review by noting that death from cardiogenic shock occurs more often when there is a delay in diagnosing myocardial infarction; therefore, the authors encourage public education efforts to inform patients of the importance of early medical care at the first sign of acute myocardial ischemia.

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hope our surgical critical care series has been informative and helpful to you and your practice. The next issue of *SRGS* will begin our two-part Trauma series.

Thanks for reading *SRGS*!



Lewis Flint, MD, FACS
Editor in Chief

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Posttest | **CRITICAL CARE OF
SURGICAL PATIENTS, PART II**
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- 1. Which of the following is the expected frequency of fatal transfusion reactions?**
 - a) 1/100 transfusions
 - b) 1/650 transfusions
 - c) 1/200,000–400,000 units transfused
 - d) 1/1,250 units transfused
 - e) 1/7,500 units transfused
- 2. Which of the following is true regarding viral disease transmission by blood transfusion?**
 - a) Since 1999, only two instances of HIV transmission by blood and blood product transfusion have been reported
 - b) Hepatitis B transmission occurs once in every 2,000–4,000 transfusions
 - c) Hepatitis C transmission is the most common cause of death resulting from transfusion
 - d) HIV transmission by blood transfusion is gradually increasing after several years of declining incidence
 - e) Hepatitis C transmission is associated with the lowest risk of chronic liver disease
- 3. Which of the following patient groups is most vulnerable to transfusion-related cytomegalovirus disease?**
 - a) Bone marrow transplant patients
 - b) Patients with chronic renal disease
 - c) Diabetic patients
 - d) Patients with a history of myocardial infarction
 - e) Liver transplant patients
- 4. Current clinical practice guidelines promulgated by the AABB suggest that blood transfusion should be considered at which of the following hemoglobin levels?**
 - a) Hemoglobin of 10 g/dL
 - b) Hemoglobin of 8 g/dL
 - c) Hemoglobin of 12.5 g/dL in patients with heart disease
 - d) Hemoglobin of 7 g/dL
 - e) Hemoglobin of 4.5 g/dL
- 5. Which of the following led to the practice of refusal of blood transfusions by Jehovah's Witnesses?**
 - a) The belief that banked blood was contaminated with animal blood
 - b) The definition of intravenous fluid administration as "intravenous feeding"
 - c) The belief that donation of blood was a sin leading to excommunication from the church
 - d) The belief that receiving bank blood increased the risk of contracting syphilis
 - e) The belief that New Testament teachings forbid blood transfusion
- 6. A Jehovah's Witness patient informs you that he will accept a blood transfusion but that his permission to administer blood is a private agreement between the two of you. During the subsequent operation, bleeding is encountered requiring transfusion of two units of packed red blood cells. Postoperatively, the surgeon should do which of the following?**
 - a) Inform the representative of the local Jehovah's Witness congregation that blood was necessary and was given consistent with the patient's wishes
 - b) Do not inform the patient that blood was given
 - c) Inform the patient, but no one else, that blood was given
 - d) Inform the hospital ethics committee that blood was given
 - e) Obtain written assurance from the patient that no malpractice action will be pursued for any reason
- 7. The "damage control" approach to managing patients with severe injury, shock, and bleeding includes which of the following?**
 - a) Prehospital electrocardiographic monitoring
 - b) Intravenous fluid resuscitation based on serial serum lactate determinations
 - c) Early tetanus immunization
 - d) Abbreviated operation to control bleeding and contamination
 - e) Prehospital administration of prophylactic antibiotics

- 8. Persistent splanchnic ischemia following resuscitation of experimental hemorrhagic shock is caused by?**
- Splanchnic microemboli
 - Occult ischemic pancreatitis
 - Exaggerated production of lactate from the lungs
 - Reduced cardiac output due to coronary artery spasm
 - Swelling of endothelial cells in intestinal microvessels
- 9. Valproic acid protects liver cells from cell death after hemorrhagic shock by what mechanism?**
- Preservation of hepatic blood flow
 - Improved hepatic tissue oxygen tension
 - Neutralization of acid metabolites
 - Stabilization of hepatic cell membranes
 - Prevention of histone deacetylation
- 10. Which of the following statements is true regarding hemodynamic monitoring of patients in shock?**
- Percutaneous arterial catheters are easily placed in shock patients
 - Automated blood pressure cuff readings are falsely high in patients with low blood pressure
 - Echocardiography is not accurate in diagnosing cardiac dysfunction in hypotensive patients
 - Patients in shock after injury are always hypotensive
 - Heart rate below 100 bpm accurately excludes the diagnosis of shock
- 11. Which of the following is a relative contraindication to the use of hypotensive resuscitation?**
- Age >55 years
 - Severe pelvic fracture
 - Suspected solid organ injury
 - High mangled extremity score
 - Presence of traumatic brain injury
- 12. According to data reported by Murthi and coauthors, evidence of myocardial dysfunction observed with the use of transthoracic echocardiography was diagnosed by simultaneous findings of reduced cardiac index recorded by pulmonary artery catheter measurements in what percentage of patients?**
- 27%
 - 50%
 - 10%
 - 74%
 - 95%
- 13. According to data reported by Giraud and coauthors, a rise in venous oxygen saturation in response to an intravenous fluid bolus predicts a favorable outcome from intravenous fluid therapy with a sensitivity range of which of the following?**
- 98%–100%
 - 22%–35%
 - 50%–55%
 - 80%–85%
 - 70%–75%
- 14. Cytosolic production of lactate results from conversion of pyruvate to lactate in a reaction catalyzed by which of the following?**
- Insulin
 - Albumin
 - Lactic dehydrogenase
 - Tumor necrosis factor
 - Tyrosine kinase
- 15. Which of the following can produce trauma-related coagulopathy without hemorrhagic shock?**
- Multiple long-bone fractures
 - Liver injury
 - Bladder injury with urinary extravasation
 - Traumatic brain injury
 - Trauma-associated adrenal hemorrhage

16. Improved mortality from coagulopathy has been associated with all of the following except which one?

- a) Early recognition of massive bleeding
- b) Early use of aprotinin
- c) Administration of fresh frozen plasma in a ratio of 1:1 with red blood cells and platelets
- d) Damage control approaches to stop bleeding, control contamination, and shorten duration of initial operation
- e) Early administration of platelets

17. Each of the following is acceptable for goal-directed therapy of patients in septic shock except which one?

- a) Red blood cell transfusion
- b) Albumin
- c) Balanced electrolyte solutions
- d) Norepinephrine
- e) Hydroxyethyl starch

18. The 2013 Surviving Sepsis Campaign practice guidelines recommendations for the hemodynamic management of septic patients include all of the following except which one?

- a) The target mean arterial pressure is 65 mm Hg to 70 mm Hg
- b) The target central venous pressure is 8 mm Hg to 12 mm Hg
- c) Elevated serum lactate should return to normal within 24 hours of admission
- d) Target urine output is 0.5 mL/kg
- e) Target venous oxygen saturation is 90%

19. All of the following are true regarding cardiogenic shock except which one?

- a) Most patients who develop cardiogenic shock have triple-vessel coronary artery disease
- b) Patients older than 75 years have lower risk for cardiogenic shock and lower mortality if it occurs
- c) Ventricular wall rupture is the cause of cardiogenic shock in 1.5% of patients
- d) Left ventricular failure is the main physiologic abnormality leading to cardiogenic shock
- e) The myocardial cell depends mainly on aerobic metabolism for energy

20. Recent data indicate that which of the following interventions does not improve mortality risk in cardiogenic shock?

- a) Percutaneous coronary revascularization
- b) Intraaortic balloon pump counterpulsation
- c) Norepinephrine
- d) Dobutamine
- e) Intravenous fluid therapy and/or blood transfusion in hypovolemic patients

The following four questions are required by the American College of Surgeons for accreditation purposes. You must complete these four questions before submitting your answers.

21. This issue met the stated learning objectives.

- a) Strongly agree
- b) Agree
- c) Neutral
- d) Disagree
- e) Strongly disagree

22. The content was relevant to my educational needs and practice environment.

- a) Strongly agree
- b) Agree
- c) Neutral
- d) Disagree
- e) Strongly disagree

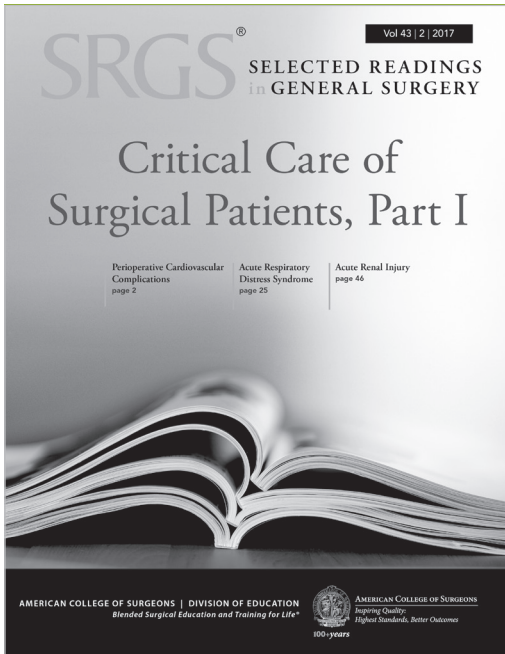
23. There are potential barriers to incorporating what I have learned from this issue into my practice.

- a) Strongly agree
- b) Agree
- c) Neutral
- d) Disagree
- e) Strongly disagree

24. The content was fair, objective, and unbiased.

- a) Strongly agree
- b) Agree
- c) Neutral
- d) Disagree
- e) Strongly disagree

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Full-text reprints of these articles are included in certain formats of SRGS.

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1. Effect of Short-Term vs. Long-Term Blood Storage on Mortality after Transfusion....61-69

Heddle NM, Cook RJ, Arnold DM, et al.

This article provides valuable data on the level of risk associated with using older stored blood for transfusion.

2. Ultrasound assessment of volume responsiveness in critically ill surgical patients: Two measurements are better than one...70-76

Murthi SB, Fatima S, Menne AR, et al.

The best approach for documenting volume responsiveness as a guide for adjusting fluid therapy for septic patients is the subject of ongoing debate. This report offers data supporting the use of complementary measurements to document fluid responsiveness.

3. Coagulopathy after traumatic brain injury...77-88

Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT

The authors review the mechanisms of coagulopathy following traumatic brain injury.

4. Choice of Fluid Therapy in the Initial Management of Sepsis, Severe Sepsis, and Septic Shock...89-98

Chang R, Holcomb JB

This is a well written, valuable review of fluid therapy approaches for the septic patient.

5. An alternate pathophysiologic paradigm of sepsis and septic shock: implications for optimizing antimicrobial therapy...99-116

Kumar A

Kumar provides data supporting the importance of the infection as a driver of the pathophysiology and outcomes of sepsis and septic shock.

6. Impact of Source Control in Patients With Severe Sepsis and Septic Shock...117-125

Martinez ML, Ferrer R, Torrents E, et al.

This report supports the importance of early source control in patients with sepsis and septic shock.

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