

Massive Transfusion and Control of Hemorrhage in the Trauma Patient



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CME QUESTIONS INCLUDED

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LEARNING OBJECTIVES OF THE MONOGRAPH

After completion of this activity, the participant will be able to:

- Evaluate the etiology and pathophysiology of traumatic shock.
- Describe the management of massive transfusion in the trauma patient.
- Discuss the clinical indications and problems related to the use of blood, blood components, hemostatic agents, oxygen-carrying volume expanders, and venous thromboembolism prophylaxis.

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The drug and dosage information presented in this publication is believed to be accurate. However, the reader is urged to consult the full prescribing information on any product mentioned in this publication for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects. This is particularly important for drugs that are new or prescribed infrequently.

Massive Transfusion and Control of Hemorrhage in the Trauma Patient

Introduction

Priorities in trauma patient management are to ensure adequate ventilation and oxygenation, control hemorrhage, and restore tissue perfusion to vital organs. The most familiar means to control hemorrhage are surgical ligatures and clips. Other means include transcatheter embolization, appropriate blood component therapy, maintenance of normothermia, and pharmacologic agents. Finally, attention must also be directed toward treatment of the hypercoaguable state that follows major traumatic injury and can lead to deep venous thrombosis and pulmonary embolism.

The management of massive transfusion and control of hemorrhage in the trauma patient were discussed during two special ITACCS seminars. The 15 reports in this monograph summarize the state-of-the art knowledge and clinical practice issues regarding surgical and nonsurgical management of massive transfusion and control of hemorrhage in the injured patient.

In the section on "Etiology and Pathophysiology," Dr. Scalea reviews the physiologic importance of recognizing and restoring hemostasis following injury and discusses the American College of Surgeons classification scheme for hemorrhage, as well as operative and nonoperative (e.g., embolization) techniques for treatment of ongoing blood loss. Dr. Dutton discusses the four phases of traumatic shock and reviews the macro- and micro-circulatory responses to traumatic shock—responses that ultimately determine patient outcome.

The "Therapeutic Strategies" section begins with a report on surgical perspectives to control bleeding in trauma. In that article, Dr. Plaisier describes the benefits and risks of topical hemostatic agents such as oxidized cellulose, collagen sponges, thrombin, denatured gelfoam, and fibrin glue. Dr. Royston reviews the hemostatic and anti-inflammatory effects of a variety of drugs in trauma. There appears to be a significant benefit of high-dose aprotinin therapy to reduce blood loss and the need for blood and blood product transfusion. Major post-traumatic morbidity and mortality may result from venous thromboembolism, and Dr. Stene discusses therapeutic strategies to prevent and treat deep venous thrombosis and pulmonary embolism in the injured patient. In the article on atraumatic blood salvage and autotransfusion, Drs. Kevy and Brustowicz critique the use of surgical suction systems as a means of reducing (or supplementing) allogeneic blood use. Dr. Smith analyzes the use of fluid and blood component therapy in trauma and addresses various issues such as delayed fluid resuscitation, hypertonic

fluids, endpoints of fluid and blood resuscitation, complications of transfusion therapy, and clinical strategies to reduce complications.

The section on "Transfusion: Clinical Practice" begins with a discussion on the immunologic consequences of transfusions and concludes that allogeneic transfusions have a dynamic immunomodulatory effect on the recipient and that leukocytes are the chief mediator of these effects. Dr. Rosenberg reviews the scientific literature and his own personal experience with the concept of "decreasing the amount of blood transfused to trauma patients" in light of transfusion-related immunosuppression and other risks. Dr. Sweeney evaluates the options, risks, and potential complications of obtaining vascular access in trauma, illustrating the different approaches in pediatric and adult trauma patients. The principles of warming IV fluid and blood are reviewed by Dr. Smith, with special emphasis on the thermal stress of infusing cold or inadequately warmed fluids, and the safety and efficacy of fluid warmers and rapid infusion devices. Dr. Desjardins focuses on the management of exsanguinating hemorrhage (otherwise known as "massive, massive transfusion") and reports on the washing and centrifuging of packed red blood cells prior to rapid infusion in order to decrease adverse metabolic consequences such as hyperkalemia. Drs. Jernigan and D'Alessio discuss their experience using rapid infusion devices to deliver massive quantities of fluids, blood, and blood products to maintain circulating blood volume. These authors point out the controversies over hy-

potensive versus normotensive resuscitation, the benefits of point-of-care testing, and the use of guidelines (in conjunction with the blood bank) for managing trauma patients who require "rapid infusion."

In the final section on "New Horizons in Synthetic Blood Substitutes," Dr. Mackenzie reviews the complex issues surrounding the use of hemoglobin solutions and hemorrhagic shock. He states that, although many of the problems associated with oxygen-carrying solutions have been overcome, there is a paucity of published data concerning the use of oxygen-carrying solutions in humans with hemorrhagic shock. Dr. Schubert concludes the monograph by examining the potential clinical uses and effectiveness of hemoglobin-based oxygen carriers and perfluorocarbons. The long shelf life, long circulation half-life, and good oxygen-carrying capacity and tissue oxygen delivery make these compounds particularly attractive in patients with high blood loss, i.e., trauma patients. In his manuscript, Dr. Schubert evaluates the different hemoglobin solutions and the pitfalls associated with their clinical use.

As editors and principal organizers of this special ITACCS symposium, we have attempted to provide a concise, up-to-date reference on massive transfusion and management of hemorrhage in the trauma patient—a reference that integrates both basic science and clinical practice. We sincerely hope that you, the reader, will obtain essential knowledge from this monograph that will improve your clinical practice when caring for trauma patients.

SECTION I: Etiology and Pathophysiology

1 Trauma, A Disease of Bleeding

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Acute blood loss is a very common problem following injury. Rapid recognition and restoration of homeostasis is the cornerstone of the initial care of any badly injured patient. Untreated, hemorrhage robs the cardiovascular system of the preload necessary to ensure adequate cardiac output and peripheral oxygen delivery. Inadequate perfusion, even if it is not associated with overt hypotension, can set off the neurohumoral cascade, ultimately leading to sequential organ failure.¹ This is especially important, as the mortality from es-

tablished organ failure has not changed since it was first described almost 25 years ago.² Thus, it is imperative that hemorrhage is recognized and treated early.

The recognition of acute hemorrhage can be difficult. The American College of Surgeons has developed the classification scheme for hemorrhage, stratifying blood loss from Stage 1 (less than 15% of total circulating blood volume) to Stage 4 (more than 40% of total circulating blood volume).³ Changes in various physiologic parameters as hemorrhage volume increases are listed in Table 1. Unfortunately, many of these signs and symptoms are nonspecific. In addition, a number of other parameters will affect the patient's vital signs and physical findings. For instance, the rapidity of volume loss may be as important as the total volume of hemorrhage.² Underlying car-

Table 1. American College of Surgeons Classification of Acute Hemorrhage

Class	I	II	III	IV
Blood loss (ml)	<750	750-1,500	1,500-2,000	≥ 2,000
% Blood volume lost	<15%	15-30%	30-40%	≥ 40%
Pulse rate	<100	>100	>120	≥ 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill	Normal	Delayed	Delayed	Delayed
Respiratory rate	14-20	20-30	30-40	>35
Urine output	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Recommended fluid replacement	0.9% saline, 3:1	0.9% saline, 3:1	0.9% saline + red cells	0.9% saline + red cells

Amounts are based on the patient's initial presentation. Assumes 70-kg male with a blood volume of ~70 ml/kg.

Adapted from the American College of Surgeons Committee on Trauma: *Advanced Trauma Life Support Program for Physicians, Student and Instructor Manual*, Chicago, American College of Surgeons, 1993.

cardiovascular reserve also plays a role. Young people with very compliant blood vessels may compensate extremely well for large-volume blood loss, even as much as 40% to 50% of total circulating blood volume.⁴ They then develop sudden cardiovascular compromise when compensatory mechanisms fail. Elderly people, on the other hand, will develop cardiovascular insufficiency and hypotension with much smaller blood loss.⁵ Prescription medication and/or illicit drugs will also influence the cardiovascular response to injury.^{6,7} The amount of resuscitation, if any, the patient receives in the field will affect cardiovascular response as well.⁴

Data from the past 10 years strongly suggest that normally followed vital signs are a very poor indication of the depth of hemorrhage.⁸ In particular, blood pressure and pulse rate, the two vital signs often used in the emergency department to gauge hemorrhage, are tremendously nonspecific. Central venous oxygen saturation and mixed venous oxygen saturation are far more sensitive and reliable measurements of acute volume loss.^{8,9} Degree of metabolic acidosis, as measured by the base deficit from an arterial blood gas, is also extremely helpful in gauging the degree of shock.¹⁰ Base deficit has been shown to correlate with transfusion requirements, ICU stay, and ultimate outcome.^{11,12} During initial resuscitation, base deficit should also correlate with serum lactate level. The ability to clear lactate to normal is one of the most important predictors of survival following hemorrhage and injury.^{13,14}

Measures such as mixed venous oxygen content, venous oxygen saturation, blood pressure, and lactate concentration are global mea-

surements. That is, flow from all vascular beds contributes to this determination. However, some vascular beds are more sensitive than others to the effects of hemorrhage. Thus, shock may be detected earlier if we are able to recognize a local decrease in perfusion. Shock is defined as inadequacy of peripheral oxygen delivery. Clinically, we use indirect measurements to gauge hemorrhage. Target organ function such as urine output or mental status are examples of this. Unfortunately, urine output is extremely variable and nonspecific. Although oliguria almost certainly indicates hypovolemia, normal urine output or polyuria is inconclusive. Renal tubular function is affected by as little as a 20% acute loss of blood volume. The kidney develops a salt-wasting nephropathy, and the patient makes more urine than is appropriate for this degree of physiologic insult.¹⁵ Blood flow to the gastrointestinal tract, however, is a relatively sensitive indicator of the loss of circulating blood volume. Intracellular pH, as measured in the stomach, small bowel, or colon, is a very sensitive measure of hemorrhage.¹⁶ Current technology does not allow us to measure intracellular pH in real time. However, that technology may be forthcoming in the not-too-distant future.

Once the clinician has made the diagnosis of acute blood loss, several issues become important. Traditional dogma suggests that restoration of forward flow by crystalloid resuscitation followed by blood is optimal therapy. However, increases in blood pressure produced by fluid may, in fact, increase blood loss by displacing the hemostatic clot that was formed at the time of hypotension.¹⁷ This issue will be discussed in Chapter 3. However, there are now data to suggest that sustained

hypotension produces a more injurious shock insult than do multiple episodes of shock and resuscitation.¹⁸ Thus, the clinician must estimate the degree of hemorrhage, the depth of shock, and the time to definitive hemostasis when making a decision.

Regardless of the resuscitation decision, patients who demonstrate ongoing bleeding require definitive hemostasis. Serial blood gas determinations and/or central venous oxygen saturation determination may be very helpful in determining whether blood loss is continuing.^{8,9} Unfortunately, the relationship between blood loss and physiologic parameters may be different after resuscitation than they were during hemorrhage. For instance, approximately 12 to 16 hours following resuscitation, the relationship changes between base deficit and anion gap versus serum lactate, and anion gap and base deficit no longer correlate with lactate.¹⁹ During this time, one must directly measure serum lactate, as it cannot be inferred from either of the other two measurements. When resuscitation decisions are based on these parameters, therapy will be inappropriate almost 50% of the time.

Elderly patients with poor underlying cardiovascular reserve often require invasive monitoring to precisely measure the physiologic deficits and to guide therapy. In fact, in high-risk elderly patients (Table 2), monitoring must be instituted extremely early, within 2 to 3 hours of injury if possible. There is a statistically significant decrease in survival when monitoring is delayed as long as 6 hours.⁵ Even young people may have inadequate cardiovascular response to substantial injuries. A surprising percentage of young patients with either blunt or penetrating trauma benefit from invasive monitoring and require volume and pharmacologic therapy to support cardiovascular performance and clear lactate.^{20,21}

Clearly, achieving hemostasis is the most important part of resuscitating the trauma victim. Resuscitation efforts will not be successful until blood loss is arrested. Substantial hemorrhage usually requires operative therapy. Recently, however, other techniques have emerged and should be considered, even in patients with hypotension. The diagnosis of ongoing blood loss with angiography and hemostasis with transcatheter embolization is a real alternative to standard operative therapy.²² This has been a mainstay of therapy for many years in patients bleeding from a blunt pelvic injury. Retroperitoneal exploration in these

Table 2. High-Risk Geriatric Patients

Initial systolic blood pressure <130 mmHg
Closed head injury
Multiple long-bone fractures
Metabolic acidosis
Pedestrian-motor vehicle mechanism

patients is fraught with danger, and embolization is far preferable in almost every case. These techniques have been extended to other areas of the body. More recently, transcatheter embolization has been used for nonoperative management of solid visceral injuries within the abdomen. Treatment algorithms using splenic artery embolization in patients managed nonoperatively have resulted in a greater than 90% rate of splenic salvage.²³ This is far higher than any series utilizing observation and/or operation alone. In addition, embolotherapy may be extremely helpful in patients with vascular injuries in relatively inaccessible areas. Exposure of the carotid artery in Zone 3 of the neck is extremely difficult. Embolotherapy has a real role in managing these injuries. Temporary hemostasis can be achieved with percutaneous balloons used at the time of diagnostic angiography. This temporary control of bleeding allows further imaging, ongoing resuscitative efforts, and time to plan definitive therapy. In addition to its usefulness in Zone 3 of the neck, angiographic hemostasis has great utility in injuries to the thoracic outlet and deep within the pelvis.

Embolization techniques can be combined with surgery, allowing the patient to benefit from both techniques. Ideally, this should be done in the operating room and, in some centers, biplanar angiography is available. Patients who may benefit from this technology are those with a combination of intra-abdominal blood loss and pelvic blood loss. The pelvic blood loss can be embolized while intra-abdominal blood loss is treated directly via surgery. Sometimes patients are too profoundly ill to allow definitive surgery. Damage control techniques should then be employed. In these settings, major vascular injuries are repaired and gastrointestinal contamination controlled. The patient is then packed with laparotomy pads and taken to the intensive care unit for ongoing resuscitation and warming techniques. Once patients are resuscitated, they can return to the operating room for unpacking, gastrointestinal reconstruction, and any other procedures necessary. Angiographic embolotherapy has a role in these patients as well and can be utilized postoperatively to supplement surgical hemostasis. Injuries deep within the substance of the liver, in the retroperitoneum, or in the pelvis may be more easily controlled via embolization than surgery.

Early recognition of hemorrhage is key to the optimal care of trauma patients. Ongoing controversies exist as to the ideal resuscitation scheme. In fact, there is probably no one ideal strategy. Care must be tailored to the patient's mechanism of injury and physiology. Nonoperative homeostasis can supplement surgical techniques and its use should be considered. Normally followed vital signs are very poor indicators of the degree of hemorrhage and the adequacy of resuscitation. Invasive monitoring is often necessary to precisely determine the physiologic deficit and guide therapy.

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2 Pathophysiology of Traumatic Shock

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Shock—a condition of decreased total body oxygen delivery—can be brought on by a number of mechanisms. These include failure of the heart to pump blood through the body (cardiogenic), loss of circulating fluid volume (hemorrhagic), decreased oxygen carrying capacity (anemic), or loss of vascular tone (neurogenic).¹ “Traumatic shock”—shock brought on by an injury in an otherwise healthy patient—is best thought of as a combination of these factors. The initial phase is usually

hemorrhagic: the patient bleeds, and perfusion decreases. This may be followed by an anemic phase as the patient is resuscitated with crystalloid solutions and simultaneously mobilizes interstitial fluid into the vasculature. A cardiogenic or neurogenic component may be present initially due to specific injuries to the heart or central nervous system (CNS) or may be the secondary result of hypoperfusion and the release of toxic factors. It is important to recognize that the traumatic shock seen clinically in severely injured patients may be quite different from the induced shock seen in laboratory animals hemorrhaged under controlled conditions.

Stages of Shock

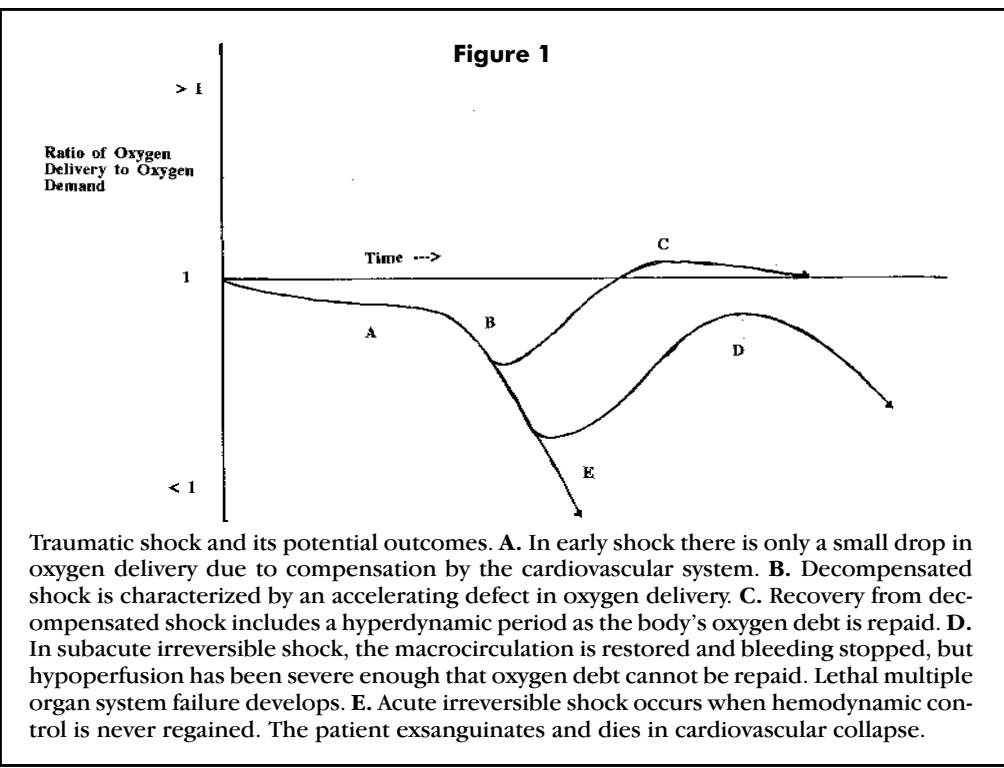
Traumatic shock may be thought of as

occurring in four phases (Fig. 1). In *compensated traumatic shock*, an increase in heart rate and vasoconstriction of nonessential and ischemia-tolerant vascular beds will allow prolonged survival and easy recovery once coagulation occurs and adequate fluids and nutrition are provided. *Decompensated traumatic shock*, also known as progressive shock, is a transitory state in which the lack of perfusion to certain tissues is building up a debt of local cell damage that will produce a toxic effect on the organism when perfusion is reestablished. Shock is still reversible at this stage. In *subacute irreversible shock*, the patient can be resuscitated hemodynamically but succumbs at a later time to multiple organ system failure as a result of the toxic effects of ischemia and reperfusion. Finally, *acute irreversible shock* is the condition of ongoing hemorrhage, acidosis, and coagulopathy that spirals steadily downward to the patient's demise.^{1,2}

The patient whose hemorrhage has proceeded to the point of decompensated shock represents a surgical and metabolic emergency. If the loss of blood (and thus the loss of oxygen-delivering capacity) can be reversed before the inflammatory cascade begins, the patient will survive. Adequate volume resuscitation leads the patient into higher-than-normal oxygen consumption—a hypermetabolic state—for hours to days after the acute injury, as the body repays the metabolic debt built up during the period of ischemia.³ Figure 1 shows this patient following curve C and eventually achieving normal equilibrium.

A few minutes too late, however, and subacute irreversible shock will have occurred, as represented by curve D. Bleeding may be controlled and vital signs may be normal or even hypernormal, but the damage has been done on the cellular level. Some tissues will continue to be ischemic due to lack of reflow caused by cellular swelling and microcirculatory obstruction. When flow is successfully restored on the cellular level, the process of reperfusion begins. This washout of toxins and inflammatory factors is as dangerous to the patient as the hemorrhage itself. This is the patient who develops adult respiratory distress syndrome then progresses to acute renal failure, gut dysfunction, immunosuppression, cardiac failure, and eventual death due to multiple organ system failure. Even though the hemorrhage is stopped short of exsanguination, the body is unable to survive the ischemic insult.^{2,4}

Curve E in Figure 1 represents acute irreversible traumatic shock. Prolonged hypotension is followed by progressive vasodilatation, loss of response to fluids and catecholamines, capillary leak, diffuse coagulopathy, cardiac dysfunction, and early death. These patients are usually said to have exsanguinated, although in the presence of modern rapid infusion techniques and aggressive transfusion, this is not strictly true. Rather, the patient dies from the acute metabolic consequences of failed perfusion, frequently in the presence of ad-



Traumatic shock and its potential outcomes. A. In early shock there is only a small drop in oxygen delivery due to compensation by the cardiovascular system. B. Decompensated shock is characterized by an accelerating defect in oxygen delivery. C. Recovery from decompensated shock includes a hyperdynamic period as the body's oxygen debt is repaid. D. In subacute irreversible shock, the macrocirculation is restored and bleeding stopped, but hypoperfusion has been severe enough that oxygen debt cannot be repaid. Lethal multiple organ system failure develops. E. Acute irreversible shock occurs when hemodynamic control is never regained. The patient exsanguinates and dies in cardiovascular collapse.

equate control of surgical bleeding and voluminous blood product replacement.¹

The Body's Response to Shock

The stages of traumatic shock are directly related to the body's response to hemorrhage. The initial response is on the macrocirculatory level and is mediated by the neuroendocrine system. Decreased blood pressure leads to vasoconstriction and catecholamine release. Heart and brain blood flow is preserved, while other regional beds are constricted. Pain, hemorrhage, and cortical perception of traumatic injuries lead to the release of a number of hormones, including renin–angiotensin, vasoressin, antidiuretic hormone, growth hormone, glucagon, cortisol, epinephrine and norepinephrine.⁵ This response sets the stage for the microcirculatory responses that will ultimately determine the patient's outcome.

On the cellular level the body responds to hemorrhage by taking up interstitial fluid, causing cells to swell.⁶ This may choke off adjacent capillaries, resulting in the "no-reflow" phenomenon that prevents the reversal of ischemia even in the presence of adequate macro flow.⁷ Ischemic cells produce lactate and free radicals, which are not cleared by the circulation. These compounds cause direct damage to the cell, as well as comprising the bulk of the toxic load that will be washed back to the central circulation when perfusion is reestablished. The ischemic cell will also produce and release a variety of inflammatory factors: prostacyclin, thromboxane, prostaglandins, leukotrienes, endothelin, complement, interleukins, tumor necrosis factor, and others.¹ These are the ingredients of acute and subacute irreversible shock.

Organ System Responses to Traumatic Shock

Specific organ systems respond to traumatic shock in specific ways. The CNS is the prime trigger of the neuroendocrine response to shock, which maintains perfusion to the heart and brain at the expense of other tissues.⁸ Regional glucose uptake in the brain changes during shock.⁹ Reflex activity and cortical electrical activity are both depressed during hypotension; these changes are reversible with mild hypoperfusion, but become permanent with prolonged ischemia. Failure to recover preinjury neurologic function is a marker for subacute irreversible shock, even if the patient's hemodynamic functions are normal.¹⁰

The kidney and adrenal glands are prime responders to the neuroendocrine changes of shock, producing renin, angiotensin, aldosterone, cortisol, erythropoietin, and catecholamines.¹¹ The kidney itself maintains glomerular filtration in the face of hypotension by selective vasoconstriction and concentration of blood flow in the medulla and deep cortical area. Prolonged hypotension leads to decreased cellular energy and an inability to concentrate urine, followed by patchy cell death, tubular epithelial necrosis, and renal failure.^{8,12}

The heart is relatively preserved from ischemia during shock because of maintenance or even increase of nutrient blood flow, and cardiac function is generally well preserved until the late stages.^{8,11} Lactate, free radicals, and other humoral factors released by ischemic cells all act as negative inotropes, however, and in the decompensated patient may produce cardiac dysfunction as the terminal event in the shock spiral.¹³

The lung, which cannot itself become ischemic, is nonetheless the downstream filter

for the inflammatory byproducts of the ischemic body. The lung is often the sentinel organ for the development of multiple organ system failure.^{4,14} Immune complex and cellular factors accumulate in the capillaries of the lung, leading to neutrophil and platelet aggregation, increased capillary permeability, destruction of lung architecture, and the acute respiratory distress syndrome.^{15,16} The pulmonary response to traumatic shock is the leading evidence that this disease is not just a disorder of hemodynamics: pure hemorrhage, in the absence of hypoperfusion, does not produce pulmonary dysfunction.^{14,17}

The intestine is one of the earliest organs affected by hypoperfusion and may be one of the primary triggers of multiple organ system failure. Intense vasoconstriction occurs early, and frequently leads to a "no-reflow" phenomenon even when the macrocirculation is restored.¹⁸ Intestinal cell death causes a breakdown in the barrier function of the gut, which results in increased translocation of bacteria to the liver and lung.¹⁹ The impact of this on the development of multiple organ failure is controversial at present.²⁰

The liver has a complex microcirculation and has been demonstrated to suffer reperfusion injury during recovery from shock.²¹ Hepatic cells are also metabolically active and contribute substantially to the inflammatory response to decompensated shock. Irregularities in blood glucose levels following shock are attributable to hepatic ischemia.²² Failure of the synthetic functions of the liver following shock are almost always lethal.

Skeletal muscle is not metabolically active during shock, and tolerates ischemia better than other organs. The large mass of skeletal muscle, though, makes it important in the generation of lactate and free radicals from ischemic cells. The classic cellular response to shock of increasing intracellular sodium and free water were first elucidated in skeletal muscle cells.²³

Conclusion

Traumatic shock is a disease not just of hemorrhage but also of tissue ischemia. Bleeding can be controlled surgically and oxygen delivery restored through adequate transfusion, and the patient can still die as a result of the accumulated metabolic load of prolonged hypoperfusion. Although control of bleeding and restoration of the circulating blood volume must remain the cornerstones of care for the traumatized patient, we must build on this foundation techniques for the management of reperfusion injury, the inflammatory cascade, and "no reflow" if we are truly going to improve long-term survival.

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SECTION II: Therapeutic Strategies

3 Surgical Perspectives to Control Bleeding in Trauma

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After establishing a secure airway and ensuring adequate oxygenation and ventilation, the highest priority in the trauma patient is to control hemorrhage. Because patients may bleed from multiple sites simultaneously, it is imperative that the surgeon establish a strategy to address all possible sources of bleeding and control them. These sources include 1) exten-

nal – blood loss onto the "street" or the trauma room floor, 2) left and right hemithoraces, 3) peritoneal cavity, 4) pelvis and retroperitoneum, and 5) long-bone fracture sites. Methods of definitive hemostatic control may be very simple, as in the application of direct pressure to a laceration, or very complex, such as in the patient with a pelvic fracture who requires embolization. This article addresses surgical, pharmacologic, and various other nonsurgical methods to control bleeding.

Hemostasis

Hemostasis is the process that terminates blood loss from an injured blood vessel. Sur-

geons depend greatly on normal hemostasis, often taking it for granted, so that surgery may be conducted safely. The process is very efficient and utilizes circulating proteins, cellular elements, and the endothelial lining (Fig. 1).¹ The first response to injury is vasoconstriction, which decreases blood flow distal to the laceration. The mechanism for vasoconstriction involves both direct injury and reflex responses. Platelets are exposed to subendothelial collagen and quickly adhere to each other and the blood vessel wall. Von Willebrand's factor acts as a bridge between the subendothelium and the platelet membrane, where it binds to receptor sites made available as a result of platelet activation. Other platelets are then recruited from the blood, and a loose plug forms to seal the blood vessel.

If this response reaches sufficient intensity, the platelet release reaction occurs whereby the contents of the platelet and its granules are liberated into the surrounding microenvironment. This is a complex reaction involving adenosine diphosphate, serotonin, platelet factor 4, platelet-derived growth factor, thrombin, calcium, and magnesium.^{1,2} The result is the formation of a stable platelet plug, which, unlike the initial loose plug, is no longer reversible.

Platelet reactions occur simultaneously with the events of the coagulation cascade. Coagulation serves to convert prothrombin into thrombin, which, in turn, converts fibrinogen to fibrin. This process utilizes circulating inactive proenzymes, which are converted into an active form and then, in turn, activate the next proenzyme in the sequence. There are two distinct divisions of the coagulation process: 1) the intrinsic pathway and 2) the extrinsic pathway (Fig. 2). The intrinsic pathway is initiated by the interaction of Factor XII and nonendothelial surfaces, which induces a conformational change in Factor XII. The complicated reactions that follow lead to clotting, kinin formation, complement activation, and fibrinolysis.¹

The extrinsic pathway is the more important pathway in hemostasis. Thromboplastin, a lipoprotein, is released from cells in response to tissue trauma. When thromboplastin is present, Factor VII becomes active and the sequence ensues.

The two pathways merge into a common pathway with the activation of Factor X, which, in turn, converts prothrombin to thrombin. Fibrinogen is then acted upon by thrombin, resulting in the formation of fibrin monomers. Polymerization of the fibrin monomers occurs, resulting in a cross-linked, stable, fibrin clot.

Fibrinolysis is the process that limits the hemostatic response to the local area of injury and maintains vascular patency throughout the organism. This system is initiated simultaneously with the clotting mechanism and is under the influence of numerous circulating mediators. The release of plasminogen activator from injured endothelium and activation of Factor XII initiate fibrinolysis. These convert plasminogen to plasmin, which can digest fibrin and fibrinogen at

Figure 1. Complex interaction of vasoconstriction, platelet factors, and coagulation reactions.
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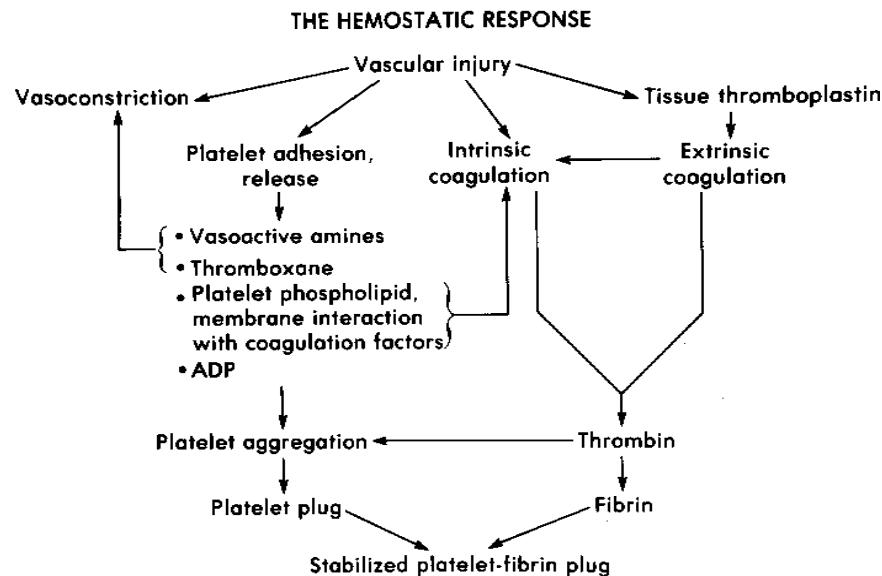
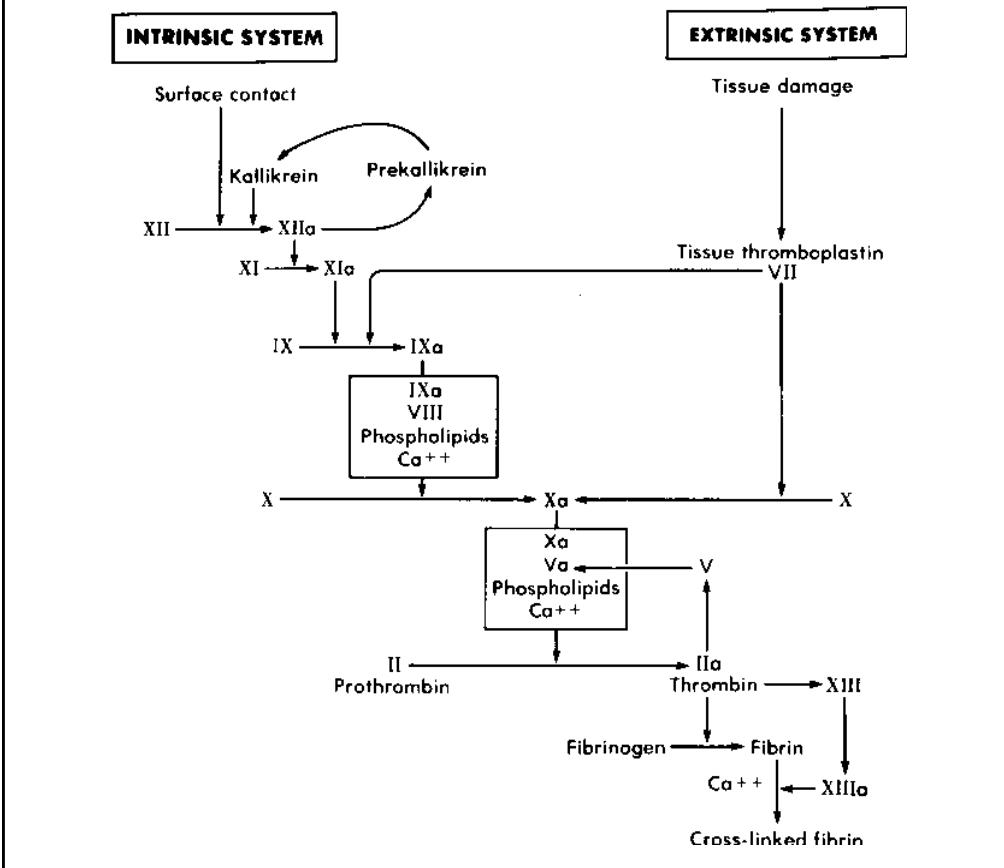


Figure 2. Coagulation reactions.
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the site of clotting. A complex inhibition system inactivates any plasmin that gains access to the general circulation. Other methods the body uses to limit coagulation, which are beyond the scope of this discussion, include products of the cyclooxygenase enzyme pathway, protein C, and anti-thrombin III.

Abnormalities of Hemostasis Resulting from Injury

Injury triggers a vast array of responses that affect hemostasis. Patients may exhibit either a hypercoagulable or hypocoagulable state following trauma. Severely injured patients have elevated serum fibrin degradation prod-

ucts, lowered platelet counts, and activation of the kallikrein–kinin system.³ In survivors, these values normalize within the first few days after injury but continue to worsen in nonsurvivors. Interestingly, a *hypercoagulable* state is seen in patients with less severe injuries. This is caused by a suppression of thrombolysis.³

Coagulopathy after injury may also result from the patient's abnormal physiology (hypoperfusion or hypothermia) or the interventions used to treat the patient (massive transfusion). It has become clear that prophylactic administration of fresh frozen plasma or platelets in the absence of clinical bleeding is not warranted.^{4,5} Hypothermia has been shown to adversely affect coagulation, and it is important that surgeons and anesthesiologists strive to maintain normothermia during treatment. Injuries to the brain and liver and those that cause either hypoperfusion or tissue devitalization have significant potential to induce coagulopathy.^{4,5} The importance of the restoration of tissue perfusion and debridement of devitalized tissue cannot be overemphasized.

Priorities in the Operating Room

At laparotomy it is absolutely necessary to control hemorrhage and gastrointestinal contamination in the most rapid fashion possible. Dr. William Halsted⁶ considered this absolutely essential for all types of surgery and eloquently stated the rationale:

The confidence gradually acquired from masterfulness in controlling hemorrhage gives to the surgeon the calm which is so essential for clear thinking and orderly procedure at the operating table.

It is only after hemorrhage is controlled that a patient's injuries may be addressed in an orderly fashion (Table 1). Control of gastrointestinal contamination is the next goal. Only after these goals are accomplished can a thorough exploration of the abdomen can be conducted and all injuries addressed definitively.

The surgeon has a wide range of tools to employ in order to control bleeding (Table 2). The most obvious method is the application of digital pressure. Although not definitive control for large vessels, the surgeon's finger is the mostatraumatic instrument available and will control bleeding temporarily while the blood vessel is exposed. The offending blood vessel must be exposed properly prior to repair or ligation. Occasionally, one may need to gain control of the aorta at the diaphragmatic hiatus to allow the anesthesiologist time to replace blood and fluids while exposure is being accomplished.

The patient's condition may not allow all injuries to be addressed fully at initial exploration. An abbreviated laparotomy to control hemorrhage, followed by continued resuscitation in the intensive care unit, is now an established concept in trauma surgery.⁷ If the patient's condition is deteriorating after con-

Table 1.
Surgical Priorities at Laparotomy in the Trauma Patient

- Control of exsanguinating hemorrhage
- Stop gastrointestinal contamination
- Thorough exploration of entire abdomen
- Definitive repair of all injuries

Table 2.
Surgical Methods to Control Bleeding

- Proper exposure
- Digital pressure
- Sutures and clips
- Thermal coagulation
- Topical hemostatic agents
- Organ wrapping

trol of surgical bleeding and if coagulopathy, hypothermia, and acidosis are present, laparotomy sponges may be placed between the abdominal wall and the bleeding organ to gain tamponade. The laparotomy is terminated quickly to allow transfer to the intensive care unit so that coagulopathy, acidosis, and hypothermia may be corrected. A second operation is required to remove the packs once the patient's condition is more stable.

The most familiar means of achieving definitive hemostasis is the placement of surgical ligatures and clips. These must be placed very accurately so as not to endanger surrounding structures. Small vessels may be managed with simple ligatures; large arteries should be controlled with a suture ligature to prevent slippage of the tie. In very confined spaces where the placement of ties would be difficult, surgical clips may be applied.

Occasionally an organ such as the liver or spleen may be lacerated, but removal may not be necessary. Organ-wrapping methods utilize a mesh net to envelope the liver or spleen to gain tamponade. This method may be used when other methods to achieve hemostasis fail or where splenectomy or extensive hepatorraphy would otherwise be required.

Thermal agents such as electrocautery produce hemostasis by heating and denaturing proteins, resulting in coagulation. Both alternating and direct current may be employed for this purpose. This method allows rapid cessation of bleeding but may result in large areas of tissue necrosis if applied carelessly.

Occasionally an organ such as the liver or spleen may be lacerated, but removal may not be necessary. Hemostasis may be accomplished by several methods, such as direct pressure or suture repair. The liver or spleen may also be wrapped with a mesh netting to envelop the organ to gain tamponade. This method may be used when other methods to achieve hemostasis fail or where splenectomy or extensive hepatorraphy would otherwise be required but may compromise chances for survival.

Table 3.
Comparison of Topical Hemostatic Agents

TOPICAL ABSORBABLE HEMOSTATIC AGENTS

MATERIAL	OXIDIZED CELLULOSE	COLLAGEN	THROMBIN	GELATIN SPONGE
	Oxidized Gauze (OG) Oxidized Regenerated Cellulose Knit (ORC)	Purified Bovine Collagen Sponge Microfibrillar — Powder — Web Non Woven Web	Protein of Bovine Origin; Powder	Purified Gelatin
TIME TO HEMOSTASIS	Average 2-8 min.	Average 1-5 min.	Concentration Dependent Usually less than 1 min.	Not Specified on Label
ABSORPTION TIME	OG = 3-4 weeks ORC = 1-2 weeks	Approximately 8-12 weeks	Absorbed Immediately	4-6 weeks
HANDLING CHARACTERISTICS	Conforms Well Easy to Wrap Packs Easily Good Suture Base	Sponges: — Easy to Apply & Remove — Conforms Wet or Dry — Holds Suture Microfibrillar — Packs Well — Difficult to Apply and Remove — Sticks to Gloves and Instruments	May be used as: — Powder — Liquid — With Gelatin Sponge Requires Preparation and/or Special Storage	Friable Sponge, May be Used Wet or Dry Conforms Only if Premoistened Poor Suture Base
SPECIAL FEATURES	ORC - Bactericidal	Good Wet Integrity	Fast Acting	

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Pharmacologic agents have gained an important place in the surgeon's armamentarium. The mechanisms of action are widely varied: some act by vasoconstriction, some by supplying a scaffold for attracting blood elements, and still others by promoting coagulation per se (Table 3).⁸ The ideal topical hemostat would have several properties: 1) rapid hemostasis, 2) easily applied and manipulated, 3) holds sutures, 4) little tissue reaction, 5) low infectious risk, 6) absorbable, and 7) easily removed. Each of these agents has particular advantages and disadvantages, which will be discussed in brief.

Topical epinephrine is used commonly in applications such as burn surgery and exerts its action by promoting vasoconstriction. The drug can be used to cover wide surfaces, but it must be applied with caution because systemic effects may result if excess drug is used.

Oxidized cellulose (i.e., Surgicel®) acts by forming a gelatinous mass on contact with blood. This compound conforms well to irregular surfaces, is relatively inert, causes little tissue reaction, and is absorbed in 1 to 2 weeks. In addition, cellulose holds sutures relatively well and is bactericidal.

Collagen sponges (Actifoam®, Helistat®, Instat®) and microfibrillar collagen (i.e., Avitene®) have a rapid time to hemostasis and are absorbed in approximately 8 to 12 weeks. Sponges are easy to apply and they remove and hold sutures well. Microfibrillar collagen packs easily into small spaces but is difficult to remove and sticks to gloves and instruments.

Thrombin is a protein that converts fibrinogen to fibrin, resulting in clot formation. Thrombin may be applied as a liquid or powder or combined with another carrier such as Gelfoam®. Hemostasis is rapid and wide surfaces may be treated.

Denatured gelatin (i.e., Gelfoam®) possesses no clotting activity itself but provides a scaffold on which clot can form. It also helps plug small blood vessels by virtue of its bulk when moistened. It may be used as a carrier for other compounds such as thrombin. The sponge should be pre-moistened with either saline or thrombin and all air should be removed from the interstices by compressing the sponge. Gelatin conforms well to surfaces, but it does not hold sutures.

Fibrin sealants have numerous applications within the field of surgery, including nerve anastomoses, intracranial operations, skin grafting, and cardiovascular procedures.⁹ Fibrin glue has also been used as a hemostatic agent in trauma surgery for lacerations of the liver and spleen. In the presence of calcium ions, fibrinogen and Factor XIII are activated by thrombin. Fibrinogen is converted to fibrin monomers and these, in turn, are polymerized to form a stable clot.

Fibrin glue has two components that must be mixed together for clotting to occur. The primary parts of the first component are fibrinogen and Factor XIII. The second component consists of thrombin and calcium chloride. An

antifibrinolytic agent such as aprotinin may be added to the second solution, depending on specific requirements.⁹ When these two parts are combined, clotting ensues. The glue may be applied by two methods: 1) In the "sandwich technique," the fibrinogen is spread onto the surface to be sealed and the thrombin solution spread over it. 2) The premixed method uses two syringes joined by a Y-connector.

Ochsner et al used fibrin glue as the primary hemostatic agent or as an adjunct to conventional suture repair in 26 patients with hepatic and splenic trauma.¹⁰ Seventeen patients had liver injuries (6 blunt and 11 penetrating) and 9 had splenic injuries (7 blunt and 2 penetrating). Liver injuries ranged from moderate to severe and the splenic injuries were all moderate. Fibrin glue achieved hemostasis in 21 patients with the first application and with the second in the remaining five. No patients were re-explored for bleeding. Eight patients had postoperative coagulopathy and thrombocytopenia, but the fibrin glue hemostasis remained effective.

A controlled *in vitro* review of topical hemostatic agents was undertaken by Wagner et al.¹¹ The tested agents included three types of collagen sponges (Actifoam®, Helistat®, Instat®), microfibrillar collagen (Avitene®), a gelatin sponge (Gelfoam®), and oxidized regenerated cellulose (Surgicel®). Actifoam® and Avitene® caused the greatest response (both statistically similar) in an *in vitro* platelet aggregation test. Gelfoam® exhibited an intermediate response, whereas Helistat®, Surgicel®, and Instat® caused a lesser degree of platelet aggregation. In a similar test using thrombin to presoak each agent, platelet aggregation occurred at a more rapid rate for all agents tested.

The agents were also tested in their ability to induce gross blood coagulation (Lee-White clotting time). Actifoam®, Avitene®, and Helistat® responded in a manner similar to thrombin, but Instat®, Gelfoam®, and Surgicel® demonstrated no significant impact on clotting time.

Wagner et al, using the above assays as well as tests of platelet deposition and platelet adenosine triphosphate secretion, constructed an overall ranking of these hemostatic agents: Actifoam® ~ Avitene® > Helistat® >> Gelfoam® > Instat® > Surgicel®. It should be noted that, although this ranking notes differences between the agents for these *in vitro* assays, it is certainly limited when considering the numerous clinical situations encountered by surgeons in a wide variety of subspecialties.

Heat energy has a significant role in treating the hypothermic trauma patient. Hypothermia causes platelet dysfunction and prolongs clotting times.¹² Laboratory assays underestimate the extent to which hypothermia affects bleeding, since the plasma and test reagents are heated to 37°C prior to running the assay. Because of this, coagulation test results and platelet counts may not correlate with nonsurgical bleeding.

Table 4.
Nonsurgical Interventions
to Achieve Hemostasis

- Pneumatic antishock garment
- External pelvic fixator
- Angiography and embolization
- Temporary balloon occlusion

Other Invasive Interventions

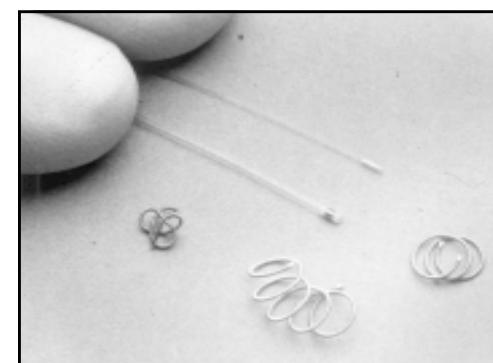
Numerous other tools for hemorrhage control may be used in the field, emergency department, or radiologic suite (Table 4). Although the surgeon does not necessarily perform all of these procedures, he or she should be responsible for combining them into a logical strategy for prompt control of bleeding when surgical methods cannot be used.

The pneumatic antishock garment is used to control bleeding temporarily in patients with pelvic and lower extremity fractures by acting as a splint to tamponade bleeding. It can be used for hypovolemic shock, but it is only a temporizing measure. Prolonged use may be associated with numerous complications, such as compartment syndrome.

The external pelvic fixator may be definitive in stopping bleeding from veins lining fractured pelvic bones. It is most effective in patients with fractures associated with a diastasis of the pubic symphysis ("open-book" pelvic fractures), since it draws the anterior elements together. This decreases the potential space into which bleeding may occur. The external fixator is not effective for fractures involving only the posterior elements of the pelvic ring or in controlling bleeding from the arteries coursing through the pelvis.

For patients with bleeding from pelvic fractures in whom an external fixator is not effective, bleeding from arteries in the pelvis must be suspected and angiography should be performed. If an offending vessel is identified, embolization may be carried out with either Gelfoam® or metal microcoils (Fig. 3). While

Fig. 3.
Microcoils used in pelvic
arterial embolization.
(Photograph courtesy of
James Newman, MD, PhD.)



not usually used for pelvic arteries, balloon occlusion may be used by the angiographer as a temporizing measure to achieve hemostasis in arteries of the chest, neck, and extremities before the causative lesions are controlled in the operating room.

I would be remiss if I did not emphasize the importance of the anesthesia service in the management of these patients. Surgeons must focus on control of bleeding at the surgical site. Anesthesiologists provide the necessary factors to assist in the correction of surgical bleeding and the prevention of nonsurgical bleeding. The proper transfusion of blood component therapy has important implications for control of bleeding, since platelets and coagulation factors may be required by severely injured patients. Anesthesiologists must also focus on the maintenance of normothermia to help prevent coagulopathy. Effective communication between the surgeon and anesthesiologist is essential. The surgeon must alert the anesthesiologist to bleeding at the surgical site, so that corrective methods may be undertaken.

Summary

Control of blood loss is one of the most important priorities in the trauma patient. We have discussed several methods of obtaining hemostasis. These include standard surgical techniques such as digital pressure and sutures. We have focussed much of our attention

on pharmacologic methods, specifically topical hemostatic agents. Each of these agents has particular advantages and disadvantages and must be applied to the appropriate situation. There are other invasive techniques that may not be performed by the surgeon but that must be orchestrated by the surgeon into a clear strategy for hemorrhage control. The anesthesiologist has an important role in helping to control hemorrhage by appropriate transfusion therapy but, more importantly, preventing bleeding at the surgical site by methods such as maintaining normothermia.

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4 Haemostatic Drugs in Trauma and Orthopaedic Practice

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Aprotinin is a naturally occurring serine protease inhibitor. It is found in the mast cells of all mammalian species as well as many lower orders of life. Unfortunately, at this time, we do not understand the true physiologic role of aprotinin in nature.

What is known is that high doses of the drug inhibit a number of the inflammatory processes involved with open heart surgery and also modify the haemostatic system to allow reductions in bleeding and thus the need for blood and blood products. The use of high-dose aprotinin therapy followed reports of the potential benefit of this approach in traumatically injured patients.¹ Large-dose aprotinin therapy has been shown to be extremely effective, and safe, in preventing blood loss and the need for blood and blood products in patients undergoing open heart surgery. The current literature contains more than 40 reports of randomised placebo-controlled studies^{2,3} that have shown that high-

dose aprotinin therapy reduced drain losses (range, 35%–81%), the total amount of transfusions (range, 35%–97%), and the proportion of patients requiring transfusions of blood or blood products (range, 40%–88%). Since the first description of the haemostatic actions of high-dose aprotinin therapy in patients undergoing re-operation⁴ or high-risk cardiac procedures, this agent has been the standard of care in this situation and is the only product licensed for use for this indication in North America.

The aim of this article is to discuss the potential for this anti-inflammatory and haemostatic action to benefit patients having elective orthopaedic and trauma surgery and also following trauma itself. The article is divided into three major sections dealing with

- The use of drugs to prevent bleeding during elective surgery
- The potential for aprotinin therapy in patients who have sustained trauma
- The potential use of serine protease inhibitors to prevent certain sequelae of trauma and surgery of bones, joints, and tendons

Transfusion therapy. In Maull KI, Rodriguez A, Wiles CE, eds. *Complications in Trauma and Critical Care*. Philadelphia, WB Saunders, 1996.

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Many forms of bone and joint surgery are associated with a significant risk of bleeding and thus the use of blood and blood products.⁵ A number of systems have been used to reduce this probability. Some of these are almost unique to orthopaedic surgery, such as creating a bloodless field by tourniquet application in limb surgery. In addition, in many countries, orthopaedic and trauma surgeons have become the principle users of predonated blood and blood product systems. However, there is still significant scope for the use of other techniques and methods, such as pharmacologic intervention, to inhibit bleeding and minimize the need for blood and blood product transfusions.

Nonemergency Orthopaedic Surgery

The three most commonly used pharmacologic interventions in nonemergency orthopaedic surgery are tranexamic acid, desmopressin (DDAVP), and aprotinin. Each of these agents has a relatively unique mode of action, although there is overlap between some of the physiologic events produced by these agents.

Desmopressin is a synthetic analogue of the natural hormone arginine vasopressin and has been shown to increase plasma levels of

factor VIII activity in patients with hemophilia and Von Willebrand's disease type I. Desmopressin had considerable support for use in complex heart surgery, but more recent data suggest that, overall, this drug provided little, if any, benefit to the patient. Conversely, more recent data suggest that the use of desmopressin in patients who are currently taking aspirin therapy has significant benefit during and after heart surgery.^{6,7} The results with desmopressin in orthopaedic surgery have been universally poor.⁸ However, at present, there is little information about the use of this agent in patients taking aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) prior to surgery. This is obviously an area that needs further investigation.

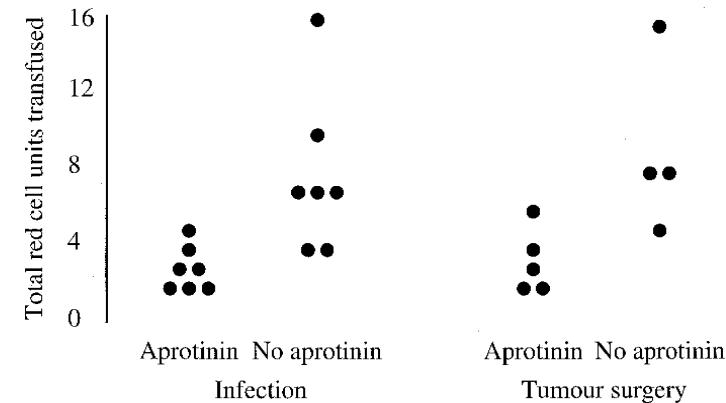
With regard to tranexamic acid, there are again few data to support its use for surgery of central bones and joints, such as spine and hip surgery. Some reports indicate a reduction in the requirement for blood in patients who are having knee replacement surgery under tourniquet.^{9,10}

Aprotinin therapy has been used with effect in a wide variety of surgeries, including orthopaedic surgery. There is, however, still only one report from a randomised placebo-controlled study in patients undergoing primary hip surgery.¹¹ This shows a significant benefit of high-dose aprotinin therapy to reduce drain losses and the need for donor blood and blood products. The dose of aprotinin used in this study from Belgium was intended to be equivalent to the high-dose regimen used during cardiac surgery.

A number of other studies have shown an effect of lower doses of aprotinin on variables such as platelet function but without showing consistent benefit to reduce the requirement for transfusions.¹²⁻¹⁶ It appears that a higher dose of aprotinin is needed to ensure reduced blood transfusions than the dose that will have significant effects on haemostatic processes.

Similarly, there is evidence that the greater the surgical risk, the more benefit the high-dose regimen appears to demonstrate. For example, a recent article¹⁷ showed that aprotinin therapy produced a three-fold reduction in the need for blood and blood products in patients undergoing hip replacement because the joint had become infected or invaded by tumor (Fig. 1). This massive reduction in the requirements for blood and blood products is similar to the observations in heart surgery, where the higher the risk of bleeding, the more obvious is the benefit of aprotinin therapy. In addition, aprotinin therapy has been used with benefit in patients undergoing spinal surgery.¹⁸

Figure 1
Total numbers of transfused red cells in patients undergoing orthopaedic surgery for removal of infected bioprosthesis or resection of tumour with and without aprotinin therapy. Individual patient data are shown and demonstrate an average three-fold reduction in need for blood products in patients given aprotinin therapy. Data are drawn from Capdevila et al.¹⁷



Soft Tissue Injury and Disseminated Intravascular Coagulopathy (DIC)

The use of blood-sparing agents in trauma surgery has potential in soft tissue injury and in patients with intraabdominal (especially hepatic) trauma. Severe soft-tissue injury presents a variety of challenges with problems associated with the initial event, the subsequent potential for ischaemia reperfusion injury, and the development of a coagulopathy during resuscitation.

Soft-tissue trauma is associated with the release of a number of procoagulant mediators, which can lead to a form of disseminated intravascular coagulation and haemorrhage. The use of factors to promote haemostasis and prevent bleeding in these circumstances is still controversial. The use of pure antifibrinolytics, such as a lysine analogue, is potentially lethal in these circumstances. These drugs are therefore contraindicated in the presence of intravascular thrombin generation. Indeed, in animal models, the use of lysine analogue antifibrinolytics such as tranexamic acid with excess thrombin generation leads to the death of the animal.¹⁹⁻²¹

In contrast to the effects of these lysine analogue agents are the effects of serine protease inhibitors. A number of odious models of tissue injury in animals have shown significantly high early mortality. These models include rotating drum experiments with rats and fracture/sepsis models in sheep. In both these experimental models, the use of aprotinin therapy prevented mortality and improved outcome.²² A number of animal models together with anecdotes about humans suggest that aprotinin therapy in addition to heparin inhibits the DIC associated with trauma and sepsis.^{19,21,23}

There are also a number of studies from

the early literature in which aprotinin was administered to patients who had sustained trauma, particularly road traffic crashes. The majority of these papers are found in the German literature. In one multiple centre study published in 1976,²⁴ 4,686 patients were entered into a multiple centre study to investigate the effects of aprotinin therapy in the treatment of traumatic shock. The dosage used was relatively low—approximately 3 million KIU over a 2-day period—but produced an impressive benefit to the patient outcome when administered within a few hours of the trauma. The most significant benefits of the use of aprotinin therapy were found in patients with injuries to the upper extremity and soft tissues, but there were significant benefits following trauma to the lower limb and spine as well. The

study found no benefit of the use of aprotinin therapy in patients with either chest or head injury (Fig. 2).

Most recently, a number of studies have focused on aprotinin therapy following blunt liver trauma. These investigations appear to be a natural progression from studies that investigated this therapy in patients having liver transplantation. In both an animal²⁵ and a human²⁶ study, significant benefits were achieved in terms of reduction in bleeding and the need for donor blood in liver trauma and resection.

These data suggest that aprotinin therapy may be beneficial in certain patients with soft-tissue injury and intraabdominal trauma.

Antiinflammatory Actions

In addition to the potential haemostatic benefits of the use of aprotinin in patients undergoing elective surgery and in those who have been injured, there are also a number of other actions of the drug that may benefit the patient. These are related to its anti-inflammatory and anticoagulant actions.²⁷

All serine protease inhibitors, including aprotinin, will inhibit platelet function. This is achieved by a number of mechanisms related to the ability to inhibit surface receptors and by intracellular metabolism processes. Indeed, the first use of aprotinin therapy in patients having hip surgery was as an adjunct to the use of heparin to prevent deep venous thrombosis after surgery.^{12,14} Preliminary data from these studies (involving small numbers of patients) suggest a small but statistically significant effect to reduce the incidence of venous thrombosis. This effect needs to be investigated in larger groups of patients using various forms of antithrombotic prophylaxis in addition to aprotinin therapy to determine if there is a significant benefit

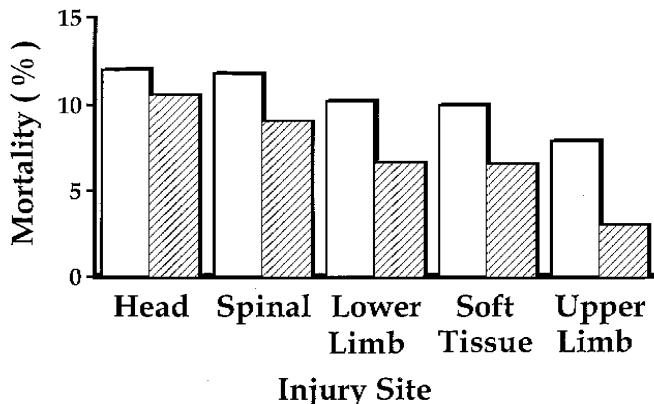
in this respect together with a reduction in the requirement for blood and blood products. Other reports suggest that the incidence and severity of pulmonary fat embolism and the fat embolus syndrome following trauma are reduced significantly with aprotinin therapy.^{28,29}

A further consequence of the use of aprotinin and its effects on intracellular metabolism is inhibition of certain aspects of ischaemia and reperfusion injury. In particular there is considerable evidence to show that aprotinin therapy is associated with improved microvascular blood flow.²⁷ This improved flow together with modifications to the metabolic process may explain why there is a significant reduction in the amount of lactic acid produced after ischaemia reperfusion in patients undergoing hip surgery^{12,30} and in those undergoing vascular surgery with aorto-bifemoral replacement.³¹

One potential area for the use of aprotinin as a treatment after bone surgery is to inhibit the oedema that occurs after trauma to bone and periosteum. Oedema formation can be associated with considerable discomfort. A number of studies suggest that the local infiltration of aprotinin significantly reduces both the oedema formation and the pain associated with bone surgery. This is especially true for patients requiring maxillofacial surgery and dental extraction.³²

Finally, there is the potential for the use of aprotinin and other protease inhibitors to be used prophylactically and in treatment of patients with progressive joint destruction or following joint and tendon repair. It is becoming increasingly recognised that many of the cells in cartilage produce proteolytic enzymes, which may be responsible for chronic joint destruction.³³ More modern methods of molecular biology suggest that one of the major participants in this process is the generation of plasmin from a urokinase plasminogen type activator. This activity is inhibited by aprotinin therapy in tissue culture.³³ The rationale for using intra-articular aprotinin therapy is suggested by the observation that chondrocytes produce a number of protease inhibitors of the proteolytic enzymes such as the plasminogen activators. One of the major inhibitors thus far categorised from human chondrocytes is a 6-kD molecule that has remarkable, if not identical, amino acid sequence

Figure 2
Percentage mortality in groups of patients with trauma and tissue injury with (hatched bars) and without (clear bars) aprotinin therapy. Data are drawn from more than 4,000 patients.²⁴ Mortality rates are significantly lower in aprotinin-treated patients for lower-limb and soft-tissue injury ($p < 0.01$) and for lower-limb trauma and spinal injury ($p < 0.05$). There was no significant difference between treatment and no treatment in patients with predominantly head injury.



homology with aprotinin.³⁴

Preliminary data from human studies suggest that the chronic injection of aprotinin into the joint space is associated with a significant inhibition of progression of disease.³⁵ A similar mechanism may also play a part in the use of aprotinin therapy to prevent adhesion formation and fibrosis following tendon repair.³⁶

Summary and Conclusion

The use of aprotinin therapy in sufficiently high doses is associated with an improvement in haemostatic function and a reduction in drain losses and blood utilisation in patients undergoing major trauma surgery and orthopaedic surgery. The anti-inflammatory actions of aprotinin may also have significant benefit in reducing mortality after soft tissue trauma alone and especially in those traumas associated with increased risk of embolic phenomena or intravascular coagulation. Although drugs such as tranexamic acid have value in patients requiring certain joint replacement surgeries, their safety in the presence of a prothrombotic state is not proven. Therefore, at this stage, it seems inappropriate to recommend these drugs for patients with soft tissue trauma. The use of drugs such as desmopressin in otherwise routine surgery has, as yet, no proven benefit, although there may be some benefit to patients who are taking anti-inflammatory medicines.

In addition to the benefit of reducing bleeding, protease inhibitors can improve patient outcome by reducing ischaemic injury and the oedema formation that may cause pain. At present, safety data on the use of aprotinin therapy in both open heart surgery and ortho-

paedic/trauma surgery suggest that the benefits of this drug can be obtained without increasing the risk of a thrombotic episode. Whether the incidence of thrombosis can be reduced further by co-administration of a protease inhibitor with other antithrombotic prophylaxis remains to be investigated.

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5 Antithrombotics in Trauma Care: Benefits and Pitfalls

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Although deep venous thrombosis (DVT) and pulmonary embolism (PE) have always been major complications of trauma, they have only recently become a major concern of trauma anesthesiologists because modern effective prevention of DVT affects anesthesia practice.¹ Recently developed low-molecular-weight heparins (LMWH) provide very effective prevention of posttraumatic DVT with far fewer bleeding complications than intravenous unfractionated heparin; however, LMWH use is also associated with epidural hematomas from epidural catheters.^{2–8} Thus, at a time when the use of continuous regional anesthesia with epidural catheters is shown to reduce trauma

morbidity, anesthesiologists are faced with patients who receive LMWH prophylaxis for DVT, which may preclude the use of epidural catheters.^{3,5} In this article, the risks and natural history of DVT and recommendations for use of continuous epidural anesthesia in conjunction with LMWH will be reviewed.

Venous thromboembolic disease—which includes both DVT and PE—is a major posttraumatic morbidity and mortality issue.^{1,2} Direct trauma to blood vessels and thrombophilia associated with the general inflammatory response to traumatic injury lead to an increased incidence of DVT and subsequent pulmonary embolism (PE).⁷ The overall incidence of DVT in the North American and European populations is 1 in 1,000. It occurs more frequently in older people, obese people, and patients with traumatic injury. Some injury patterns such as spinal cord injury are associated with a very high incidence of DVT.

Other high-risk conditions for DVT include bed rest for longer than 72 hours; lower-extremity fractures, especially pelvis and acetabular fractures; penetrating venous injuries; head injuries inducing a low Glasgow Coma Scale score; family history of thrombi; and a history of DVT or PE. Also associated with appreciable DVT risk are comorbid conditions such as age greater than 40; obesity; malignancy; pregnancy, up to 1 month postpartum; use of oral contraceptives; and lung operations.⁷

Virchow noted in the 19th century that DVT was initiated by one or more of the following conditions: stasis of blood flow in the deep veins of the leg, trauma to the endothelial lining of the veins, and increased coagulability of the blood. Because trauma patients are at risk for the entire Virchow's triad, they are at increased risk of DVT and thus PE. Aside from the obvious vascular trauma and venous stasis caused by bed rest, the inflammatory state of trauma (e.g., cytokine re-

lease) causes a generalized thrombophilia. This thrombophilia may cause multiple microvascular thrombin formation and DIC or lead to large-scale thrombus in the deep veins of the leg.

Patients with congenital forms of thrombophilia are at especially high risk for DVT and PE. These inborn errors of metabolism (Table 1) vary in incidence from 3% to 4% in the population for activated protein C resistance (Factor V Leiden) to 0.02% for antithrombin deficiency.⁷ Although protein C and protein S deficiency were involved in the earliest descriptions of thrombophilia, they are not nearly as common as factor V Leiden deficiency. Hyperhomocysteinemia, which is also a risk factor for arterial thrombosis such as coronary arterial occlusion, may be related to folic acid, vitamin B12, and vitamin B6 deficiency and its incidence is not well defined.⁹

The main reason to worry about DVT in the trauma patient is fatal PE. PE occurs symptomatically in 30% of patients with a DVT; asymptomatic PE increases the overall incidence of PE to 50% to 60% in patients with DVT. The death rate caused by PE is 50,000 per year in the United States. Because there is no adequate treatment for a diagnosed PE and diagnosis is difficult, prevention of DVT is the most effective measure to reduce the incidence of PE.^{7,8} Therefore, many trauma patients will receive DVT prophylaxis, and the use of LMWH is the most effective prophylaxis.

DVT is diagnosed with physical examination, chemical markers of coagulation such as d-dimer, venous duplex Doppler, and venography (Table 2).¹⁰⁻¹² Symptoms and signs of DVT include pain, a venous cord along the leg, edema distal to the occlusion, and pain induced by forceful dorsiflexion of the foot. D-

Table 1. Inborn Errors of Coagulation

Factor	Population Incidence
Activated protein C resistance (Factor V Leiden)	3%-4%
Hyperhomocysteinemia	5%
Protein C deficiency	0.2%-0.4%
Protein S deficiency	0.1%
Antithrombin deficiency	0.02%

Dimer is released into the circulation when intravascular clots are broken down by thrombolysis.¹² Venous duplex Doppler reveals noncompressibility of flow in the proximal deep veins of the leg. Venography is the gold standard of diagnosis for DVT, allowing filling defects to be seen after injection of contrast dye in a peripheral limb vein. Approximately 2% of DVTs occur in the upper extremities, with a risk of 12% for PE from an upper-extremity DVT.¹³ Upper-extremity DVT is diagnosed by detection of obstruction to flow in the deep veins of the shoulder or upper arm.

PE is diagnosed by physical examination, radioisotopic ventilation perfusion (V/Q) scan, spiral computed tomography (CT) of the chest, or pulmonary angiography (Table 3). Physical signs and symptoms of PE include pleuritic chest pain, dyspnea, hemoptysis, abnormal breath sounds, atrial dysrhythmias, hypoxia, and an increase in arterial to end tidal carbon dioxide gradient. The presence of a known DVT increases the probability that these signs and symptoms represent a PE. A perfusion defect not matched with a simultaneous ventilation defect demonstrates a PE on radioiso-

topic V/Q scans.¹¹ Spiral CT of the chest enhanced with contrast medium may reveal a filling defect of a major branch of the pulmonary artery in patients with PE.¹⁰ A pulmonary artery angiogram remains the gold standard for diagnosing PE by revealing filling defects in the pulmonary artery or its branches.

Treatment of known DVT is anticoagulation to prevent further propagation of the thrombus. Therapeutic heparinization is usually performed with intravenous heparin titrated to a PTT in the range of 60 to 80 seconds. Because patients with one episode of DVT are at risk for another episode, therapeutic heparinization is usually followed by 3 months to a lifetime of warfarin or long-term subcutaneous LMWH.¹⁴

Treatment of PE is mostly supportive of pulmonary function along with administration of heparin to prevent further clot buildup. Heparin dose is adjusted for PTT of 60 to 80 seconds. Embolotomy of the pulmonary artery has been used for "saddle emboli" obstructing both branches of the pulmonary artery, but embolotomy must be initiated almost immediately to be effective.

Prevention of DVT relies on a combination of mechanical methods such as stockings, sequential compression devices, or foot pumps and pharmacologic techniques (Table 4). Inferior vena caval filters are designed to prevent PE but have no effect on the development of DVT.

Pharmacologic prevention of DVT has been attempted with aspirin, dextran, heparin, warfarin, and LMWH, and thrombolytics have been used to lyse established DVT. Of these pharmacologic agents, LMWH, low-dose subcutaneous heparin, warfarin, and intravenous high-dose heparin have proven effective in preventing DVT.^{2,4,6,7,15} LMWH is more efficacious than low-dose heparin, especially in preventing PE, and has fewer complications.^{4,2,15} Because of its ease of use, efficacy, and low incidence of side effects, LMWH is the drug of choice for DVT prophylaxis in trauma patients. Table 5 lists the recommended doses and dosing intervals for available LMWH, as well as the current indications for these drugs.

The complications of DVT prophylaxis include bleeding, epidural hematoma, heparin-induced osteopenia, heparin-induced thrombocytopenia (HIT), and warfarin-induced skin necrosis. LMWH is much less likely to cause osteopenia than unfractionated heparin, but both are likely to cause HIT.⁷ For patients who develop HIT, DVT prophylaxis and treatment of PE can be controlled with danaparoid or hirudin.

The use of regional anesthesia in trauma patients receiving anticoagulation therapy for DVT prophylaxis requires the compulsive following of guidelines to prevent epidural hematomas.^{3,5} Table 6 lists recommendations for epidural catheter use in patients receiving LMWH. With the use of sequential compression devices during periods when LMWH cannot be administered safely, prophylaxis against venous thromboembolic disease as well as ex-

Table 2. Diagnosis of Deep Venous Thrombosis

Physical examination	Simple and inexpensive; needs laboratory confirmation
D-Dimer	Indicates intravascular coagulation
Venous duplex Doppler	Useful screening tool
Venography	Gold standard

Table 3. Diagnosis of Pulmonary Embolism

Investigation	Comments
History and physical examination	Simple; easy to use
Dyspnea	
Chest pain	
Hemoptysis	
Atrial dysrhythmias	
Friction rub	
Hypoxia	
Decrease in $P_{ET}CO_2$	
V/Q scan	Useful only to confirm physical findings
Spiral CT of chest	Good sensitivity and specificity
Pulmonary angiography	Gold standard
$P_{ET}CO_2$, end-tidal carbon dioxide; V/Q, ventilation-perfusion; CT, computed tomography	

Table 4. Techniques to Prevent Posttraumatic DVT

Technique	Effectiveness
Sequential compression device	Effective; easy to use with minimal complications
Foot pumps	Effective; easy to use with minimal complications
Compression stockings	Not effective; cheap; easy to use
Subcutaneous heparin	Inexpensive; easy to use; high incidence of bleeding
Low-molecular-weight heparins	Easy to use; highly effective; low incidence of bleeding
Vena caval filters	Effective; highly invasive; may lead to chronic venous obstruction

Table 5. Low-Molecular-Weight Heparin Preparations

Drug	Indications	Subcutaneous Injection Dose
Ardeparin	DVT prophylaxis: Knee replacement surgery	50 antiXa U/kg BID
Dalteparin	DVT prophylaxis: Hip replacement surgery, abdominal surgery (at-risk patients*)	2,500-5,000 IU QD
Danaparoid†	DVT prophylaxis: Elective hip surgery	750 antiXa units BID
Enoxaparin	DVT prophylaxis: Hip and knee replacement surgery, abdominal surgery (at-risk patients*)	Prophylaxis hip and knee: 30 mg BID or 40 mg QD Prophylaxis abdominal: 40 mg QD
	Inpatient treatment of acute DVT with or without PE, in conjunction with warfarin	Inpatient treatment: 1 mg/kg BID or 1.5 mg/kg QD
	Outpatient treatment of acute DVT without PE, in conjunction with warfarin	Outpatient Treatment: 1 mg/kg BID
	Prevention of ischemic complications of unstable angina and non-Q wave MI (when used concurrently with aspirin)	Ischemia: 1mg/kg BID

DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism.

*At-risk: age > 40, obesity, general anesthesia >30 minutes, history of malignancy or DVT or pulmonary embolism.

†Danaparoid is an antithrombotic agent with an average molecular weight of ~5,500 daltons.

cellent analgesia from continuous epidural analgesia can be provided to trauma patients.

Summary

The use of LMWH for reducing the risk of DVT and PE has gained increasing popularity in trauma patients with pelvic fractures requiring operative fixation or prolonged (>5 days) bed rest, in patients with complex lower extremity fractures requiring operative fixation or prolonged bed rest, and in spinal-cord-injured patients with complete or incomplete motor paralysis. However, the use of LMWH in trauma can be a challenge, necessitating a fine balance between bleeding risk and DVT/PE risk. There are many unresolved issues concerning the use of antithrombotics in trauma patients, which require further investigation, especially in patients receiving continuous neuraxial analgesia.

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Table 6.

Use of Neuraxial Block in Anticoagulated Patients

- Do not mix ASA and other anticoagulants.
- Bloody tap requires a 24-hour delay of anticoagulation.
- Delay needle placement for 12 hours after LMWH administration.
- Delay catheter withdrawal for 12 hours after LMWH administration.
- Delay LMWH dosing until at least 2 hours after needle placement and/or catheter removal.
- Be extremely vigilant in patients with epidural catheter who are receiving LMWH.

LMWH, low-molecular-weight heparin

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6 Atraumatic Blood Salvage and Autotransfusion in Trauma and Surgery

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The experience with many trauma victims has emphasized the need for a blood source other than banked blood. Cardiopulmonary bypass and vascular surgery have established unwashed filter autotransfusion as a safe and practical means to supplement homologous blood usage. During major orthopedic surgical procedures, autotransfusion has been demonstrated to reduce blood requirements.

The properties of an ideal autotransfusion system include 1) ease of operation, 2) relatively low cost, 3) in-line filtration system, 4) simplified anticoagulation, 5) high fluid aspiration rate and minimal hemolysis whether evacuating a pool of blood or surface skimming from the operative field, and 6) the ability to concentrate the aspirated blood.

The BloodStream Recovery System (BRS) (Harvest Technologies LLC, Norwell, Massachusetts) (Fig. 1) is a surgical suction system that automatically senses the pressures required and adjusts from 20 to 40 mmHg during surface skimming and a maximum of 100 mmHg when evacuating a pool of blood. During trauma and cardiovascular surgery, the BRS can be utilized as a stand-alone autotransfusion system by transferring from the collection reservoir to a reinfusion bag that contains an integral 40-micron filter. During orthopedic surgery, the BRS can be used as the front-end col-

Fig. 1. BloodStream Recovery System (Harvest Technologies LLC, Norwell, Massachusetts).

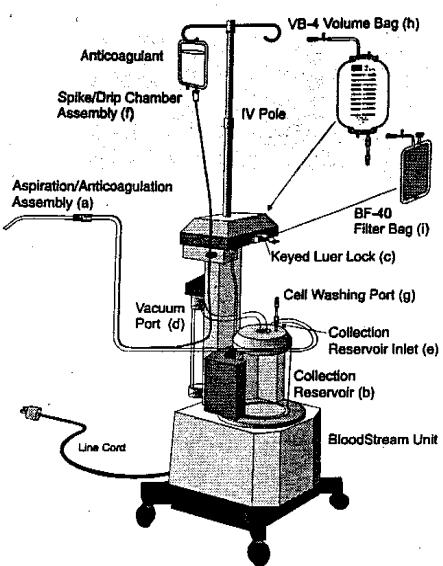


Table 1. Comparison of the BloodStream System with Wall Suction Using Yankauer (Y) and Frazier (F) Suction Wands

Method/Pressure	Flow rate (L/min)* SD ± ml/min
BloodStream/100 mmHg	3.74 ± 25
Wall suction/100 mmHg	
Y50515	1.36 ± 20
F3310	0.64 ± 14
Wall suction/150 mmHg†	
Y50515	1.75 ± 15
F3310	0.84 ± 19
Wall suction/200 mmHg†	
Y50515	2.10 ± 18
F3310	0.98 ± 20
Wall suction/250 mmHg†	
Y50515	2.19 ± 17
F3310	1.12 ± 22
Wall suction/450 mmHg†	
Y50515	3.03 ± 18
F3310	1.66 ± 19

*Mean flow rates observed during evacuation of a pool of blood (volume, 3,000 ml; hematocrit, 24%)

†These pressure levels are not recommended for collection for autotransfusion.

lection system to cell-washing systems by connecting the BRS reservoir to the intake line of the cell-washing machine.

Methods

The BloodStream was compared with wall suction (SS) at vacuum pressures of 100 to 450 mmHg during blood pool evacuation and surface skimming. A variety of suction wands were used with both suction systems.

Multiple red cell pools were required for the studies. The pools are identified by duration of storage, hematocrit, and pertinent control values.

Results

Results obtained during evacuation of a pool of blood are shown in Tables 1 and 2. Flow rates obtained with the BRS are more than twice those obtained with a Yankauer or Frazier suction want at vacuum pressures of 100 and 150 mmHg (Table 1). The latter level is greater than that recommended for autotransfusion or intraoperative blood salvage. When the BloodStream serves as the vacuum source, flow rates obtained with Yankauer and Frazier suction wands are comparable to those obtained with a wall suction system at 200 mmHg (Tables 1 and 2).

Table 2. Comparison of the flow rates obtained with the BloodStream, Yankauer (Y), and Frazier (F) Suction Wands when the BloodStream was the Vacuum Source

BloodStream as the Vacuum source (100 mmHg)	Flow Rate (L/min)* SD ± ml/min
BloodStream wand	3.60 ± 223
Yankauer 50515	2.00 ± 19
Frazier 3310	0.92 ± 21

*Mean flow rates observed during evacuation of a pool of blood (volume, 3,000 ml; hematocrit, 25%).

Table 3 illustrates an example of the results obtained during surface skimming. As one increases the vacuum pressure, there is a tendency for the Frazier wand to grab onto tissue, reducing the flow rate and increasing red cell damage. The BRS has significantly greater flow and results in significantly less damage to red cells, as determined by plasma hemoglobin levels. A wall suction vacuum pressure of 200 mmHg is required to achieve the flow rate obtained with the BRS at 40 mmHg. However, this results in a two-fold increase in plasma hemoglobin.

The BRS system can be used for autotransfusion of unwashed shed blood during cardiac and vascular surgery.

Conclusions

The BloodStream system can rapidly evacuate a pool of blood at more than twice the flow rate achieved with a wall suction system at recommended pressures. The BloodStream results in significantly less damage to red cells as determined by plasma hemoglobin levels compared with wall suction. The data demonstrate that the BloodStream system can be used as a stand-alone mobile surgical suction system in operating rooms, emergency departments, and trauma centers.

Table 3. Comparison of the BloodStream System with Wall Suction at Vacuum Pressures Between 100 and 450 mmHg Using Yankauer (Y50515) and Frazier (F3310) Suction Wands During Surface Skimming

Method/Pressure	Flow rate (L/min)*	Plasma Hemoglobin (mg/dl)
Blood Stream/20-40 mmHg	270 ± 17	24.3 ± 2
Wall suction/100 mmHg Y50515	242 ± 21	32.7 ± 5
	165 ± 19	60.3 ± 3
Wall suction/150 mmHg* Y50515	250 ± 19	40.0 ± 3
	140 ± 18	53.0 ± 4
Wall suction/200 mmHg* Y50515	268 ± 22	59.3 ± 5
	153 ± 19	97.6 ± 7
Wall suction/300 mmHg* Y50515	279 ± 24	63.9 ± 7
	143 ± 16	117 ± 11
Wall suction/450 mmHg* Y50515	277 ± 27	109.0 ± 8
	138 ± 13	500 ± 27

*These pressure levels are not recommended for collection for autotransfusion.

SECTION III: Transfusion: Clinical Practice

7 Current Practices in Fluid and Blood Component Therapy in Trauma

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The acutely volume-depleted trauma patient will have cool, moist, pallid, or cyanotic skin, especially at the extremities. Initial evaluation of the patient will include an estimate of blood volume deficit (Table 1), rate of additional blood loss, primary and secondary survey according to ATLS™ principles, and an evaluation of cardiopulmonary reserve and co-existing hepatic or renal dysfunction.¹ The major goal in resuscitation is to stop the bleeding and replete intravascular volume to maximize tissue oxygen delivery. Cardiac output, blood pressure, and oxygenated blood flow to vital organs are important determinants of outcome.

Management priorities in the trauma patient who is bleeding acutely include ventilation and oxygenation; measurement of blood pressure; placement of ECG, pulse oximeter, and capnograph; and establishment or verification of adequate intravenous (IV) access for infusion of normothermic fluids (See also

Chapters 10 and 12). Monitoring of temperature, urine output, arterial blood gases, hemoglobin, hematocrit, electrolytes, and parameters of coagulation is routine in severely injured patients. An arterial catheter is usually warranted after basic management priorities are fulfilled. Consideration is given to placement of invasive monitors (e.g., central venous catheter, pulmonary artery catheter), transesophageal echocardiography, and provision of anesthesia as needed.

For induction of anesthesia in hemodynamically unstable patients, etomidate or ketamine is useful.² Titrated opioids and amnestic concentrations of volatile agents can

then be used for maintenance of general anesthesia until the intravascular volume deficit has been corrected and bleeding is under control. Neuromuscular relaxants, benzodiazepines, and other agents are given as clinically indicated.²

Fluid Options

There is controversy about which IV solutions should be used for resuscitation. During hemorrhage, the interstitial space, in addition to the intravascular compartment, is diminished, with a compensatory increase in reabsorption of fluid into the capillaries. To replete the intravascular and interstitial compartment, crystalloid solutions such as isotonic 0.9% saline are given initially.³ Glucose-containing solutions are avoided because hyperglycemia aggravates central nervous system injury.^{4,5} Lactated Ringer's solution has an osmolality of 273 mOsm/L, which is hypotonic with respect to plasma. Moreover, lactated Ringer's cannot be used to dilute packed red blood cells. Thus, 0.9% saline is preferred. Colloid solutions such as hetastarch have been shown to be as effective as 5% albumin for volume expansion. Hetastarch is used after the

Table 1.
Estimation of Blood Volume Deficit in Trauma

Unilateral hemothorax	3,000 ml
Hemoperitoneum with abdominal distension	2,000–5,000 ml
Full-thickness soft-tissue defect 5 cm ³	500 ml
Pelvic fracture	1,500–2,000 ml
Femur fracture	800–1,200 ml
Tibia fracture	350–650 ml
Smaller fracture sites	100–500 ml

initial phase of resuscitation, which occurs after cessation of bleeding, and is characterized by interstitial fluid sequestration and maximal weight gain. Large amounts of hetastarch ($>15\text{--}20 \text{ ml/kg}$) are avoided because of the risk of coagulopathy.⁶

Delayed Fluid Resuscitation

The use of large quantities of fluids for immediate resuscitation of victims of penetrating trauma before hemorrhage is controlled by surgical means has been questioned.⁷ Disadvantages of immediate fluid resuscitation are that inserting venous cannulae and giving fluid boluses in the prehospital setting may delay transfer and surgical intervention, may contribute to secondary hemorrhage by disrupting or decreasing resistance to flow around a partially formed thrombus or by increasing blood pressure, may dilute clotting factors, and can contribute to hypothermia. In a randomized, prospective trial of immediate versus delayed fluid resuscitation in patients with penetrating trauma, there was increased mortality, length of stay, and postoperative complication rate in the immediate versus the delayed group.⁷ However, the study was limited to isolated torso injuries, and the receiving trauma center had a very rapid response time such that most patients were in the operating room within 1 hour of injury. Therefore, results of this study may not be applicable to other types of injuries such as blunt trauma, head injury, and multiple sites of penetrating trauma or to patients in remote locations requiring long transport times.

Red Cell Transfusion

The lower limit of anemia is not established in humans. Oxygen delivery is generally adequate with a hemoglobin of 7 g/dl, which corresponds to an oxygen delivery of $\sim 500 \text{ ml/min}$ in a 70-kg patient, assuming normal cardiac output and hemoglobin/oxygen saturation. In otherwise healthy, normovolemic individuals, Messmer and colleagues⁸ demonstrated that tissue oxygenation is maintained with hematocrit between 18% and 25%. The heart and brain are often considered to be most vulnerable to the effects of anemia. The heart begins to produce lactic acid at hematocrits between 15% and 20%,⁹ and heart failure generally occurs at hematocrit of 10%.¹⁰ Generally, hematocrits between 25% and 30% result in optimal oxygen delivery, but therapy must be individualized.¹¹

Factors affecting the transfusion trigger for red cells include the rate and magnitude of blood loss; degree of cardiopulmonary reserve; presence of atherosclerotic disease of the brain, heart, and kidneys; and oxygen consumption.¹¹ If the patient has lost large amounts of blood and is in class III or IV shock (see table on page 4), blood administration is required.² Available options are type O-negative, type-specific, typed and screened, or typed and cross-matched packed red blood cells.

Whole blood is not available at the author's institution. The initial choice will depend on the degree of hemodynamic instability. One unit of packed red blood cells will usually increase the hematocrit by ~3% or the hemoglobin by 1 g/dl in a 70-kg non-bleeding adult.

Type O-negative red cells have no major antigens and can be given reasonably safely to patients with any blood type. Unfortunately, only 8% of the population has O-negative blood, and blood bank reserves of O-negative, low-antibody-titer blood are usually very low. For this reason, O-positive red cells are frequently used. This is a reasonable approach in males but may be a problem in childbearing-aged females who are Rh negative.

If 50% to 75% of the patient's blood volume has been replaced with type O blood (e.g., ~ 10 units of red cells in an adult patient), one should continue to administer type O red cells. Otherwise, risk of a major cross-match reaction increases since the patient may have received enough anti-A or anti-B antibodies to precipitate hemolysis if A, B, or AB units are subsequently given.²

Obtaining type-specific red cells requires 5 to 10 minutes in most institutions, and temporizing measures can sometimes be employed to gain the necessary time. At our institution, we use a tube system to deliver blood samples and products to and from the operating room or trauma resuscitation suite. This system significantly reduces delays and "lost" samples. The use of type-specific red cells is preferred over O-negative and the risk of a hemolytic transfusion reaction is very low.¹² If one can wait 15 minutes, typed and screened blood should be available. When blood is typed and screened, the patient's blood group is identified and the serum is screened for major blood group antibodies. A full cross match generally requires about 45 minutes and involves mixing donor cells with recipient serum to rule out any antigen/antibody reactions.¹³

Coagulation Factors and Platelets

The primary cause of bleeding after trauma is surgical, while the second leading cause is hypothermia. In the past, coagulopathy after massive transfusion with *whole* blood was usually caused by dilutional thrombocytopenia. However, this is not necessarily the case with red cells reconstituted in 0.9% saline. Murray et al have shown that microvascular bleeding and clinical evidence of coagulopathy occurred in the setting of massive transfusion and was associated with decreased coagulation factor levels, decreased fibrinogen, elevated prothrombin times and platelet counts $>100,000/\mu\text{l}$.^{14,15} Moreover, administration of fresh frozen plasma corrected the microvascular bleeding. Two units of fresh frozen plasma (10–15 ml/kg) will achieve 30% factor activity in most adults. Coagulation factor deficiencies may be present due to other causes such as preexisting defects or disseminated intravascular coagulopathy resulting from tissue injury.

Cryoprecipitate may then be indicated to correct specific factor deficiencies. It should be noted that 1 unit of fresh whole blood or 1 unit of single-donor apheresis platelets also has similar factor levels as 1 unit of fresh frozen plasma. Similarly, 4 to 5 multiple donor platelet units have similar factor levels as 1 unit of fresh frozen plasma because the platelets are suspended in plasma.

Dilutional thrombocytopenia in the trauma patient also occurs. Leslie and Toy¹⁶ showed that platelet count was reduced to $<50,000/\mu\text{l}$ after administration of 20 units of red cells. Platelet transfusions are usually indicated in the presence of clinical bleeding and a platelet count $<75,000$ to $100,000/\mu\text{l}$. Platelet concentrates are stored at room temperature and contain about 70% of the platelets in a unit of blood. One unit of platelets, equivalent to 50 ml, increases the platelet count in an adult by 5,000 to $10,000/\mu\text{l}$, and is given through a $170-\mu$ filter.

Hypertonic Fluids

Lesser amounts of hypertonic fluids, as opposed to isotonic fluids, can also provide rapid volume expansion and improved hemodynamics and have the added advantage of decreasing tissue edema, intracranial pressure, and brain water. These hypertonic solutions result in an osmotic translocation of extracellular and intracellular water. Because the intravascular half-life of hypertonic saline is similar to that of isotonic saline, these fluids can be combined with colloid solutions such as hetastarch or dextran to prolong their plasma volume expansion effects. Hypertonic saline has been associated with bleeding, hemodynamic deterioration, and increased mortality in animal studies of uncontrolled hemorrhagic shock.¹⁷ Further, it does not improve cerebral oxygen delivery after head injury and mild hemorrhage in animals.¹⁸ Nonetheless, hypertonic saline combined with 6% hydroxyethyl starch has been shown to improve neurologic function and cerebral perfusion pressure in patients with traumatic brain injury.^{18a} This hypertonic fluid solution is currently used in Austria for resuscitation of all head-injured and major trauma patients in the field (Mauritz W, personal communication).

Endpoints of Resuscitation

Blood and fluid resuscitation is continued until perfusion has been improved and organ function has been restored. Manifestations of improved cardiac output include improved mental status; increased pulse pressure; decreased heart rate; increased urine output; resolution of lactic acidosis and base deficit; brisk capillary refill; and improvement in oxygen delivery, oxygen consumption, and central venous or pulmonary artery oxygen saturation (Table 2).¹⁹

Blood and Fluid Warmers

Fluid and blood resuscitation of the

Table 2. Resuscitation Endpoints Within the First 24 Hours After Trauma

Parameter	Value
Oxygen delivery index	>600 ml/min/m ²
Oxygen consumption index	>150 ml/min/m ²
Mixed venous oxygen tension	>35 mmHg
Mixed venous oxygen saturation (central venous or pulmonary artery)	>65%
Base deficit	>-3 mmol/L
Lactate	<2.5 mmol/L

Adapted from Ivatury RR, Simon RJ. Assessment of tissue oxygenation (evaluation of the adequacy of resuscitation). In Ivatury RR, Cayten CGC, eds. *The Textbook of Penetrating Trauma*. Baltimore, Williams & Wilkins, 1996, pp 927-938.

trauma patient is best accomplished with large-gauge intravenous catheters and effective fluid warmers with high thermal clearances.²⁰ Because alterations in red cell integrity are not apparent until 46°C,²¹ fluid warmers with set points of 42°C are now commonly used. Countercurrent water and other fluid warmers using 42°C set points will not damage red cells, will result in consistently warmer fluid delivery, and will allow the clinician to maintain thermal neutrality with respect to fluid management over a wide range of flow rates.²²

Complications of Transfusion Therapy

Impaired Oxygen Release from Hemoglobin

The ability of the red blood cell to store and release oxygen is impaired after storage. The erythrocytic levels of 2,3-diphosphoglyceric acid decrease both with CPD and CPDA-1 stored blood. Low levels of 2,3-diphosphoglyceric acid will shift the blood's oxygen dissociation curve to the left, and the red cell will have a higher affinity for oxygen at physiologic PO₂ and will release less oxygen at a given tissue PO₂.²³ Impaired oxygen release from hemoglobin can be minimized by warming all blood and by avoiding factors that shift the O₂ dissociation curve to the left, e.g., hypothermia.

Dilutional Coagulopathy

Most coagulation factors are stable in stored whole blood, except factors V and VIII.¹³ These factors gradually decrease to 15% and 50% of normal, respectively, after 21 days of storage. However, most centers today use packed red blood cells and not whole blood during massive transfusion. Microvascular bleeding and clinical evidence of coagulopathy can occur in the setting of massive transfusion with 1 blood volume and are associated with decreased levels of Factor V, VIII, and fibrinogen and increased prothrombin times.¹⁴⁻¹⁶ Microvascular bleeding in this case can be treated appropriately with fresh frozen plasma. Dilutional thrombocytopenia is a cause of hemorrhagic diathesis after 1.5 to 2.0 blood volumes have been transfused. This corresponds to ~15 to 20 units of red cells in an adult

trauma victim.¹⁶ In the author's opinion, the platelet count should be monitored and maintained at or greater than 75,000 to 100,000/µL to achieve adequate surgical hemostasis. It is advisable that prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrin degradation products be monitored because deficiencies may be present due to dilution, preexisting defects, or disseminated intravascular coagulopathy.²⁴ Point-of-care testing and rapid reporting of coagulation test results should be used to guide decisions regarding administration of fresh frozen plasma, platelets, or cryoprecipitate.

Hypothermia

The adverse effects of hypothermia in the trauma patient include major coagulation derangements, peripheral vasoconstriction, metabolic acidosis, compensatory increased oxygen requirements during rewarming, and impaired immune response.²⁵⁻²⁷ Standard coagulation tests are temperature corrected to 37°C and may not reflect hypothermia-induced coagulopathy.²⁸⁻³⁰ Hypothermia impairs coagulation because of slowing of enzymatic rates and reduced platelet function. Hypothermia can cause cardiac dysrhythmias and even cardiac arrest due to electromechanical dissociation, standstill, or fibrillation, especially with core temperatures below 30°C. Hypothermia also impairs citrate, lactate, and drug metabolism; increases blood viscosity; impairs red blood cell deformability; increases intracellular potassium release; and causes a leftward shift of the oxyhemoglobin dissociation curve. A mortality of 100% has been reported in trauma patients whose body temperature fell below 32°C, regardless of severity of injury, degree of hypotension, or fluid replacement.³¹

The importance of fluid warming cannot be underestimated in the trauma patient. It requires 16 kCal of energy to raise the temperature of 1 liter of crystalloid infused at 21°C to body temperature and 30 kCal to raise the temperature of cold 4°C blood to 37°C. Infusion of 4.3 liters of crystalloid at room temperature to an anesthetized adult trauma patient who cannot increase heat production can

result in a decrease of 1.5°C in core temperature. Similarly, infusion of 2.3 liters of red cells could result in a core temperature decrease of between 1 and 1.5°C.^{32,33} Since the thermal stress of infusing fluids at normothermia is essentially zero, it follows that use of fluid-warming devices effective at delivering normothermic fluids to the patient at clinically relevant flow rates permits more efficient rewarming of hypothermic trauma patients using other methods such as the patient's own metabolically generated heat, or externally provided heat such as convective warming.²²

Citrate Intoxication, Hyperkalemia, and Acid-Base Abnormalities

Blood is stored in citrate phosphate dextrose with adenine or ADSL at 4°C. Citrate intoxication is caused by acutely decreased serum levels of ionized calcium, which occurs because citrate binds calcium.³⁴ Administration of calcium is warranted during massive transfusion if the patient is hypotensive and measured serum ionized serum calcium is low or large amounts of blood are infused rapidly (50 to 100 mL/min). Ionized serum calcium levels will usually return to normal when hemodynamic status is improved. The potassium level in stored blood rises with length of storage and can be as high as 78 mmol/L after 35 days. The potential for clinically important hyperkalemia still exists in patients receiving blood administered at rates >120 mL/min³⁵ and in patients with severe acidosis. Monitoring the ECG for signs of hyperkalemia is always warranted, and treatment of hyperkalemia with calcium chloride, bicarbonate, glucose, and insulin may be life saving.

The pH of bank blood decreases to about 6.9 after 21 days of storage because of accumulation of CO₂, lactic acid, and pyruvic acid by red blood cell metabolism. Thus, the acidosis seen in stored blood is partly respiratory and partly metabolic. The respiratory component is of little consequence with adequate patient ventilation. The metabolic component is not usually clinically significant. It is unwise to administer sodium bicarbonate on an empiric basis, because there is already a pool of bicarbonate generated from the metabolism of citrate, which is present in large quantities in stored blood.

Hemolytic Transfusion Reactions

Immediate reactions occur from errors involving ABO incompatibility. More than half of these errors happen after the blood has been issued by the blood bank, which highlights the importance of verifying and identifying each and every donor unit for recipient compatibility. Intravascular hemolysis occurs when recipient antibody coats and immediately destroys the transfused red cells. Classic signs of hemolytic transfusion reaction are masked by general anesthesia. The only evidence may be hemoglobinuria, hypotension, and a bleeding diathesis. Treatment is supportive and involves

stopping the transfusion and maintaining systemic and renal perfusion.

Microaggregates

Microaggregates begin forming after approximately 2 days of blood storage. During the first 7 days, microaggregates are mostly platelets or platelet debris. After the first week, the larger fibrin-white blood cell-platelet aggregates begin to accumulate.³⁶ Whether these microaggregates contribute to lung dysfunction during blood transfusion and whether they need to be removed by micropore filters is controversial.

Infection

Hepatitis C accounts for more than 90% of posttransfusion hepatitis. Every year, at least 2,600 patients develop cirrhosis as a result of hepatitis after blood transfusions.³⁷ Each unit of fresh frozen plasma or platelets has the same risk of infection as a unit of packed red cells. Recent estimates of infectious rates per unit transfused include hepatitis C, 1:103,000; hepatitis B, 1:63,000; HIV, 1:493,000; and HTLV I or II, 1:641,000.³⁸ New screening tests using nucleic acid/genomic amplification techniques will shorten the window period and reduce the risk for these viruses even further. The risk per unit for *Yersinia*, malaria, babesiosis, and Chagas is estimated at <1:1,000,000. Other types of infectious diseases such as toxoplasmosis and cytomegalovirus, Epstein-Barr virus, and bacterial infections may also be transmitted via transfused blood and blood products. The risk of bacterial contamination per unit of random donor platelets is 1:2,500.

Transfusion-Induced Immunosuppression (See also Chapters 8 and 9)

Blood transfusion therapy is also associated with allosensitization, immunosuppression, and an increased incidence of postoperative infections.³⁹ These effects may be mediated by reduced lymphocyte function, downregulation of macrophage function, and altered cytokin production and activity. Strategies to reduce the risk of immunomodulation include the use of third-generation leukocyte filters, lower transfusion trigger, red cell salvage, and blood substitutes (Table 3).^{11,40-42} It is anticipated that new devices for autotransfusion, together with the introduction of hemoglobin-based red cell substitutes, will dramatically alter the current approach to fluid and blood component therapy in trauma.

Summary

The bleeding trauma patient requires rapid evaluation and treatment to ensure adequate tissue perfusion and successful outcome. Resources such as thermally efficient fluid warmers, effective transfusion services, and rapid availability of coagulation tests are practical aspects of trauma resuscitation that deserve priority. Preventing hypothermia and recognizing other complications of massive

transfusion, as well as following trends in vital signs, urinary output, central venous pressures, and arterial and central venous blood gas analysis, are of vital importance to managing patients with hemorrhagic shock.

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Table 3.
Clinical Strategies to Reduce Complications of Transfusion Therapy

Complication	Clinical Strategies to Reduce Complication
Impaired oxygen release from hemoglobin	Warm all blood. Avoid alkalosis. Maintain normothermia (core temperature 36-37°C)
Dilutional coagulopathy	Fresh frozen plasma for PT>1.5 x normal and clinically excessive bleeding. Platelets for thrombocytopenia <75,000/µl and clinically excessive bleeding.
Hypothermia	Warm all IV fluids and blood. Warm room >28°C. Convective warming. Humidify all inspired gases.
Decreased ionized calcium	Treat with calcium chloride, 20 mg/kg, in setting of massive transfusion and hypotension
Hyperkalemia	Monitor ECG and treat with calcium chloride, 20 mg/kg, if hemodynamically significant. Otherwise, monitor and treat with glucose and insulin and/or bicarbonate.
Hemolytic transfusion reaction	Check and recheck every donor unit. Once occurred, stop transfusion and maintain systemic perfusion and renal blood flow. Alkalize urine. Watch for DIC. Send suspected unit to blood bank for crossmatch.
Infection	Lower transfusion trigger. Red cell salvage. Avoid indiscriminate platelet transfusions. Oxygen-carrying red blood cell substitutes.
Transfusion-induced immunosuppression	Lower transfusion trigger. Red cell salvage, oxygen-carrying red blood cell substitutes. Third-generation leukocyte filters.

DIC, disseminated intravascular coagulation

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8 Immunomodulatory Effects of Transfusion

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The administration of blood and its components can be life-saving, particularly during resuscitation in trauma patients when blood loss can be severe enough to result in cellular hypoxia.¹ Also, during other critical illness such as systemic inflammatory response syndrome, especially if the patient is septic with significant acute lung injury, blood is administered to augment oxygen delivery to avoid cellular hypoxia and lactate production.² Even though there are risks following blood transfusions, the benefits appear to be insurmountable³ (Table 1). In spite of this, the risks of infection, especially from HIV, have taken center stage even in the lay press. Thus, the immunologic effects of transfusion have not gained the attention deserved. Nonetheless, in certain disciplines—hematology, critical care medicine, oncology, surgery, and particularly transplantation—have appreciated the immunologic potential from its use. This presentation will discuss the basics of immunology, concentrating on the immunologic consequences of transfusions, the clinical and

Table 1. Risks of Transfusions

Reactions	Frequency: unit
Febrile (FNHTR)	1:4:100
Allergic	1:4:100
Delayed hemolytic	1:1,500
Acute hemolytic	1:12,000
Fatal hemolytic	1:100,000
Anaphylactic	1:150,000
Infections	
Hepatitis C	1:103,000
Hepatitis B	1:200,000
HIV-1	1:490,000
HIV-2	Unknown
HTLV-I (II)	1:641,000
Malaria	1:4,000,000
Miscellaneous	
RBC alloimmunization	1:100
HLA alloimmunization	1:10
Graft vs. host disease	Rare

From Dzieckowski and Anderson.³

animal studies affecting tumor recurrence, and infection.

T-Cell Recognition and Activation

T-cell recognition of an antigen with T-cell activation is key in the initiation of rejection and/or tolerance of foreign tissue. Typically, T cells require two signals for activation. The first occurs when an antigen is processed into peptides by an antigen-presenting cell (APC) and loaded into the groove of a major histocompatibility complex (MHC) molecule. The antigen is then presented to the T cell, which is recognized in the context of self-MHC (Fig. 1). The second signal occurs when the T cell receives stimulation by a cytokine or by the interaction of the T cell with surface molecules of an APC. Numerous cytokines (interleukins, alpha-tumor necrosis factor, and interferon) are involved in this process as well as cell surface receptors, adhesion molecules, and lymphocyte functioning antigen.⁴⁻⁶ Other significant cell surface molecules are the CD3 complex and CD45. The former is associated noncovalently with the T-cell receptor on mature T cells and is a target for OKT3, whereas the latter does not have a known ligand and allows continued activation of the T cell.⁷

Generally, T cells recognize antigens presented as short peptides that are bound in the MHC groove. Allo-MHC molecules stimulate a greater response (*in vitro* mixed lymphocytes response and cytotoxic T-lymphocyte assay) than antigens that are not foreign.⁸⁻¹⁰ The pathways for these alloreactivities are both indirect and direct.¹¹⁻¹³ In the direct pathway of alloantigen presentation, the T cells recognize intact donor MHC molecules on the surface of the donor APC. This pathway may be responsible for early acute rejection of grafts.¹² Early in the care of these patients, radiation and other immune modulation strategies were used to affect this pathway directly by removing or destroying these graft leukocytes.¹³ The exact mechanism is not known and is, without a doubt, multifactorial. In the indirect pathway, T cells recognize processed donor allo-MHC bound to and presented in the context of self-MHC molecules on the surface of self-APC. This pathway is normally associated with a nominal antigen.

History of Donor-Specific Transfusion

As early as 1953, Billingham and associates demonstrated white blood cells as immune modulators when neonatal mice of one strain injected with blood from another subsequently accepted skin grafts from the immunizing strain. This effect was long term only in the neonatal mice, not in the adults.¹⁴ The first solid organ transplantation (kidney) was performed in 1954 between monozygotic twins. The success was probably related to matching of the ABO blood type with compatibility of the (MHC) antigens, not from immune suppression. (The complexity of the immune system was not well understood during this era.)

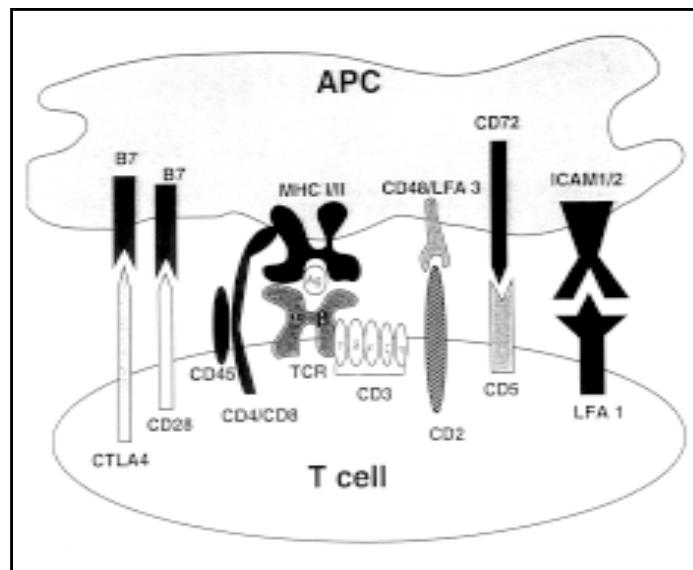


Figure 1
Representation of the antigen-presenting cell (APC) interacting with the major histocompatibility complex (MHC). In addition this interaction is presented to the T cell, which acts with the service molecules and APC.

However, successful transplantation of kidneys from HLA-mismatched donors was not possible (1963) until the advent of immunosuppressive agents, prednisone and azathioprine.^{15,16} The immunosuppressive agents had to be continued to ensure "acceptance" of the foreign tissue or organ. In addition, early in transplantation, efforts were directed to minimize exposure to or sensitization from transfusions. However, in 1972 two animal studies challenged that premise. Jenkins et al revealed that transfusions administered prior to cardiac allografting improved survival of transplanted hearts in rats.¹⁷ Separately, Fabre and associates showed that rejection of the transplanted kidney in rats can be diminished by pretransplant transfusions.¹⁸

Possibly realizing these attributes, Newton and Anderson, in 1973, attempted to manipulate the immune response to renal allografts of four patients with donor-specific peripheral lymphocyte buffy-coat transfusion from their potential living related donor over an extended time (22 to 66 days). Allosensitization did not ensue. Critics believed that the addition of azathioprine contributed to the allograft's success rather than the administration of blood.¹⁹ Subsequent to this new era of cadaveric donor

renal transplantation and at the same time, Opelz et al, following the success in animal models, provided evidence (by reviewing transplant data from multiple centers) in humans that blood transfusion prior to renal transplantation improved renal allograft survival. Compared with patients who did not receive blood transfusions, the transfused patients (>5 transfusions) had a higher survival rate of the renal allografts, approaching 20%. Interestingly though in this study, this effect appeared to have a dose-response relationship.^{18,20,21} Even though this seminal publication was retrospective, recently there appears to be more direct evidence for this response.²² In 1979, Cochrum and colleagues used pretransplantation-directed donor-specific whole blood in patients with renal failure. In strong mixed lymphocyte culture-responsive, one haplotype-mismatched, and living-related donor transplants, directed transfusions improved survival up to 90%. This rate is not that different from that in HLA-identical siblings.^{23,24} Following this success, there was equivalent survival in patients with two haplotype-mismatched, related and unrelated donor-recipient combinations.^{25,27} From these studies and others, the presence of leukocytes and one shared HLA-DR antigen within the transfusions are sufficient enough for optimal immunosuppression.^{20,28} Overall, there is sufficient evidence documenting that transfusions prior to solid organ transplantation improves survival and reduces the incidence of rejection.

Although the precise mechanisms involved in tolerance and sensitization are not completely understood, the laboratory findings have been consistent²⁹ (Table 2). Generally, blood transfusions induce predictable immune responses stimulating alloantibody production when exposed to red cell, white cell, and platelet alloantigens.³⁰⁻³³ Investigations have shown the development of Fc receptor-blocking factors, lymphocyte activation, lymphocyte subpopulation changes, and down regulation of APC after transfusion³⁴ (Table 3). These results

Table 2.
Possible Mechanisms of Transfusion-Associated Immunomodulation

- Anergy
- Tolerance
- Cytokines released during blood storage
- Iron-mediated immune suppression
- Suppressor cell network inhibition
- Anti-idiotypic and anti-clonotypic antibodies
- Clonal deletion

From Brennan et al.²⁹

Table 3.
Immunologic Laboratory Tests in Transfused Patients

Decreased lymphocyte response to mitogens/alloantigens
Down-regulation of natural killer, cytotoxic T lymphocytes
Decreased IL-2 production
Decreased CD4 cells
Increased CD7 cells
Decreased natural killer cell number
Increased B cells
Macrophage function
Decreased migration to chemotactic stimuli
Decreased deposition in inflammatory foci
Increased macrophage prostaglandin E2 production
Decreased antigen-presenting cell activity
Decreased delayed-type hypersensitivity

From Blumberg and Heal.³⁴

are not reproduced in the neonate as compared with the adult immune system. Neonates who received washed and irradiated blood failed to exhibit similar effects seen in adult recipients.³⁵

Tumor Recurrence

There appears to be a beneficial effect of blood transfusions on the immune systems in solid-organ transplantation, but there is a down side—the reemergence of cancer cells in patients with neoplastic disease. However, the results are divergent, ranging from stimulation of tumor growth, suppression of growth, and varied to no response to the tumor cells. In 1982, Burrows and colleagues retrospectively reviewed 122 patients following colorectal surgery. They found a shorter disease-free interval (6 to 12 months) in patients who received a transfusion.³⁶ A similar investigation detected contrasting results and revealed that 43% of transfused patients developed recurrent disease or died, compared with 9% who did not receive a transfusion.³⁷ However, a large multicenter, randomized, controlled study of colorectal patients ($n=475$) with cancer found no direct relationship between allogeneic transfusion and prognosis (cancer-free survival rates after 4 years were no different between the two groups), but the data did suggest an increased in recurrence no matter if the blood was allogeneic or autologous³⁸ (Table 4). These studies did not filter the white cells from the blood components. In an investigation that did filter, the results were confusing because a number of patients received both types of blood products. This study did not reach any conclusions.³⁹ Unfortunately, retrospective studies have inherent flaws and conflicting conclusions. These results

should be reviewed skeptically. To counteract or attempt to explain the association with tumor recurrence and blood, a meta-analysis was performed, reviewing retrospective studies of colorectal cancer patients. In this statistical review, this association was not confirmed.⁴⁰ This study was in contradistinction to another meta-analysis review, in which there was a higher recurrence rate in patients with colorectal and head and neck cancer.³⁰

In a prospective, nonrandomized study, 315 consecutive patients with prostatic cancer who underwent radical retropubic prostatectomy were analyzed. Group 1 received at least one unit of allogeneic blood with or without autologous blood; group 2 received autologous blood only or no blood. These patients received no adjuvant hormonal therapy or radiotherapy. The incidence of reoccurrence was similar: 25% vs. 23%, respectively. In addition, mortality was not affected by the administration of blood.⁴¹

In patients with high-grade soft-tissue sarcomas of the extremities and osteosarcomas of long bones, there is a suggestion that transfusion can alter outcome.⁴²⁻⁴⁴ In Rosenberg's study of patients with soft-tissue tumors who underwent various prospective, randomized treatment protocols, the patients without any transfusions had a 70% actuarial 5-year disease-free survival rate while patients who received 1 to 3 units of blood had a 48% rate. The overall 5-year survival rates were 85% and 63%, respectively. As expected, tumor size correlated inversely with outcome, but after this was taken into consideration, the effect of transfusion still was a negative prognostic indicator.⁴² In a related study that focused primarily on the cardiotoxicity of doxorubicin in patients with high-grade soft-tissue sarcoma, factors that were associated with distal metastases included blood transfusion within 24 hours, tumors >5 cm, tumors extending into the deep fascia, and other histologic subtypes.⁴³ Similar correlation was seen between survival and transfusions in patients with nonmetastatic osteosarcoma of long bones. In this retrospective study, the

survival rate was 34% with blood and 53% without blood. An apparent criticism (not minimizing a retrospective analysis) was that 61% of the transfused patients had femoral tumors while the nontransfused group included only 50%.⁴⁴

In animal studies of tumor augmentation, the data are provocative but still suggestive of transfusions as a factor. One important issue addressed in these animal models is the removal of leukocytes and its timing. In athymic mice transfused with either allogeneic or syngeneic blood or saline prior to tumor cell infusion, the subsequent tumor size was of equal dimensions. However, in immunocompetent mice, there were larger and heavier tumors after transfusion with allogeneic blood.⁴⁵ Correspondingly, rats transfused with allogeneic or syngeneic blood stored for 1 day had higher rates of tumor growth and shorter survival times than controls with saline infusion.⁴⁶ Contrary to these studies, Shirwadkar et al gave mice various doses of tumor cells with the transfusions and concluded that the immunomodulatory effect of transfusion is solely dependent on the dose of the inoculated cells.⁴⁷

In addressing the issue of leukocyte depletion, Blajchman and colleagues preempted 10 days before the infusion of tumor cells either leukocyte-reduced or nonleukocyte-reduced blood. The pulmonary metastatic nodules were assessed 3 weeks later. The recipients of allogeneic transfusion had two- to five-fold increases in these nodules compared with the animals receiving either leukocyte-reduced allogeneic or syngeneic blood.⁴⁸ In an acute experiment (tumor cells injected within 60 to 90 minutes of transfusion), pulmonary metastatic nodules were greater (four- to seven-fold) in the group with allogeneic blood. In this investigation, the authors believed that the removal of allogeneic leukocytes ameliorated the tumor growth potential.⁴⁸ Consequently, these same investigators found that removal of leukocytes following storage did not have similar extent of amelioration.⁴⁹

Table 4.
Multivariate Analysis of Factors Related to Disease-Free Survival in Patients Undergoing Colorectal Curative Surgery

Factors	Relative Recurrence Rate	95% Confidence Interval	p
Transfusion group			
Allogeneic	1	—	—
Autologous	1.1	0.7-1.6	0.74
Dukes' classification			
A	1	—	—
B	4.0	1.7-9.5	0.002
C	10.8	4.7-25.1	<0.001

From Busch et al.³⁸

Tumor Recurrence and Infection

Since there appears to be an immunomodulatory effect of transfusions, the question arises, particularly in regard to patients with cancer, is there a higher rate of infection? In reviewing the data in Heiss's series, the postoperative infection rate was higher in the allogeneic group (27%) compared with the autologous group (12%). Multivariate regression analysis revealed that infection was related to transfusion, with an odds ratio of 2.84. Segmenting the groups revealed that the infection rate also increased with a greater certainty with allogeneic blood compared with the autologous group.⁵⁰ In a large prospective study of colorectal patients (n=871), patients were randomly assigned either leukocyte-filtered blood (<0.2 x 10⁹ leukocytes) or blood without a buffy coat (0.8 x 10⁹ leukocytes per unit). At 3-year follow-up, there was no statistical difference in the infection rate. It is interesting to note that in this study a certain number (>3) of transfusions was a marker or independent risk factor for survival as well, similar to tumor location or size. This correlated with the incidence of infection in the curative surgery patients.⁵¹ Even though statistical analysis selected certain factors, such as >3 units of blood (which had greater postoperative morbidity and mortality), was this associated with the more complex patient with extensive disease and technically difficult surgery?

Infection

Similar controversy surrounds the association between blood transfused and the incidence of postoperative infection. Animal models suggest that allogeneic transfusion increases the appearance of infection.⁵² In traumatic burn or induced peritonitis experimental models, animals had shorter survival with allogeneic transfusions than the groups receiving either crystalloid or syngeneic blood.^{30,31,33} Interestingly, contrasting this traumatic model, Brunson did not induce injury and only infused blood. They found that the addition of trauma, not the dose of blood, altered the immune system, suggesting trauma alone ablated the immune response toward infection.⁵³ To challenge this premise, Gianotti et al subjected

mice to burn injury and infused *Escherichia coli*. They found that enhanced gut permeability and bacterial challenge responded synergistically in secondary infection.⁵⁴ A follow-up investigation showed an association between allogeneic leukocytes and an adverse effect on host bacterial mechanisms.⁵⁵

Clinically, the results are more confusing. A retrospective analysis of orthopedic patients revealed that allogeneic transfusions are associated with increased frequency of postoperative infections, including pneumonia and urinary tract infection.⁵⁶ Other reports (one retrospective and one prospective) showed an association.^{57,58} In a study of patients undergoing total hip replacement, Murphy and associates found a proven or suspected infection in 32% of their select group, e.g., patients without prior infections, malignancy, and infusion of <3 units of blood with allogeneic infusions. This is in comparison to 3% of patients given autologous blood. The hospital stay was considerably longer in patients with suspected infection.⁵⁷ In a nonrandomized, prospective trial, Triulzi and colleagues detected infection in 20.8% of the allogeneic blood recipients compared with 4% of the nontransfused individuals. Apparently, the amount of units given correlated with the infection rate.⁵⁸ In another retrospective review in patients undergoing either hip, spinal, or knee surgery, the data between the groups were not conclusive.⁵⁹ Howard and Vamvakas corroborated these inconclusive findings.^{60,61} In a different population (cardiac surgery patients), the results are more revealing. A multivariate analysis demonstrated contributing factors for postoperative infection as reoperation, blood transfusions, early chest reexploration, and sternal rewiring. The difficulty with this statistical review is that one would expect the infection rate to be higher in emergency reoperations. Controlling clinical factors would be almost impossible.^{62,63}

Conclusions

The weight of scientific evidence from both basic science and clinical studies suggests that allogeneic transfusions have a significant but varied effect on the immune system. There is no doubt there is dynamic

immunomodulatory effect on the recipient. The leukocytes appear to be the culprit. The reason why removing white cells prior to storage to minimizes complications (infections, recurrence of tumor) is not understood. One thing certain is that the extent of transfusions correlates with these secondary problems, but in patients who receive a greater number of blood products, what is the predominant indeterminate factor: the underlying disease process, the patient's co-morbidity factors, or the aggressiveness of surgical eradication?

No large clinical trials of transfusion in trauma patients (who tend to be young and not have complicating medical diseases) have been undertaken to determine the incidence of infection when leukocytes are removed prior to storage. In the author's opinion, one group will benefit, and that group includes patients transfused with <10 units of blood. However, this investigation must be initiated upon arrival to the definitive area and it must be blinded and prospective. Should the standard of blood banking include prestorage filtering of all blood? Economically, it would be feasible to filter the blood when the potential risk of infection and cancer is there. The precedent for accepting increased cost without clearly demonstrated benefit has already been set by the much greater costs involved in the prevention of transmission of the AIDS virus by p24 antigen testing in blood banking⁶⁴ (Table 5).

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Table 5. Allogeneic Transfusion Immunomodulation-Related Postoperative Infection and Cancer Recurrence: Theoretic Estimates of U.S. Mortality Rates

Estimated % Causal Contribution	Infection		Cancer Recurrence		Total	
	Deaths per Year	Death Rate per Million Transfusions	Deaths per Year	Death Rate per Million Transfusions	Deaths per Year	Death Rate per Million Transfusions
100	1,500	250	20,000	33,000	21,500	33,250
50	750	125	10,000	16,667	10,750	16,892
10	150	25	2,000	3,300	2,150	3,325
1	15	2.5	200	330	215	332.5

From Blumberg.⁶⁴

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9 Blood Transfusions

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The trauma patient frequently requires multiple blood transfusions during resuscitation to achieve a stable hemodynamic state. Adequate oxygen-carrying capacity necessitates transfusion based on the patient's pathophysiology after being injured, the patient's baseline medical condition, and actual and anticipated blood loss.

Transfusion is often necessary, but it is not always benign. To even consider the concept of decreasing the amount of blood transfused to trauma patients, we must determine whether we can accomplish this goal without affecting outcome. Obviously, many patients would die without transfusion. Although blood transfusions increase oxygen-carrying capacity, massive transfusion is associated with physiologic alterations, immunomodulation, and postoperative infection. Two questions have become important in transfusion medicine: 1) What is in the blood? and 2) What are the systemic effects of transfusion other than increasing the hematocrit?

Despite safeguards and tests to ensure that blood is not contaminated, blood is being released that is in fact contaminated. Transfusion of tainted blood can transmit the human immunodeficiency virus (HIV), hepatitis, cytomegalovirus (CMV) and syphilis. Testing for HIV has become increasingly accurate, so the window period for possible infection has been shortened because of earlier detection. The window period for HIV is that time in which a person is infected with the virus but has not yet demonstrated infectivity by available testing methods. In a study conducted a number of years ago, 39 patients became seropositive

from 182 "seronegative" donors. This resulted from the long period necessary to develop detectable levels of antibodies to HIV. Current antibody testing has diminished the window to 22 days. In March 1996, the U.S. Food and Drug Administration mandated P24 antigen testing, which decreased the window period to 16 days.

In addition to HIV transmission, hepatitis B, hepatitis C, and CMV can be transmitted easily if blood is not tested adequately. CMV is frequently present in transfused blood, its prevalence determined by geographic location. Special care must be taken in the immunosuppressed patient to ensure that CMV is not present in transfused blood. Bacterial and parasitic infections can also be transmitted. Other complications known to occur with transfusions include allergic reactions, hemolytic transfusion reactions, and volume overload.

Transfusions may also result in immunosuppression or immunomodulation of the recipient. Studies have demonstrated that renal transplant patients had improved allograft survival times and lower allograft rejection rates if they received transfusions of bank blood (allogeneic blood) prior to receiving their allograft.¹ During the 1970s, some protocols required patients receiving cadaveric renal transplants to receive transfusions prior to the transplant procedure. Transfusion of whole blood was a stronger enhancer of allograft survival than packed red blood cells. The prevalent thought was that transfusion induced an immunosuppressive effect in the patient and thus, after the patient received the transplant, rejection did not occur. Fortunately, the need for preoperative allogeneic transfusion has been mitigated by the introduction of cyclosporin.²

In addition to evidence that allogeneic transfusions result in immunosuppression, there is evidence that cancer patients who receive these transfusions at the time of surgery have lower survival rates and an increased incidence of recurrence.² Meta-analysis has demonstrated this finding to be true in patients

- with colorectal cancer and head and neck cancer.³ Osteosarcoma patients who receive perioperative blood transfusions have an increased incidence of metastases and shorter survival time.²
- An altered immunologic state results from receiving a blood transfusion. Allogeneic blood transfusions have been associated with decreases in cell-mediated immunity, macrophage migration, and natural killer cell activity. Additionally, allogeneic transfusion affects the cells that incite B-lymphocytes to differentiate and produce antibodies. These immunosuppressive effects are thought to be the result of either antigen excess, a graft-versus-host phenomenon, reactivation of immunosuppressive viruses, or the white blood cells that are transfused along with red blood cells.²
- Allogeneic blood transfusions have also been implicated in postoperative infections. Independently, Murphy and Triulzi, in separate studies on orthopaedic patients, demonstrated the effect of allogeneic blood transfusions in producing postoperative infection.^{4,5} A significant increase in postoperative infection rates occurred in patients who received allogeneic blood transfusions during either total hip or spine surgery compared with patients who did not receive allogeneic blood. Of patients who received allogeneic transfusions, there was an infection rate of 20.8% in a study of 102 patients undergoing 109 spinal fusions. The infection rate was only 3.5% in those who did not receive allogeneic blood. Natural killer cell activity, an indicator of immunologic function, decreased in the patients who received allogeneic transfusion. A specific dose-response curve demonstrated that patients who received two transfusions had a higher infection rate than patients who received either one or no transfusion at all.^{4,5} Fernandez demonstrated that patients who received homologous whole blood had a higher incidence (20%) of infection compared with the overall (6.1%) infection rate for all

patients in the study.⁶ Some orthopaedic studies do not demonstrate an association between allogeneic transfusion and infection. In a meta-analysis, Vamvakas et al were unable to demonstrate a clear relationship between transfusion and infection. Their study criteria, however, defined a significant relationship occurring between transfusion and infection as one that would result in an infection rate more than double the baseline occurrence rate.³

There is significant evidence that transfusions are associated with immunomodulation and increased infection in trauma patients.^{7–11} Rosemurgy demonstrated an increased incidence in postoperative infection in a population of 390 uncrossmatched trauma patients who received type O blood. In the 61% of patients who survived at least 7 days, the infection rate was higher in those who received seven or more units of packed red blood cells.⁷ Dellinger noted that, while wound infections after open fractures of the arm or leg were affected by local factors, nosocomial infections were related to Injury Severity Score (ISS), the incidence of blood transfusion, patient age, and the mode of injury. Edna and Bjerkeset, in a Norwegian study of 484 trauma patients who survived longer than 2 days, demonstrated a 9.5% infection rate, with a univariate relationship between infection and transfusion.¹⁰ This relationship was independent of ISS, age, and surgical procedure. The risk of infection after colon injury is associated with blood transfusion, age, and the number of associated injuries and splenic injury. Agarwal, in a study of 5,366 consecutive trauma patients, documented that blood transfusion was a predictor of infection after controlling for patient's age, sex, mechanism, or severity of injury.¹¹

In a study of 619 geriatric patients with hip fracture, a study at the author's institution documented a significantly higher incidence of urinary tract infections in patients who received allogeneic transfusion compared with those who did not require any transfusion.¹²

Riska demonstrated a linear relationship between the number of units transfused and mortality, with 21 to 39 units being associated with a 25% mortality and more than 40 units associated with a 52% mortality.¹³ Wudel documented 5 survivors of more than 50 units of blood after massive transfusion.⁹ Blunt and penetrating trauma patients receiving multiple transfusions had similar survival rates (59%). Shock, closed head injury, and age predicted increased mortality but did not preclude survival.

Massive transfusion may be associated with high citrate and acid load, possible hemostatic failure, disseminated intravascular coagulation, large amounts of infused blood debris, inadequate 2,3-DPG levels, and thrombocytopenia. Thus, although multiple transfusion is indicated under many conditions, we need to consider what are appropriate transfusion triggers. What factors are considered important in determining the need for trans-

fusion? In order to tolerate low hemoglobin, patients must be able to compensate for the decreased oxygen-carrying capacity associated with decreased concentrations of red blood cells. Healthy patients can frequently compensate, but this ability becomes compromised with age and cardiac and respiratory disease. Increases in cardiac output must be sufficient to overcome existing deficits. Since oxygen delivery depends on cardiac output and arterial oxygen concentration, in addition to supplying enhanced oxygen concentration, the patient must be able to increase stroke volume and heart rate. The trauma patient is faced with acute decreases in hemoglobin levels and not afforded the ability to compensate, as do patients with chronic anemia. Once volume status is repleted, hemoglobin (Hb) levels must be evaluated to determine the need for transfusion. Most patients require transfusion when the Hb is less than 6 gm/dl and few require it when the Hb is more than 10 gm/dl. Transfusion in the intermediate area requires consideration of physiologic status and the individual's ability to ensure adequate oxygenation to vital organs.

Conclusion

Many trauma patients require blood transfusions to replenish massive blood loss from wounds. The advantages of predonation and cell salvage techniques are not present under emergency conditions or are inappropriate based on the type of injury. Currently, this leaves banked blood as the source of blood for transfusion. The advantages afforded by administering allogeneic blood to enhance oxygen-carrying capacity must be weighed against its adverse side effects, which include immunomodulation, transmission of infectious diseases, and the possibility of a transfusion reaction.

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10 Vascular Access in Trauma: Options, Risks, Benefits, Complications

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Vascular access in the trauma patient is essential for three reasons:

- administration of intravenous fluids
- administration of drugs
- measurement and monitoring of cardiac parameters

In the trauma patient presenting with multiple serious injuries and hemorrhagic shock, vascular access is necessary to restore circulatory volume rapidly. The urgency of the placement and the size and number of intravenous (IV) lines is dictated by the degree of shock, the apparent rate of bleeding, and the type of injury. Advanced Trauma Life Support (ATLS™) protocol recommends proceeding with attempts at percutaneous peripheral access, followed by a surgical venous cutdown before resorting to central venous access. The rationale is that, in a hypovolemic patient, the

likelihood of success with a venous cutdown is greater than with a central line. Additionally, the rate of complications (e.g., pneumothorax and arterial puncture) is higher with central IV access.¹ However, the most important factor in considering the procedure and route for vascular access is the individual physician's level of skill and expertise.

Location of the injury must be considered when choosing a site for venous access. Venous access must never be initiated in an injured limb. In patients with injuries below the diaphragm, at least one IV line should be placed in a tributary of the superior vena cava, as there may be vascular disruption of the inferior vena cava. Patients with upper thoracic and neck injuries should have large-bore access in the lower extremity, as there may be superior vena cava disruption. In patients with severe multitrauma in whom occult thoracoabdominal damage is suspected, it is recommended to have one IV access site above the diaphragm and one below the diaphragm, thus accessing both the superior vena cava and inferior vena cava, respectively.^{2,3}

For rapid administration of large amounts of intravenous fluids, short large-bore catheters should be used. Based on Poiseulle's law, the rate of fluid flow is inversely proportional to the length of the catheter and directly proportional to its internal diameter:

$$Q = \frac{\Pi r^4 (\Delta P)}{8nL}$$

where Q=flow, r=radius of the catheter, P=driving pressure through the catheter (gravity or externally applied), n=viscosity of the solution, and L=length of IV tubing. Doubling the internal diameter of the venous cannula increases the flow through the catheter 16-fold. A 14-gauge, 5-cm catheter in a peripheral vein will pass fluid twice as fast as a 16-gauge, 20-cm catheter passed centrally. Although resistance to flow is added by multiple stopcocks and connections, stopcocks are recommended for universal precautions. When using 8.5 French pulmonary catheter introducers, the side port should be removed, as this increases the resistance roughly four-fold. For subclavian, internal jugular, femoral, and antecubital lines, 8.5 French introducers can be used.⁴

Percutaneous Intravenous Insertion

ATLS™ guidelines recommend rapid placement of two large-bore (16-gauge or larger) IV catheters in the patient with serious injuries and hemorrhagic shock. The first choice for IV insertion should be a peripheral extremity vein. The most suitable veins are at the wrist, the dorsum of the hand, the antecubital fossa in the arm, and the saphenous in the leg. These sites can be followed by the external jugular and femoral vein.

The complication rate of properly placed intravenous catheters is low. Intravascular

placement of a large-bore IV should be verified by checking for backflow. An IV site should infuse easily without added pressure. Intravenous fluids can extravasate into soft tissues when pumped under pressure through an infiltrated IV line, and a compartment syndrome can result. It is always best to have intravenous sites out where they can be examined.

Central Venous Access

Rapid peripheral percutaneous IV access may be difficult to achieve in patients with hypovolemia and venous collapse, edema, obesity, scar tissue, history of IV drug abuse, or burns. Under such circumstances, central access with wide-bore catheters can be advantageous. An additional benefit is the ability to monitor central venous pressure. However, subclavian and internal jugular catheterization should not be used routinely in trauma patients, as the complications can be dangerous.

Subclavian Catheterization

Subclavian catheterization provides rapid and safe venous access in experienced hands. The most frequent complication of subclavian venipuncture is pneumothorax. Pneumothorax is more likely to occur on the left side because the left pleural dome is anatomically higher. Subclavian and internal jugular catheters should be inserted on the side of injury in patients with chest wounds, reducing the chances of collapse of the uninjured lung. A simple pneumothorax may result in respiratory compromise in individuals with pulmonary contusions or a pneumothorax in the contralateral hemithorax.² A suspected injury to the subclavian vein is an exception to this principle because the infused fluid may extravasate into the mediastinum or thoracic cavity.

A hemothorax may result from laceration of the subclavian vein or subclavian artery. If the subclavian catheter is placed inadvertently in the thoracic cavity, subsequent infusions of blood or crystalloids will produce a hemothorax or hydrothorax. Catheter placement should be ensured prior to IV infusions, whether by aspiration or by lowering the IV infusion bag below the patient and verifying backflow. These tests are suggestive of IV placement but none is diagnostic.⁴ When inserting introducers over guide wires, it is important not to force the introducer if resistance is encountered. Forcing the introducer could result in perforation of large veins or arteries and bleeding.

Venous air embolism is another complication of central line insertion. Occlusion should be maintained over the catheter lumen with a gloved finger or by increasing the pressure in the subclavian vein by Trendelenburg position or Valsalva maneuver. Even with prompt therapy, the fatality rate with significant air embolism is high.⁵ Embolization of catheter fragments can occur when withdrawing a catheter with a through-the-needle technique.

Arrhythmia may occur during line placement when the catheter or wire contacts the

endocardium of the atrium or ventricle. Proper positioning of the catheter in the superior vena cava (SVC) usually abolishes this problem. Myocardial perforation and tamponade rarely occur.

Thrombosis or thrombophlebitis occurs with malpositioned or misdirected catheters. The subclavian catheter is often malpositioned into the internal jugular vein. When the catheter is placed properly in the SVC, thrombosis usually does not occur because of the high flow and large caliber of the vessel. A kinked or knotted catheter in the SVC may lead to thrombosis.

Injury to the brachial plexus or phrenic nerve may result from attempts to place a subclavian line. The nerves are posterior to the vein, and injury occurs when the needle has penetrated both walls. Left-sided central line attempts can result in thoracic duct injury.

Infectious complications associated with line placement can be prevented by using proper sterile technique. Any lines placed during resuscitation of a trauma patient without strict aseptic technique should be removed.

Internal Jugular Vein Catheterization

Percutaneous placement of internal jugular (IJ) catheters is also an excellent means of attaining rapid large-bore catheter access. Cervical trauma is a contraindication for internal jugular placement. Trendelenburg position and Valsalva maneuver help to distend the internal jugular vein and improve the rate of success for venipuncture.

Carotid artery puncture is a common complication of IJ catheter placement. Local direct pressure can prevent hematoma formation. Carotid puncture is a contraindication to attempting IJ catheter placement on the opposite side, because bilateral hemorrhages could compress the airway.

Other complications from IJ venipuncture are similar to those associated with subclavian venipuncture. The incidence of pneumothorax is less with IJ catheter placement than with placement of a subclavian line. The incidence of hemothorax, mediastinal migration of the catheter, and intrapleural catheter placement tends to be greater with left IJ placement than right because the left IJ is more circuitous, and advancement of a catheter can rupture the vessel. Stellate ganglion injury is a possible complication.

Femoral and Basilic-Cephalic Central Lines

Femoral vein cannulation is another alternative for line placement and is associated with fewer acute complications. Bowel perforation can occur, especially in patients with femoral hernia. Penetration of the hip could result in septic arthritis. Thrombophlebitis occurs more often with femoral than with IJ or subclavian catheters; however, this is most likely with prolonged use.

Basilic-cephalic catheterization may be

used for central access and central venous pressure monitoring with a “long-arm” catheter. Introducers can also be inserted safely. They are easily placed and associated with a low complication rate.

Venous Cutdowns

Venous cutdowns can be performed when rapid, secure, large-bore venous cannulation is desirable, such as in hemodynamic shock and in situations where percutaneous peripheral or central access is either contraindicated or impossible to achieve.

Most favored sites for cutdowns are the cephalic, basilic, and median antecubital veins in the upper extremity and the greater saphenous in the lower. These veins can accept large catheters, allowing rapid infusion. Strict aseptic technique should be used. Surgical masks and caps should be worn.⁶

Venous cutdown has a low potential for anatomic damage. Cutaneous nerve injury is the most common problem. The infection rate is relatively low when used acutely but increases precipitously over time. Therefore, it is recommended that venous cutdown catheters be removed as soon as it is possible to achieve IV access through standard percutaneous IV catheters or a central venous catheter.⁵

Vascular Access in Pediatric Patients

Ideally, venous access in severely injured children should be established via a percutaneous route. Unfortunately, this often proves to be a difficult task. ATLS™ recommends that after two unsuccessful percutaneous attempts, consideration should be given to intraosseous infusion in children younger than 6 years of age or direct venous cutdown in children over

6 years of age.¹ Scalp veins should not be used when rapid fluid administration may be needed. Internal jugular and subclavian catheterization can be done in children but should be performed only by experienced personnel. In awake children, there is a higher incidence of pneumothorax and arterial puncture.

Intraosseous catheters can be used in all age groups but are most successful in those younger than 2 because the cortical bone is softer. Fluids and drugs can be given through the catheter. Specially designed intraosseous needles are available but 18- to 20-gauge needles, bone marrow aspiration needles, and 18-gauge spinal needles can be used. Eighteen-gauge spinal needles are readily available, but they often bend and make placement difficult. In children younger than 6 years of age, the locations of choice are the proximal tibia and the distal femur. When using the proximal tibial plateau, the needle should be placed 2 to 3 cm distal to the level of the tibial tuberosity on the anterior medial surface of the proximal tibia. In adults, a site 2 cm proximal to the tip of the medial malleoli is selected, with the needle directed slightly cephalad. The distal tibia, distal femur, sternum, clavicle, and humerus can also be used. Pressure and a rotary motion should be used until there is a decrease in resistance, indicating that the medullary cavity has been entered. It is not always possible to aspirate marrow, but IV fluid should run easily without a pump.⁷

Complications of intraosseous infusions include extravasation of fluids into surrounding tissues, cellulitis, and osteomyelitis. Multiple attempts at insertion should be avoided since the other holes in the bone could allow leakage of fluid into the adjacent soft tissue.

The incidence of osteomyelitis is low when catheters are removed early. Standard peripheral or central venous placement should be attempted when the patient is stable. Bones with fractures and sites with open wounds should be avoided.⁵

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11 Principles of Fluid Warming in Trauma

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Hypothermia occurs frequently in trauma patients because of exposure, infusion of cold fluids and blood, opening of body cavities, decreased heat production, and impaired thermoregulatory control.¹⁻⁷ Infusion of unwarmed or inadequately warmed IV fluids and cold blood is a well known cause of hypothermia and may contribute to the multiple adverse consequences of hypothermia such as peripheral vasoconstriction, metabolic acidosis, coagulopathy, wound infection, and cardiac morbidity.^{1-3,8-13} This manuscript reviews the

principles of fluid warming as they apply to the trauma patient.

Importance of Warming IV Fluids

Conclusive evidence demonstrating the harmful effects of cold fluid infusion was provided by Boyan and Howland.¹⁴ In their study, infusion of 0.5 L of cold blood reduced core temperature of anesthetized cancer patients by 0.5 to 1.0°C. When 3.0 L or more of cold blood was administered, esophageal temperature decreased markedly and was associated with a high incidence of cardiac arrests (12 of 25 patients).¹⁴ When blood was warmed, the incidence of cardiac arrests in a matched group of patients with similar surgeries, blood loss, anesthesiologist, and surgeon was only 3 of 105 patients.^{15,16}

The use of large quantities of unwarmed fluids for immediate resuscitation of patients with penetrating trauma prior to emergency surgical intervention has been discouraged.¹⁷ It is possible that the use of unwarmed fluids

may contribute to a hypothermia-induced or dilutional coagulopathy, although experimental evidence suggests that hydraulic factors may play a more important role (e.g., disruption of soft clot, decreased resistance to flow around a partially formed thrombus).¹⁸

Thermal Stress of Infusing Cold or Inadequately Warmed Fluids and Blood

The theoretical impact of infusing fluids on body temperature can be calculated as follows:

$$\text{Change in body temperature} = \frac{\text{Thermal stress of infused fluids}}{(\text{Weight} \times \text{Sp heat})}$$

where:

Thermal stress = Temperature difference between core and infused fluids \times specific heat of infused fluid \times volume of fluid infused

Weight = weight of patient in kg

Sp heat = specific heat of the patient (0.83 kcal/L/°C)^{19,20}

According to the specific heat of water, 1 kCal of heat is required to raise the temperature of 1 kg of water by 1°C. Assuming that 1 L of crystalloid weighs 1 kg and that its specific heat is the same as water, one needs 16 kCal of energy to raise the temperature of 1 liter of crystalloid infused at 21°C to body temperature (37°C).¹⁹⁻²² Similarly, infusion of 4.3 L of crystalloid at room temperature to an adult trauma patient would require 71 kCal, the equivalent of 1 hour of heat production in an awake adult, or 1.5 hour of heat production in an anesthetized adult male (heat production decreased by 33%).

The negative thermal balance of 4.3 L of room temperature fluids is thus equivalent to a decrease of 1°C body temperature in an awake individual and a 1.5°C temperature decrease in an anesthetized patient. Conversely, 30 kCal are required to raise the temperature of cold 4°C blood to 37°C, such that infusion of 2 L could result in a body temperature decrease of between 1.0 and 1.5°C.¹⁹⁻²²

Temperature Setpoints of Warmers

In the United States, blood can be warmed safely so as not to cause hemolysis using a temperature setpoint of 42°C in conjunction with an FDA-cleared blood warming device. This setpoint is based on observations by Uhl and colleagues²³ and is supported by a large body of experience with cardiac perfusion. In the study by Uhl et al,²³ red cells were incubated at 37, 40, 42, 44, 46, 48, and 50°C for up to 2 hours in a constant-temperature waterbath. Even subtle alterations in red cell integrity such as increased plasma hemoglobin and osmotic fragility were not apparent until 46°C.²³

There has been renewed interest in delivering very hot fluids in an attempt to transfer heat to hypothermic patients. For example, infusion of crystalloid at 54°C will transfer ~21 kCal/L to a hypothermic patient whose core temperature is 33°C. This technique has been shown to be relatively safe in a series of patients undergoing operative burn debridement and immediate skin grafting.²⁴ Fluids were infused at a rate of 110 ml/hr. In the study, there was no evidence of intravascular hemolysis or other overt complications such as excessive bleeding or hyperkalemia.²⁴ There is currently not enough safety information to recommend this technique and there is danger that very hot fluids may result in local vascular damage and other complications such as hemolysis.

Fluid Warming Devices (Table 1)

Intravenous administration of large volumes of inadequately warmed fluid can lead to significant hypothermia. Several methods to warm IV fluids are currently available. These methods include immersing coiled IV tubing in a warm water bath, microwaving the bag of fluid to be infused, adding heated saline to blood to be infused, passing the IV tubing through a heating block or through a plastic tube warmed with forced air, passing the IV

Table 1. Commercially Available Warming Devices

Instrument	Technology	Comments
Flotem IIe	Dry heat	IV tubing sandwiched between heating plates
DW-100	Dry heat	Plastic bag wrapped around heating cylinder
Fenwall	Dry heat	Plastic bag with channels sandwiched between heating plates
Dupaco	Water bath	Coiled IV tubing immersed in a bath
Level 1 H250	Countercurrent water bath	Tube in tube heat exchange
Level 1 H500	Countercurrent water bath	Tube in tube heat exchange, larger heater than H250
Hotline	Countercurrent water bath	Entire 254-cm patient IV line is warmed to ensure delivery of warm fluids at flow rates between 5 and 90 ml/min (300-5000 ml/hr)
Level 1 H1000	Countercurrent water bath	Tube in tube heat exchange combined with a 254-cm patient IV line with Hotline characteristics to prevent heat loss at moderate flow rates (<100 ml/min)
BairHugger 2.4.1	Convective air	Spiral IV tubing suspended in same convective warming hose that delivers forced air to a warming blanket
FMS 2000	Magnetic induction	High-speed volumetric pump with automatic air detectors, line pressure sensor, and flow rate control up to 500 mL/min; 122-cm patient line
R.I.S. (Haemonetics)	Countercurrent water bath	High-efficiency pump with 3-L reservoir, three air/bubble detectors, line pressure sensor, and automatic flow rate control up to 1500 ml/min
Arrow Thermostat 900	In-line microwave	Direct microwave energy transferred in a heating chamber to coils of IV tubing wound on a disposable cartridge
Baxter Thermacyl	Dry heat	Disposable canister sets that fit over the heating unit; bubble trap to remove microbubbles
Mallinckrodt Warmflo FW538	Countercurrent metal	Metal foil cassette inserted between two heated plates; IV tubing inserts directly into metal fluid channels within the cassette
Alton Dean	Countercurrent metal	Metal foil cassette inserted between two heated plates; IV tubing inserts directly into metal fluid channels within the cassette
Ranger	Countercurrent metal	Cartridge-style plastic disposable set inserted between conductive warming plates

tubing through a conductive surface interfaced with a counter-current heated water bath, magnetic induction, and inline microwaving.²⁵⁻²⁹

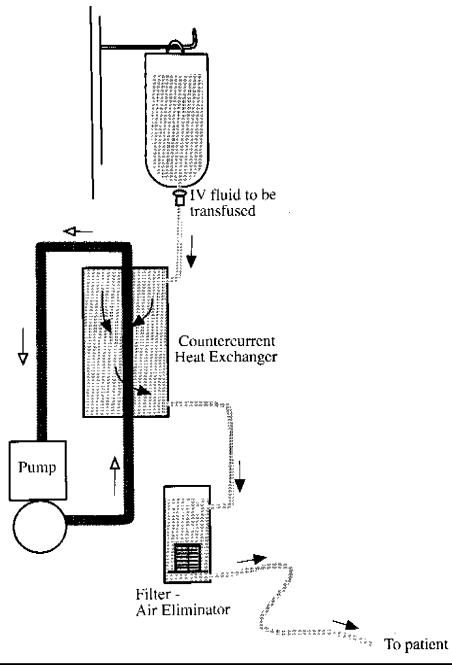
The ideal fluid warmer should be capable of safely delivering fluids and blood products at normothermia at both high and low flow rates. The ability of blood warmers to safely deliver normothermic fluids over a wide range of flows is limited by several factors, including limited heat-transfer capability of materials

such as plastic, limited surface area of the heat exchange mechanism, inadequate heat transfer of the exchange mechanism at high flow rates, erythrocyte damage, and heat loss after the IV tubing exits the warmer.^{25,30-32} For example, adding warmed saline to blood could have catastrophic results unless the saline is not heated above a certain temperature—the maximum safe temperature would be highly dependent on the relative volume of saline and

Figure 1.

Schematic of the Level 1 250 and 500 warmer. The device consists of a heater that warms water and circulates it through a pump and a heat-exchange segment with a central tube for water flow (countercurrent heat exchange technology).

Fluid flows through the outer sheath, which surrounds the water core. Note the filter and air eliminator distal to the heat exchanger.



blood. The dangers of using unproven methods and nonapproved approaches to blood warming cannot be overemphasized.

The heat-transfer capabilities of warming devices using dry heat exchange technology is limited by use of poorly conducting materials such as plastic and by limited heat transfer surface area. Warming devices that utilize countercurrent heat exchange (Level 1 H250 [Fig. 1], H1000 [Fig. 2], and FW537) are capable of warming fluids even at very rapid flow rates due to better conduction materials interposed between the heating elements and the infused fluid.^{32,33} Therefore, both these devices are appropriate for situations where rapid (>100 ml/min) volume resuscitation is necessary.

At moderate flows (<100 ml/min), there is significant heat loss after the IV tubing exits the warmer. The continual countercurrent warming of fluids in the tubing (Hotline [Fig. 3] and H1000) essentially eliminates the loss of heat along the tubing distal to the warmer.³³

Table 2 summarizes the implications of using various fluid warmers during commonly encountered clinical situations: pressure-driven infusion, and gravity-driven infusion with the roller clamp wide open.^{32,33} In the first situation, the patient presents with severe circulatory shock due to massive blood loss. Fluid resuscitation via large-bore IV cannulas is required to prevent acidosis and irreversible shock. In

Table 2. Implications of Using Warming Devices for Crystalloid Fluid Resuscitation (5 and 10 L) in Anesthetized Adult Trauma Patients

Device	Flow Rate (ml/min)	Outlet Temperature	Decrease in MBT* (5 L infusion, °C)	Decrease in MBT* (10 L infusion, °C)
Flotem IIe	260	24	-1.12	-2.24
	90	27	-1.03	-2.06
Astotherm	260	25	-1.03	-2.06
	90	30	-0.60	-1.20
BairHugger 2.4.1	360	24.2	-1.10	-2.20
	80	29.6	-0.63	-1.27
Hotline	220	29.8	-0.62	-1.24
	80	34.8	-0.19	-0.38
Level 1 250	600	33	-0.34	-0.69
	290	36	-0.09	-0.17
Level 1 H1000	470	39.5	+0.22	+0.43
	150	39.4	+0.21	+0.41
FW537	580	38.9	+0.16	+0.32
	200	39.9	+0.25	+0.49
Cardioplegia Heat Exchanger	700	35	-0.17	-0.34
	150	35	-0.17	-0.34

For all devices, fluids were infused during two conditions—pressure-driven infusion and gravity-driven infusion with the roller clamp wide open. Data from references 32 and 33.

*Change in mean body temperature (MBT) was calculated as follows:

$$(T_{\text{fluid}} - T_{\text{patient}}) S_{\text{fluid}} / \text{Weight} \times S_{\text{patient}}$$

where

T_{fluid} = Outlet temperature of fluid delivered to the patient

T_{patient} = Temperature of the patient, assumed to be 37 °C

S_{fluid} = Specific heat of infused fluid, 1 kcal/L/°C

S_{patient} = Specific heat of the patient, 0.83 kcal/l/°C^{19,20}

Weight of patient was assumed to be 70 kg

the second scenario, the fluid and blood volume deficit is not as severe, although ongoing blood loss may necessitate moderately fast infusions with the roller clamp wide open to maintain normovolemia and hemodynamic stability. It can be seen from the calculations in Table 1 that the thermal stress of infusing cold fluids may result in considerable changes in mean body temperature, especially if the patient is unable to increase heat production or prevent further heat loss. The larger the gradient between the temperature of the infused fluid and

core temperature, the greater the drop in mean body temperature. As well, the greater the fluid requirement relative to body weight, the greater the potential drop in body temperature.

Because of the marked inefficiencies of conventional warming devices such as the Flotem IIe, Astotherm (Fig. 4), and others (Fig. 5), these devices are no longer in use at the author's institution and have been replaced with the Level 1 H250 and H1000 for rapid infusion (>100 ml/min or 6 L/hr) and the Hotline device for all other situations.

Figure 2a and b.

Level 1 H1000 warmer. The device consists of a cylindrical aluminum heat exchanger mounted on the warming unit and heated by a countercurrent water bath, similar to the Level 1 250. After the fluid exits this first heat exchanger, it enters a 254-cm patient line in which heat loss is prevented by surrounding the central lumen with warmed water circulating in a countercurrent direction, similar to the Hotline device.

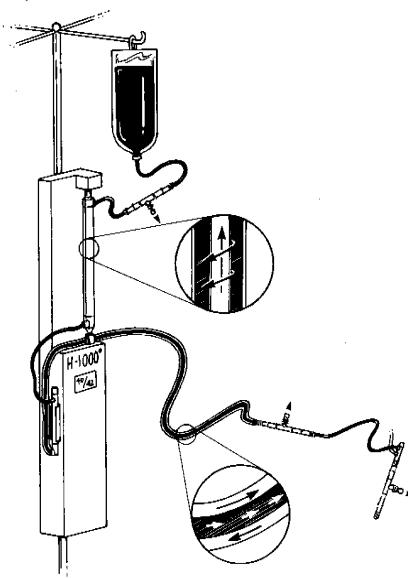


Figure 4.

Schematic of the Astotherm warmer. This device consists of IV tubing coiled around a circular heating element (dry heat technology).

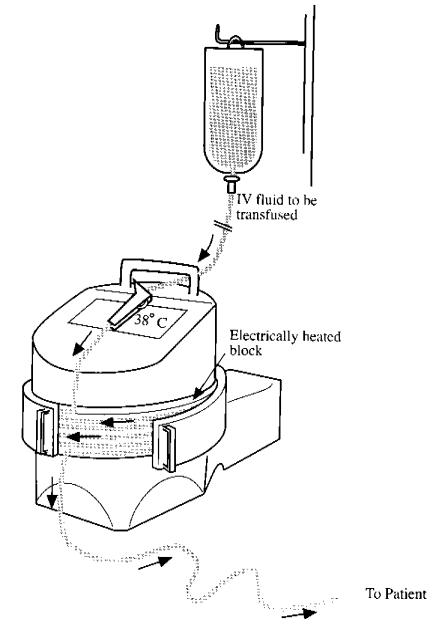


Figure 3a and b.

Hotline warmer. This device consists of a water bath and an L-70 disposable. The L-70 disposable heats fluid within the 254-cm patient line, which consists of a central lumen for the IV fluid surrounded by an outer layer through which warm water circulates down one side and then back up to the warm water reservoir in a countercurrent fashion (countercurrent heat exchange technology).

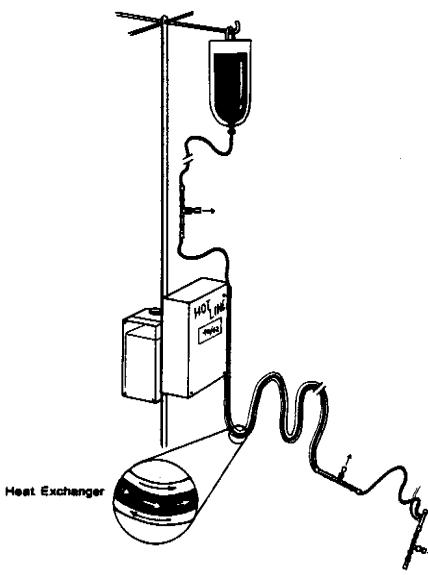
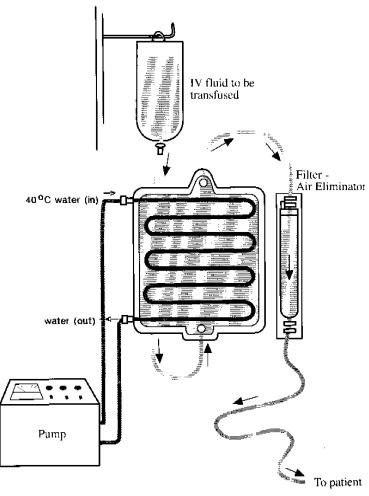


Figure 5.

Schematic of the modified cardioplegia heat exchange warmer. The device consists of a water bath that circulates water through a stainless steel cardioplegia heat exchanger in a countercurrent fashion. This device is no longer used at the author's institution because of delays in setup and de-airing and high disposable costs.



Safety of Rapid Infusion Devices with Constant Pressure

Because of the high flow rates generated by newer warmers when used with constant-pressure devices, the limiting factor in fluid resuscitation is the time required to identify red cell donor and recipient information, to spike and hang the fluid, and to ensure absence of air from the fluid system. In the

author's experience, it is wise to have one individual solely responsible for pressurized infusion of fluids. This individual must utilize extreme vigilance and caution because of the danger of infusing air at these high flow rates. This author is aware of four cases of massive air embolus at other institutions following use of pressurized infusions. Therefore, it is the author's belief that constant pressurized infu-

sion devices not be used unless the patient is in profound hemorrhagic shock, and all air has been removed from the fluid to be infused rapidly. The automatic air eliminator incorporated into the design of the Haemonetic RIS and Level 1 devices make these units somewhat safer, but does not eliminate the risks of massive air embolus.

Summary

Adverse consequences of perioperative hypothermia include myocardial ischemia, cardiac arrhythmias, coagulopathy, shivering, increased oxygen consumption, alteration in drug metabolism and increased wound infection. Administration of cold or inadequately warmed intravenous fluids contributes to hypothermia, whereas administration of normothermic fluids may reduce both the incidence and complications of hypothermia. Therefore, infusion of adequately warmed fluids is important in order to minimize thermal stress and maintain thermal homeostasis.

Acknowledgement

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12 Management of Massive Hemorrhage and Transfusion in Trauma

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Trauma is the most common cause of death in Americans under the age of 45.¹ In the United States, deaths from unintentional injuries are most often the result of motor vehicle crashes, falls, poisoning, fires, or drowning. Although the number of deaths from motor vehicle crashes has decreased over the past few years, there has been an alarming increase in firearm-related deaths. If this trend continues, deaths from firearms are likely to exceed those from motor vehicle crashes by the year 2003.¹

Trauma anesthesiologists are faced today with sicker patients than in the past because of

improvements in emergency prehospital care, initial resuscitation of trauma victims in emergency departments, and rapid transport to operating rooms. It is not uncommon to care for patients with blunt injuries to the great vessels, penetrating injuries to the heart, severe blunt injuries to the liver, severe open-book pelvic fractures, and penetrating injuries to the trunk and to then see these patients leave the hospital to lead constructive, functional lives.

Hypotension and hypovolemia are generally regarded as detrimental to the brain and other organs and are associated with worse outcome, particularly in association with severe head injury. In recent reports, there is speculation that hypovolemia and associated hypotension are beneficial in some circum-

stances when hemorrhage is uncontrolled.^{2,3} The most frequently stated example is a lacerated major artery, when the administration of fluid and associated increase in blood pressure might dislodge a clot from the area of injury, increase the hemorrhage, and turn stable hypotension into lethal recurrent hemorrhage. The evidence for the occurrence of these theoretic effects from fluid resuscitation is stronger for penetrating trauma than for blunt trauma, which is more common in patients with head injuries. Currently there is general support for fluid administration as a mainstay of initial resuscitation after blunt trauma. The initial hemodynamic stabilization is still intravenous access, correction of hypovolemia, and hemorrhage identification and control.

This review focuses on the management of exsanguinating hemorrhage and massive transfusion from blunt or penetrating trauma after the patient's arrival in the operating room.

Definition

Resuscitation of the severely injured patient with fluids and blood products for hemorrhagic shock is often associated with complex metabolic alterations. Several definitions for massive blood transfusions have been proposed.^{4,5} These range from the replacement of the patient's whole blood volume in 24 hours to replacement of 50% of the volume in 3 hours.

When reviewing the physiologic consequences of massive transfusion, knowledge of these different definitions would seem essential, as they are quite different. Another definition that we would like to submit is the concept of *massive massive transfusion*, which we define as the replacement of a patient's estimated blood volume in less than 30 or 60 minutes. Certainly, the metabolic abnormalities associated with blood replacement and resuscitation in this type of patient should be anticipated to be worse than for patients who get 20 units of packed red blood cells (PRBCs) in 24 hours.

Initial Evaluation

After initial evaluation and resuscitation, the trauma victim requiring surgery should be monitored during transport and be accompanied by members of the trauma team. The basic monitoring devices for transport include an electrocardiogram, automated blood pressure device, and pulse oximeter. End-tidal CO₂ monitoring should be considered if the patient is intubated. Ideally, the trauma team leader should transfer care directly to the anesthesiologist involved in the case. Information accompanying the transfer should include mechanism of injury, injuries that have been identified, results and omissions of investigations, medical history, and allergies. Giving this advance notice to the team in the operating room before the actual arrival of the patient will avoid delays and keep the focus on continuity and quality of care.⁶

After the arrival of an exsanguinating patient in the operating room, the anesthesiologist will have to modify his or her evaluation

and induction techniques to set new priorities and techniques for the resuscitation. This modification is the *crash emergency anesthesia technique*. It is in fact a combination of the ATLS™ initial evaluation⁷ and the regular anesthesia induction set-up. The first priorities will be evaluating and managing the airway, oxygenation, ventilation, followed by measuring the blood pressure; sorting out the intravenous lines already in place; finding access for drug injection; attaching an ECG; infusing fluids through blood warmers; getting blood in the room; checking the patient identity and history of allergy; placing an arterial catheter; drawing blood for blood gases, hematocrit, and other lab tests; titrating an anesthetic, if possible; checking temperature and urine output; inserting a central venous or pulmonary artery catheter or the TEE probe for monitoring needs; and finally inserting a gastric tube.

The route for fluid administration in trauma is a source of controversy. There is general consensus that the first choice for cannulation is a vein that is visible, which most often means a peripheral vein on the upper extremities. Two large-bore peripheral intravenous catheters (16 gauge or larger) should be placed as quickly as possible for the administration of fluids and blood. Using 14- or 16-gauge 2-inch peripheral catheters should allow a flow rate of 300 ml/min of crystalloid or 150 ml/min of blood when used in combination with a pressure bag.⁸ In areas with well-developed emergency medical systems, most trauma victims arrive at the hospital with these intravenous catheters already in place.⁹

If peripheral intravenous access was unsuccessful in the field or in the resuscitation room or if hypotension persists, additional sites should be considered to ensure immediate intravenous access. Some authors suggest, as a second choice, the cannulation of the external jugular vein; as third choice, the use of the femoral vein; and as last choices, venous cutdown and catheterization through the internal jugular or subclavian veins.⁹

If the patient does not have adequate intravenous access, spinal precautions are still

being applied (cervical collar, backboard, triple fixation of the cervical spine), and unstable vital signs are present, several problems can be anticipated. Moving the head and neck or opening the cervical collar would be necessary to perform easy and timely cannulation of either the external or the internal jugular vein. Removing some of the spinal precautions before clinical or radiologic clearance would not be ideal and waiting for the radiologic evaluation would be impractical. In these circumstances, the femoral vein could be an excellent second choice for venous access because of its large size and easy access. However, a major concern with the use of the femoral vein as the "main IV" in the acute phase of resuscitation is the possibility of vascular injuries from the original trauma in the pelvic and/or the abdominal region, especially in patients with penetrating trauma to the abdomen and in patients who have sustained major pelvic fractures, in whom associated vascular injuries are frequent. Relying mainly on femoral access in this situation might lead to loss of resuscitation fluid into the extravascular space. Use of a venous cutdown in the lower extremities has the same limitation. Although a venous cutdown in the upper extremities would avoid this problem, it is technically more difficult and therefore often more time consuming. When there is inadequate intravenous access in the severely injured patient with suspected intra-abdominal injuries, it is our practice to use the subclavian vein as our second choice for fluid administration⁶ (Table 1). In situations of advanced hypovolemic shock or exsanguination, where percutaneous techniques of IV insertion via peripheral central veins are unsuccessful, venous cutdown at the saphenofemoral junction may be used.¹⁰

The use of an 8.5 or 9.0 French introducer allows a flow rate higher than 500 ml/min with the use of a pressure bag and large-caliber IV tubing.^{8,11} Strict aseptic technique should be used even in emergency situations. As a general rule, all intravenous catheters placed in the prehospital phase and in the resuscitation room should be changed in the first 24 hours after insertion, because they may have been inserted under less-

Table 1. Intravenous Access in the Patient with Multiple Injuries

Option 1 — Peripheral IV x 2 in visible vein of the upper extremities

Option 2 — If unsuccessful, suggested second choice:

- If cervical spine injury is unlikely:
External or internal jugular vein access with large-bore IV catheter
- If abdominal or pelvic injuries are unlikely:
Femoral vein access with large-bore IV catheter
or
Venous cutdown in the lower extremities
- If abdominal or pelvic injuries are suspected:
Subclavian vein with large-bore IV catheter

than-ideal aseptic conditions.⁸ Our practice is to provide the history of all IV lines to the ICU or ward teams, who will then change all central catheters over a guidewire, culture the intracutaneous segments and tip of the catheter with a semiquantitative techniques, and remove the peripheral lines placed during the prehospital and resuscitation phases of care.⁶ These changes should be done only after relative hemodynamic stability has been established and/or additional “clean” intravenous access has been secured.

All intravenous fluids and blood products should be warmed. The H1000 infusion system (Level One Technologies, Inc., Rockland, Massachusetts) is capable of infusing and heating 800 ml/min of crystalloid or 500 ml/min of blood. The Rapid Infusion System (RIS, Haemonetics Corporation, Braintree, Massachusetts) can infuse blood products (red cells, fresh frozen plasma), crystalloids, or colloids at rates up to 1,500 ml/min. This system is extremely useful in the management of exsanguinating hemorrhage. The use of blood warming/high-volume infusion systems in addition to warming the resuscitation room or operating room to temperatures at high as 30°C is essential if hypothermia is to be prevented effectively during resuscitation of the trauma patient.

Metabolic and Hemostatic Effects of Massive Blood Transfusions

Since banked blood undergoes a number of metabolic and structural changes over time, multiple severe derangements of physiology are theoretically possible when large volumes of banked blood are given to critically ill or injured patients. Although the volume of blood transfused may lead to a variety of problems (Table 2), both the depth and duration of shock appear to be more significant determinants of physiologic derangements than the transfusion of blood itself.¹² If the patient receiving massive transfusion receives adequate fluid resuscitation and maintains oxygen delivery and organ perfusion, the sequelae of massive transfusion may be minimized. The volume of blood products that the patient receives should not be the primary determinant of therapeutic decisions or prognosis.^{13–15}

The ability to provide massive transfusion is a relatively recent medical accomplishment resulting from a series of advances (large blood banks, rapid infusers of warm fluids, and better understanding of the physiology of transfusion). The varied definitions of massive transfusion, the numerous associated clinical conditions, and the relative lack of detailed rigorous studies have created controversy in the literature regarding the metabolic effects of massive transfusion. The confusion is compounded by the use of blood of varied storage life, nonuniform resuscitation protocols, and comparison of patients suffering from shock of differing severity and duration.

The storage and refrigeration of pRBCs results in progressive changes that are termed *storage lesions*.¹⁶ The change in deformability

and increased hemolysis is linked to the decreased levels of intracellular ATP. This in turn is linked to the increased levels of potassium, ammonia, and hemoglobin in the supernatant plasma or preservative solution. The change in oxygen affinity of hemoglobin for oxygen is, in large part, a consequence of decreased levels of intracellular 2,3-DPG. The increase in vasoactive substances is a result of their release from leukocytes and platelets contained in the blood or red cell concentrate. Finally, the development of microaggregates is due to the formation of small amounts of fibrin strands during storage and the adherence of senescent platelets and leukocytes to them.

Massive transfusion of blood components containing sodium citrate can lead to transiently decreased levels of ionized calcium. Hypocalcemia can cause hypotension, narrowed pulse pressure, and biventricular dysfunction. Electrocardiographic abnormalities such as prolonged QT interval can occur. Adults who have normal hepatic function, are normothermic, and are not in shock can tolerate the infusion of one unit of PRBCs every 5 minutes (20 units/hr) without developing hypocalcemia.¹⁷

Since stored blood commonly has elevated potassium concentration, up to 30 to 40 mEq/L by 3 weeks of storage, hyperkalemia is possible with massive transfusion. Hyperkalemia may cause elevated peaked T waves on the electrocardiogram. It can significantly alter cardiac function, especially if associated with hypocalcemia. The incidence of intraoperative hyperkalemia increases with infusion rate of PRBCs above 150 ml/min. Hyperkalemia can be treated early with intravenous calcium, insulin, and bicarbonate and with PRBC washing before administration.¹⁸

Although stored PRBCs have an acid pH (about 6.3), alkalosis is the usual result of massive transfusion without shock. Sodium citrate contained in the anticoagulant is converted to sodium bicarbonate in the liver. The alkalosis initially increases the oxygen affinity of hemoglobin, resulting in less oxygen off-loading to the tissues. The clinical significance of this alkalosis is unknown.

Hypothermia may occur with rapid transfusion of large volumes of cold blood components. It remains the most under-recognized and under-treated cause of coagulopathy in trauma patients.¹⁹ It increases the affinity of

hemoglobin for oxygen and impairs clotting function. Low temperature also increases the potential for hypocalcemia because of decreased hepatic metabolism of citrate. Prevention of hypothermia is essential and can be achieved by warming intravenous fluids and blood during administration, warming the operating room to 30°C, and using convective warming blankets in all cases of severe trauma.

As the amount of blood replacement increases, the trauma patient's own blood begins to take on characteristics of bank blood, with low levels of 2,3-DPG and low activities of Factor V and VIII, as well as dilutional thrombocytopenia. When blood is stored at 4°C for 24 to 48 hours, the platelets have only 5% to 10% of normal activity. Following transfusion, these platelets are essentially nonfunctional. The massive transfusion of packed RBCs will rapidly dilute the patient's existing platelet pool. The decrease is often less than expected on the basis of simple dilution because of some release of platelets from the spleen and bone marrow. Prompt platelet administration should be considered once abnormal bleeding is noted. In the patient who has microvascular bleeding without hypothermia, a platelet count below 50,000/ μ l or a falling count below 100,000/ μ l indicates the need for platelet transfusion. Indications for fresh frozen plasma (FFP) and cryoprecipitate are not clear. In trauma patients who receive between one and two blood volume replacement, dilutional thrombocytopenia and fibrinogen levels below 75 mg/dL often occur.²⁰ Low levels of coagulation Factors V and VIII are usually a clinical problem after two blood volume replacement. Fibrinogen can be replaced with FFP or cryoprecipitate. In trauma patients, low coagulation factors are usually replaced with FFP.

In addition to the metabolic changes observed with massive transfusion, infectious and immunologic effects can complicate the care of trauma patients. Viral hepatitis remains the major infectious risk of transfusion. With better donor blood screening in the United States, the estimated risks (per unit of blood transfused) of transmission of viral infection are as follows²¹: HIV, 1:493,000; hepatitis B, 1:63,000; hepatitis C, 1:103,000; and HTLV, 1:641,000. (See Chapters 8 and 9.) Transfusion has the potential to modify the recipients' immune response. This is a potentially serious problem in many survivors of massive transfusion, who generally develop immune compromise and are at high risk for sepsis and multiple organ failure.

Management of Massive Transfusion

One thing is clear: the goal of hemorrhagic shock resuscitation is prompt restoration of adequate perfusion and oxygen transport. The objective of resuscitation is to reestablish oxidative metabolism by providing adequate oxygen flow to cells, preventing reperfusion damage, and avoiding blood loss.

Patients in hemorrhagic shock develop low pH from the buildup of intracellular hy-

Table 2.
Metabolic and Hemostatic Effects
of Massive Blood Transfusions

Decreased oxygen dissociation
Hypocalcemia
Hyperkalemia
Derangement of acid-base balance
Hypothermia (<35°C)
Dilutional coagulopathy (platelets, coagulation factors)

drogen ions, which occurs during the anaerobic conversion of glucose to lactate. Some of the intracellular lactate and associated hydrogen ions eventually leave the cell and produce the characteristic metabolic acidosis of hemorrhagic shock. The pH, lactate level, and base deficit are highly correlated with mortality and are thought to be an underlying cause of decreased cardiac contractility and eventual mortality. However, the clinical hemodynamic consequences of low serum pH are unclear. Many clinicians give bicarbonate to increase cardiac contractility. There is some evidence that contractility does not decrease substantially until the pH is 6.9 or 6.8, unless adequate oxygen is not available.²² The most significant determinants of depressed cardiac contractility in shock appear to be hypercarbia and hypoxia.^{23,24} Clinically, if perfusion has been restored, oxygen delivery is adequate, and the patient is well ventilated, pH correction with exogenous bicarbonate is unnecessary.

Conventional fluid warmers, such as those in which fluid (crystalloid, colloid, or blood) is passed within plastic tubing through heating blocks or those in which the tubing is submerged in warm water, are inefficient in delivering normothermic fluids at fast flow rates (≥ 250 ml/min). With aggressive fluid resuscitation and blood transfusions, clinicians are confronted with five distinct problems: hypovolemia, hypothermia, coagulopathy, hyperkalemia, and hypocalcemia. Fluid warmers are designed to prevent and treat some of these problems. The H1000 infusion system (Sims Level One Technologies, Inc., Rockland, Massachusetts) is a very effective fluid-warming device. It consists of a cylindric aluminum heat exchanger mounted on the warming unit and heated by a countercurrent water bath with a set point of 42°C. To decrease heat loss even more, a second device can be added—the Hotline warmer (Sims Level One Technologies)—on the 25.4-cm line between the H1000 and the patient. The central lumen of the intravenous line is warmed by water circulating in a countercurrent direction. The countercurrent circulation water is warmed by a heated reservoir, with a set point of 42°C.

Countercurrent water fluid warmers using 42°C set points do not damage red cells, deliver warm intravenous fluids, and allow the clinician to maintain thermal neutrality with respect to fluid management up to 400 ml/min. With flow rates above that, the infusion fluid temperature will decrease slightly in proportion to the increase in flow rate.

The H1000 infusion system is very useful for resuscitation of trauma victims, as it delivers warm fluid at rapid rates. It takes care of hypovolemia and prevention of hypothermia very well. Unfortunately, it is difficult to deliver more than 800 ml/min with this infusion system. To achieve infusion rates above this level, our practice is to use the Rapid Infusion System (RIS, Haemonetics). This device is capable of delivering 1,500 ml/min of blood

products at normothermia. At our institution, the system is primed with a crystalloid solution and blood products are added to the 3-liter reservoir as indicated during the resuscitation. Platelets are not infused with the RIS device. They are infused through a separate intravenous access. The usual ratio of blood products used with the RIS follows the University of Pittsburgh protocol, with 2 units of packed red cells (600 ml), 2 units of FFP (400 ml), and 500 ml of a colloid or crystalloid solution. The hematocrit of this solution is 28%. All blood is filtered through a 150-micron filter as it is introduced into the reservoir. It then passes through a 40-micron filter. The heat exchanger system also uses countercurrent technology. The fluid is infused with the aid of a roller pump from a minimal rate of 10 ml/hr to a maximum of 1,500 ml/min. To our knowledge, at present, no other infusing system can deliver normothermic units at this rate.

The use of the RIS has introduced new problems during resuscitation of trauma victims. Although coagulopathies, hyperkalemia, and hypocalcemia have been well described in the literature as rare phenomena, we have noticed a high incidence of them after massive transfusions. As discussed previously, coagulopathies and hypocalcemia are well known problems associated with rapid and massive transfusions. Hyperkalemia is a relatively new phenomenon. Its incidence is high when using flow rates of 500 to 1,000 ml/min. As described by Jameson et al,¹⁸ for prevention of transfusion-associated hyperkalemia, our practice is to use the Haemonetics Cellsaver blood salvage system in combination with the RIS. The Cellsaver system is used not only to recycle blood from the surgical field but also, and more importantly, to wash the blood bank PRBCs before transfusion to the trauma victim. Washing the PRBCs decreases the H⁺ and K⁺ concentrations of the blood transfused and, in our experience, decreases the incidence of severe transfusion-associated hyperkalemia.

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13 Rapid Infusion and Point-of-Care Chemistry Testing in Massive Transfusion: Avoiding Common Pitfalls

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For multiple trauma patients with massive hemorrhage presenting for surgery, preoperative efforts have been directed at stabilizing (or at least temporizing) hemodynamic status. Obtaining adequate intravenous access and infusing crystalloid and packed red blood cells are important measures in supporting circulating blood volume. However, anesthesiologists are still faced with precarious situations in which either all the above has taken place in the face of ongoing hemorrhage, or some stabilization has occurred but surgical management will, of necessity, entail increased blood loss. In either case, the clinical sequelae of hemorrhage and shock (such as acidosis, hypothermia, and coagulopathy) will begin to present at this point, problems that become all the more difficult if not managed early and effectively.

In this section, we will discuss our experience in the clinical management of patients' problems regarding massive transfusion. This discussion is not intended to represent a definitive management protocol, since much debate continues about such topics as appropriate resuscitation strategies, desired clinical end-points, and proper use of blood products. Rather, it is a "walk through" of the questions, trials, and decision-making processes that have led us to our current use of the Rapid Infusion System (RIS) (Haemonetics Corporation, Braintree, Massachusetts) in conjunction with point-of-care chemistry-testing devices in managing these difficult problems.

When our trauma center opened in 1983, we were using standard pressure bags connected to a pneumatic pump with six outlets and infusing fluids through a separate blood warmer. Although this approach was adequate for several years, we were constantly struggling with problems of acidosis, hypothermia, and coagulopathy in the face of ongoing and, occasionally, exsanguinating hemorrhage. Therefore, we began looking for ways to improve our ability to keep up with massive hemorrhage.

We initially considered the fluid-warming pressure infusers manufactured by Level I (Level I Technologies, Rockland, Massachusetts). This system consisted of two pressure infusers connected to a blood warmer we had already been using. The advantages of this system were ease of use and portability. However, only two pressurized bags could be connected to this system at any one time. Infusion rates were comparable to or slightly faster than the pneumatic pumps used previously (approximately 500 cc/min).

The only commercially available system

specifically developed for volume infusion >500 cc/min is the RIS. This device utilizes roller pumps that propel fluids from a 3-liter reservoir through two limbs of high-capacity tubing at rates of up to 1,500 cc/min. The system also delivers 100-cc or 500-cc boluses over 1 minute. Additionally, there are three air detectors, which automatically stop the infusion in the event of bubbles in the infusion path. While some planning and a brief set-up period of 3 to 5 minutes are required, it was readily apparent that significantly greater volumes of fluid could be infused in a short time. However, this device is relative large and expensive, and it requires maintenance of an adequate supply of disposable tubing/reservoir set-ups.

We currently employ both of these systems, the Level I System 1000 being the more widespread of the two, with units in each operating room (OR), shock trauma admitting, and the intensive care unit. The combination of the two systems has proven very useful, the Level I being used perioperatively, with the option of large-volume infusions with the RIS if need for massive transfusion arises in the operating room.

Questions arose when we began using the RIS routinely in the OR. We found we had altered the dynamics of blood administration in our trauma OR, in that we were no longer the "rate-limiting step." The blood bank raised concerns regarding appropriate use of blood products and maintenance of an adequate supply of these valuable resources. Additionally, some of our surgical colleagues expressed concern about striving for normotension with aggressive fluid administration and the effects this may have on hemostasis. These issues were a direct result of our dramatically increased ability to infuse large volumes.

Other questions arose regarding some of the problems well known to be associated with massive transfusion,¹⁻⁵ which are discussed elsewhere in this monograph. We noted clinically significant hyperkalemia on at least one occasion. Such related complications previously thought to be infrequent were now more likely to be encountered as infusion capability increased.¹

As we worked through these issues, Hambly and Dutton concluded that using the RIS was associated with increased mortality. They also asked the question (raised by others⁷⁻¹¹) whether hypotensive resuscitation may be advantageous in this setting. This followed the article by Dunham and associates,¹² which showed a positive outcome associated with fluid administration through the RIS. These considerations led to a reassessment of our use of the RIS.

Despite the problems we encountered, we felt there were distinct advantages in using the RIS. The primary, overriding advantage is the

dramatically improved ability to maintain circulating blood volume. The ease and efficiency with which these volumes are administered allows the anesthesia team to devote more mental and physical energy toward other critical aspects of the case in progress. Further, with the RIS there is much greater flexibility in the rates of infusion. If one accepts the notion that hypotensive resuscitation is desirable, this would appear to be all the more reason to use the RIS in such a scenario. In addition, the ability of the RIS to arrest and reverse hypothermia to the point of warming a cold patient to normothermia is significant and cannot be ignored.

Thus, it was evident that the RIS possesses several undeniably desirable characteristics. Indeed, when one considers the five major problems encountered during massive transfusion (hypovolemia, hypothermia, coagulopathy, hyperkalemia, and hypocalcemia), our experience has been that the RIS addresses hypovolemia and hypothermia effectively which, in turn, has beneficial effects in dealing with acidosis and coagulopathy.² However, we concluded the increased risks of significant hyperkalemia and hypocalcemia needed to be addressed separately.

Since there is greater risk of physiologic derangement in this setting, we felt a need for closer monitoring of physiologic parameters by laboratory tests. To obtain turnaround times faster than the hospital laboratory could provide, we considered point-of-care testing devices. Point-of-care testing has gained favor in recent years, one example being glucometers developed for home use, which enable diabetics to monitor their glucose levels. Newer technologies have expanded this concept into other areas involving a variety of laboratory parameters relevant to intensive care and surgical settings.

After discussion with our laboratory director, we chose the i-STAT Portable Clinical Analyzer (i-STAT Corp, Princeton, New Jersey). This device is hand-held and battery powered and comes with a portable printer. It is easy to use and relatively inexpensive and provides reliable accurate results in 2 minutes. The system employs a "thin film" biosensor housed in a small cartridge. Two to three drops of blood are placed into the cartridge, which is inserted into the analyzer. The lab values obtained depend on the particular cartridge used. There are several types available. The cartridge we use measures sodium, potassium, ionized calcium, arterial blood gases, hematocrit, and hemoglobin. There were early concerns about the biosensor technology regarding manufacturing and failure rate. We have had no problems in these areas. However, the i-STAT does not provide point-of-care testing for coagulation studies, so we continue to send these to our trauma laboratory.

In addition to federally mandated quality assurance guidelines, there are a number of point-of-care testing guidelines, which vary from state to state. Federal guidelines were set forth in the Clinical Laboratory Improvement Act of 1967 and amended in 1988. The current rules and regulations are referred to as the CLIA '88 (Clinical Laboratory Improvement Amendments of 1988). They divide laboratory tests into three categories: 1) waived (no special qualifications to run tests); 2) moderately complex (requires high school diploma); and 3) highly complex (requires an associate degree in laboratory science). The federal government may inspect, fine, and even close facilities found not to be in compliance.¹³ An institution that performs laboratory tests is responsible for compliance regardless of where within the facility that testing is done. In addition, four states (California, Florida, New York, and Tennessee) require that anyone not a certified medical technologist (including MDs and CRNAs) must be granted a waiver in order to run lab tests. Thus, in order to avoid these types of problems, we recommend consulting the lab director of your institution if one of these devices is being considered.

Another option available in avoiding complications of massive transfusion is washing red blood cells (RBCs) prior to infusion. Storage of packed red blood cells (PRBCs) results in accumulation of potassium over time.¹⁴ Washing RBCs prior to administration removes much of this potassium as well as a significant proportion of existing citrate, which, in some cases, can result in hypocalcemia and cardiovascular depression.¹⁵ The removal of these agents can preempt some of the problems associated with massive transfusion. This option has been employed successfully in a variety of clinical settings.^{1,16,17} We do not perform this routinely, except when treating patients with a history of renal insufficiency.

In using the RIS in conjunction with the i-STAT, we employ the following strategy when massively transfusing a patient:

- * When the decision is made to use the RIS, we notify the blood bank than an RIS case is starting. The blood bank then sets up what are termed "RIS units" consisting of 10 units PRBCs, 4 units FFP, and 4 units of platelets (not to be infused through the RIS). The blood bank continues to hold one of these units until informed by us that we are no longer in a massive transfusion mode.
- * Baseline labs are drawn, consisting of arterial blood gasses, complete blood count, PT/PTT, fibrinogen, potassium, and ionized calcium.
- * In filling the pump reservoir, PRBCs are diluted with 500 cc normal saline per unit.

- * We aim for a hematocrit in the low to mid-20s.
- * FFP are infused through the RIS in addition to the NS.
- * Platelets are infused separately.
- * With each five units of packed cells given in 15 minutes or less, 1 gram of CaCl₂ is given.
- * Labs are repeated after each 10 units PRBCs.
- * Hyperkalemia (>6.0) is treated with 10 units regular insulin with D5W.
- * Acidosis is treated with volume infusion and sodium bicarbonate as deemed appropriate.
- * Cryoprecipitate is given based on fibrinogen levels.
- * We continue to strive to maintain a relatively normotensive state in this setting. Communication with the surgical team, monitoring of urine output, and consideration of cerebral perfusion help guide decisions regarding target pressures.

As to the controversies concerning hypotensive resuscitation, use of the RIS in this scenario, and possible increased mortality associated with its use, close examination of the pertinent literature led us to the following analysis.

The conclusions reached in the study by Hambly and Dutton are clouded by two problems. First, selection bias may have played a significant role, as noted by the authors. Second, their findings are predicated on a comparison of expected versus observed mortality between the study groups. They defined expected mortality in this population based on a logistic regression equation published by Dunham et al from their institution in 1986.¹⁸ This equation was written as a statistical descriptor of observed events at that institution, not as a predictor of mortality. They state, "To ensure validity of the equation used to determine the probability of death, a prospective assessment needs to be performed on another population." A search of the literature and conversations with the author have not revealed such a study. Therefore, the applicability of this equation in predicting mortality in this population must be questioned. Such an equation or similar predictive tool remains elusive.

Regarding the question of hypotensive resuscitation, it should be noted that the study by Bickell et al deals with penetrating trauma, whereas Hambly and Dutton raise this issue in their study on blunt trauma patients. Further, Bickell found increased survival with minimal resuscitation prior to, not in, the operating room, and full resuscitation once surgical con-

trol of blood loss was obtained. This would not appear to be applicable to intraoperative use of the RIS as studied by Hambly and Dutton, since their patients were, presumably, resuscitated in the usual fashion prior to and after arrival at the Shock Trauma Center. Before conclusions can be drawn regarding the appropriateness and timing of use of the RIS, more uniformity between Bickell's and Dutton's patients would have to be demonstrated.

Unanswered questions remain, along with the need for further controlled, well-focused studies. Whatever strategy is employed during fluid resuscitation of the trauma patient and massive transfusion, it is important to remember to treat each patient individually, globally, and according to clinical judgment rather than by strict protocol. Use of the RIS together with point-of-care testing and improved communication with blood bank personnel, laboratory personnel, and surgeons improves our ability to manage trauma patients requiring massive transfusion.

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SECTION IV: New Horizons in Synthetic Blood Substitutes

14 Hemoglobin-Based Oxygen-Carrying Solutions & Hemorrhagic Shock

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There has been only one reported use, in 1949, of a hemoglobin solution for resuscitation of a human in hemorrhagic shock.¹ A woman suffering from postpartum hemorrhage was given 2.3 liters of 9% hemoglobin solution in saline after all available compatible blood had been given. Consciousness returned, her blood pressure rose, and her heart rate fell. However, the patient died 9 days later from renal failure.

Attempts to develop blood substitutes go back many hundreds of years² (Table 1). In 1916, hemoglobin solutions were given in small quantities to 33 subjects to determine the renal threshold for hemoglobin without adverse effects. Many studies, however, using larger quantities of hemoglobin solutions, had adverse effects, including hypertension, bradycardia, oliguria, and anaphylaxis.³ In 1957, Chang encapsulated hemoglobin,² and since then development of liposome-encapsulated hemoglobin has continued. The problems associated with disposal of the encapsulated

hemoglobin and stimulation of the reticuloendothelial system and macrophages have not been resolved. Leland Clark demonstrated that a mouse could survive while breathing liquid perfluorocarbons saturated with oxygen.⁵ In 1972, Benesch discovered reagents that could bind the 2,3-DPG binding site so that they could reduce hemoglobin affinity for oxygen. The most widely used agent is pyridoxal, 5 PO₄ (so-called pyridoxalation), which is used to reduce oxygen affinity.⁶ The normal P5O (the partial pressure of oxygen when Hb is 50% saturated) of blood is 26.7 mmHg. P5O is increased by pyridoxalation. Human stroma-free hemoglobin has a P5O of 12 to 15 mmHg and therefore has a high oxygen affinity and tends to hold onto the oxygen rather than give oxygen up at the tissue level.

General Properties

Red cells can be stored in liquid form with citrate phosphate dextrose adenine (CPDA) anticoagulant for 35 days and in AS-1 for 42 days. They can also be frozen after addition of glycerol to prevent lysis or they can be instantly freeze-dried or lyophilized. Oxygen-carrying solutions (Table 2) may consist of free hemoglobin from which the stroma or cell wall has been removed, or liposome-encapsulated hemoglobin containing hemoglobin with a synthetic membrane. Perfluorocarbons are organic solutions with high oxygen solubility.

Toxicities of free hemoglobin solutions

Table 2.
 Currently Available Products That Can Be Used As Oxygen-Carrying Solutions in Humans

Whole blood
Liquid red cells
Frozen red cells
Lyophilized red cells
Free hemoglobin
Encapsulated hemoglobin
Perfluorocarbons

(Table 3) include vasoactivity, with binding of nitric oxide by free hemoglobin being the main suspect causing vasoconstriction.⁷ Nephrotoxicity from stromal remnants is probably of only historical interest, because better purification techniques have resulted in lack of renal toxicity with newer hemoglobin-based oxygen carriers.⁸ In human volunteers given recombi-

Table 3.
 Toxicities and Interferences of Hemoglobin-Based Oxygen-Carrying Solutions

Vaso-activity
Interference with mononuclear phagocyte system
Antigenicity
Oxidation to methemoglobin
Activation of complement, kinin, and coagulation
Thrombocytopenia
Red cell and platelet aggregation
Histamine release
Fever, chills, gastrointestinal upset, headache, backache
Iron deposition
Binding nitric oxide
Colorimetric interference, pulse and fiberoptic oximetry
Interference with liver function, blood compatibility, and chemical testing

Table 1. History of Transfusion and Oxygen-Carrying Solution Use

1667	First human blood transfusion (Denis), causing death and moratorium
1863	Gum-saline transfusion (Ludwig)
1916	Hemoglobin infusion in humans (Sellards and Minot)
1941–45	Albumin and hemoglobin infusion
1957	Encapsulated hemoglobin described (Chang)
1966	Perfluorocarbon "bloodless mouse" (Clark and Gollman)
1969	Amberson's report of hemoglobin infusion in human hemorrhagic shock
1972	Pyridoxalation to reduce hemoglobin affinity (Benesch et al)
1978	Human safety trial, unmodified hemoglobin (Santsky et al)
1980–97	Human trials with human and bovine hemoglobin-based solutions
	Human trials with second-generation perfluorocarbons

nant hemoglobin, 0.23 g/kg, there was no evidence of nephrotoxicity. Immunologic effects of hemoglobin-based oxygen-carrying solutions remain somewhat of an unknown. In fact, the immunologic effects of blood transfusion have been extensively explored only recently. Interferences occur with free hemoglobin solutions (Table 3). Use of hemoglobin-based oxygen-carrying solutions interferes with fiberoptic oximetry because of the red color.⁹ Mixed venous oxygen saturation is overestimated at low levels of 60% to 70%—a dangerous situation that may cause patients to be underresuscitated. The interference is nonlinear, as it overestimates oxygen saturation at high venous oxygen tension. Pulse oximetry interference occurs because of methemoglobin.¹⁰ Hemoglobin-based oxygen-carrying solutions make it impossible to carry out some liver function tests such as alkaline phosphate measurement¹¹ and coagulation tests such as partial thromboplastin time.¹² They can also interfere with cross-matching, but this can be overcome with dilution.

Methods to Prevent Complications of Oxygen-Carrying Solutions

For many reasons, including avoidance of human disease transmission, sources other than outdated human blood have been used to produce hemoglobin solutions. Transgenic pigs and mice have been bred to produce human hemoglobin, and recombinant hemoglobins can be produced from bacteria and yeast by modifications that incorporate globin genes. For example, it is possible to express both human a and b globin chains in *Escherichia coli*; however, the yields are still very low. About 750 liters of cell culture would be needed to produce 1 unit of blood. Endotoxin contamination may also occur.²

Sources of hemoglobin other than human include bovine hemoglobin. In addition, any of these hemoglobins can be modified to optimize their characteristics such as retention time; oxygen affinity, reduction of dimer conversion into tetramers, and prevention of oxidation to methemoglobin. Bovine hemoglobin has a high P50 without modification and is therefore of interest since it is also in plentiful supply.¹³

Because of osmotic effects, most hemoglobin-based oxygen-carrying solutions are in concentrations no greater than 7 to 8 g/dL. Perfluorocarbons have a linear oxygen dissociation curve, and a relatively high oxygen content of 50% or more is required for them to carry equivalent amounts of oxygen to hemoglobin. The second-generation perfluorocarbons (Perflubron) have more efficient oxygen carriage, even breathing 50% oxygen, whereas the first-generation (Fluosol) required 100% oxygen breathing to achieve even one-fourth the oxygen carriage of blood.²

Hemoglobin may be modified by polymerization¹⁴ (Table 4). Polymerized hemoglobin is produced by addition of reactive groups to the surface of hemoglobin. These reactive groups

prolong intravascular retention time but also make the hemoglobin more rigid. The polymerization reaction is very difficult to control, so there is some batch-to-batch variability. An alternative to polymerization is conjugation to a larger molecule, and this also prolongs retention time. Some solutions can be polymerized and conjugated. Intravascular retention time can be prolonged from 7 hours in the unmodified form to about 36 hours after modification.

The hemoglobin can be incorporated into an artificial cell, and liposome encapsulation is currently under study. However, the liposomes cause substantial drops in platelet counts, and during excretion, they block the reticuloendothelial system.⁴ A hemoglobin solution that has been studied in hemorrhagic shock is a pyridoxalated hemoglobin polyoxyethylene conjugate made from stroma-free hemoglobin by conjugation with polyoxethylene to increase its half-life from 7 to 36 hours and by pyridoxalation to increase P50 from 15 to 20 mmHg. Maltose is added to prevent oxidation to methemoglobin.¹⁵

The stimulus for all recent activity in development of hemoglobin-based oxygen-carrying solutions is reduction of disease transmission, particularly of human immunodeficiency virus (HIV) and hepatitis virus. From the perspective of the manufacturers of oxygen-carrying solutions, there is much interest because it is estimated to be a potential \$12 billion a year industry. Their use in hemorrhagic shock is important because huge quantities of blood are currently used for this. In 1993, at the Shock Trauma Center at the University of Maryland, 1,300 patients were given 8,500 units of blood, an average of 6.5 units per patient, or about 50% to 60% of blood volume replacement. The potential for replacing some of this blood use with an alternative is very enticing for the manufacturers of oxygen-carrying solutions and is also of interest to the Red Cross, which goes to great efforts to maintain this vital supply.

Vascular and Other Physiologic Effects of Hemoglobin-Based OxygenSubstitutes

How do we judge whether hemoglobin-based oxygen-carrying solutions are efficacious

Table 4. Characteristics of Some Clinically Used Hemoglobin-Based Oxygen-Carrying Solutions

1. Stroma-free hemoglobin (SFH): simple removal of the cell wall
Human and bovine SFH
2. Modifications include
 - a. Cross-links
(alpha-alpha and beta-beta)
 - b. Polymerization
 - c. Configuration
 - d. Encapsulation

in hemorrhagic shock? The objectives of successful resuscitation from hemorrhagic shock include 1) restoration of intravascular pressures, 2) increase in cardiac output, and 3) reversal of the increased oxygen extraction that occurs in hemorrhagic shock. When studies using red cell substitutes to achieve the first two of these objectives are examined, difficulties in interpretation occur. The protocol and animal model can influence the judgment of efficacy. In one study in which a hemoglobin solution was tested, the protocol specified that fluid resuscitation should be given to restore cardiac filling pressures to baseline values.¹⁶ If a vasoconstrictor response occurred with infusion of the hemoglobin-based oxygen-carrying solution, it would appear very efficacious at restoring vascular pressures. In addition, the evidence for a vasoconstrictor response would be minimized. Furthermore, if an awake dehydrated pig model had been used instead of a dog, as other studies have shown, the animal may have died as a result of the hemoglobin-based oxygen-carrying solution causing profound vasoconstriction and reduced cardiac output.¹⁷

If cardiac output and arterial blood pressure changes during resuscitation with oxygen-carrying solutions are examined, confounding data are also obtained. In two studies, cardiac output or blood pressure was less with hemoglobin solution infusion than with autologous blood transfusion.^{18,19} In these four studies, cardiac output and arterial pressure changes were no different with hemoglobin solution and blood resuscitation.²⁰⁻²³ Only one study showed that the hemoglobin solution sustained oxygen transport at higher levels than did non-oxygen-carrying solution volume expanders such as albumin or lactated Ringer's solution.¹⁶ Transient cardiac output and blood pressure increases were greater half an hour after resuscitation began with hemoglobin solution resuscitation compared with autologous blood reinfusion in another study.¹⁵ So there are no clear-cut data showing what effects hemoglobin solutions in general have on arterial pressure and cardiac output, nor is there much information showing they are conclusively more beneficial than non-oxygen-carrying volume expanders. In some studies, oxygen transport was significantly impaired compared with whole blood because of a fall in hematocrit,¹⁵ whereas in other studies oxygen transport is no different than with autologous blood resuscitation.²⁰⁻²³

How can oxygen-carrying solutions have added value over blood as a means of delivering oxygen to tissues? There are several potential ways, some of which have been confirmed by experiments in animals. Because oxygen-carrying solutions are acellular, they are less viscous than blood and flow more easily through narrow vessels and the microcirculation. It is therefore possible that oxygen-carrying solutions may be useful in hemorrhagic shock. There is experimental evidence

that hemoglobin-based oxygen-carrying solutions can enhance oxygen diffusion from the vascular to the intracellular space.²⁰ In addition, when compared with whole autologous blood, a hemoglobin-based oxygen carrier preserved exercise capacity in humans. Diffusion of carbon monoxide across the alveolar-capillary membrane (DLCO) and blood lactate levels were measured during exercise in humans.²⁵ There was a greater oxygen uptake and for CO₂ production and normal lactate levels were maintained in those given hemoglobin-based oxygen carriers in comparison with subjects given autologous blood. Infusion of 1 gram of hemoglobin-based oxygen carriers increased DLCO as much as 3 grams of autologous blood.

In addition to the short-term benefits of enhanced diffusion, hemoglobin-based oxygen carriers may have longer lasting effects, as it has been shown that serum iron, ferritin, and erythropoietin increase in parallel with plasma levels of hemoglobin. The iron infusion adds the equivalent of one unit of blood transfusion within 1 week of hemoglobin infusion.²⁵

Newly discovered allosteric and electric properties of hemoglobin appear to control blood pressure and may facilitate tissue oxygenation. S-Nitrous-hemoglobin (SNO-Hb) is free of vasoactivity and may be a route for efficient delivery of nitric oxide to the mitochondria. Nitric oxide controls mitochondrial respiration. Cell-free SNO-Hb may be a good hemoglobin-based oxygen-carrying solution.⁷

Other properties besides oxygen transport affect assessment of efficacy of red cell substitutes. Profound increases in pulmonary pressures can cause fatalities in some animals and prevented any benefit from being realized due to hemoglobin solution infusion.¹⁷ When changes in pulmonary artery pressure are compared after resuscitation from hemorrhagic shock with oxygen-carrying solutions, interspecies differences as well as protocols and models become confounding variables. The rise in pulmonary artery pressure after resuscitation in the swine model greatly exceeds that seen in the dog.¹⁷ In some studies, fluid resuscitation is given with the objective of returning filling pressures to baseline values, so that if a vasoconstrictor response occurred with infusion, the protocol used would prevent this difference from becoming apparent.²⁰ Several investigators have also noted thrombocytopenia after infusion of red cell substitutes, and clearly it is critical that red cell substitutes for use in the management of hemorrhagic shock should not interfere with resident blood cells or the coagulation system, as these toxicities would preclude their use in the management of patients with trauma or those undergoing surgery.

Hemostatic Effects

The effects of free hemoglobin solutions on coagulation and blood cellular components

were examined with resuscitation from severe hemorrhagic shock in dogs.²⁴ The solutions used were 8% pyridoxalated hemoglobin polyoxyethylene conjugate and 8% maltose, known as PHP88, a 4% solution of the same solution made by diluting PHP88 with equal volume of Plasmalyte A (PHP44), and stroma-free hemoglobin (SFH), a simple non-conjugated hemoglobin solution. Both hemoglobin solutions were highly purified and endotoxin free. Use of these three hemoglobin solutions was compared with re-infusion of autologous blood. The volume of blood removed to produce 2 hours of shock was 63% of the estimated blood volume. Resuscitation began with fluids infused at 20 ml/min by infusion pump; in four dogs, no resuscitation was given. Samples for coagulation and hematology profiles and a blood smear were taken one-half hour after resuscitation began, when all the hemoglobin-based oxygen-carrying solutions were infused or, in the case of non-resuscitated dogs, no additional fluids were given. Measurements were repeated at 2, 4, and 6 hours after resuscitation, and then daily for 7 days after awakening from anesthesia.

All dogs not resuscitated died within 2 hours. All autologous blood and PHP44 dogs survived 8 days, while mortality among PHP88 dogs was 63% and among SFH dogs, 14%. Clinical coagulopathy occurred in all dogs given PHP88 and in four of the six dogs given SFH, and there was evidence of hematoma formation around cannulation sites in all six dogs given PHP44 and five of the six dogs given autologous blood when autopsy was performed. Clinical coagulopathy with spontaneous development of oozing from percutaneously placed cannulae, spontaneous development of hematomas in the femoral areas where catheters were placed, and in some dogs receiving both PHP and SFH petechiae were visible subcutaneously all over the body, and submucosally in the mouth. In the dogs that died, exsanguination was the major cause of mortality secondary to thrombocytopenia. Death occurred between 7 and 254 hours after infusion of the hemoglobin solution.

There was a fall in hematocrit (Hct) in all animals resuscitated with these cellular fluids. However, the fall in animals given PHP88 was significantly greater than in those receiving the other solutions, with an average Hct of 3% after resuscitation.¹⁵ Since 63% of the estimated blood volume was removed and because hematocrit was, on average, about 40% before resuscitation, it was expected on the basis of hemodilution alone, that Hct would be about 25%. The finding that Hct was between 9% and 11% with PHP44 and SFH suggests that these hemoglobin solutions also had some adverse effect on red cells. The possibility of hemolysis occurring was explored by hemoglobin electrophoresis of the plasma samples—the PHP and SFH were both derived from human hemoglobin. If hemolysis had occurred, canine hemoglobin would be found in the

plasma. None was identified by hemoglobin electrophoresis (which can clearly distinguish the two types of hemoglobin). In addition, measurements of plasma hemoglobin gave values consistent with the quantities of hemoglobin-based oxygen-carrying solutions infused. Red cell counts show the same picture as Hct. These data strongly suggest that cells were being removed from the circulation. It was postulated that they may be sequestered in circulatory beds as a result of endothelial or other interactions.

Why thrombocytopenia occurred and why there was a reduction in all other cellular components remains the cause of much speculation and investigation. Many factors are known to give rise to platelet adhesiveness and rouleaux formation, including release of thromboxane, and endothelial reactions, including binding of nitric oxide by free hemoglobin; the presence of free heme also induces platelet aggregation. Hemodilution is another important factor causing thrombocytopenia, as this was a severe hemorrhagic shock model in which 63% of the circulating blood volume, and therefore cellular components of the blood, were removed from the circulation. In addition, the high colloid oncotic pressure of these hemoglobin solutions may have further accentuated the circulating volume increase and dilution of cellular components.¹⁵ It was speculated that, as a result of platelet aggregation and rouleaux formation, platelets and red cells are trapped in the microcirculation and this sequestration prevents their subsequent employment in coagulation and oxygen transport. A factor that may additionally or singularly be the cause of the problem is the polyoxyethylene moiety attached to hemoglobin in PHP. It is used to increase molecular size and prolong vascular retention time. However, it may also cause electrostatic charges that increase the likelihood of platelet aggregation and red cell rouleaux formations. Mediators released during hemorrhagic shock are probably an important determinant of the cell aggregation seen with infusion of PHP. No coagulopathy or mortality was found in dogs undergoing exchange transfusions with PHP of 80% of blood volume or in nonvolemic dogs given 20 ml/kg of PHP. Changes that occur during hemorrhagic shock exacerbate the effects of large doses of PHP.

The whole issue is very complex. An obvious possible mechanism of platelet aggregation, namely, binding of nitric oxide by free hemoglobin, has not been excluded. Free heme can cause platelet aggregation, as can thromboxane release secondary to hemorrhagic shock. The coagulopathy that occurred with PHP may be a combination of some or all of these mechanisms.

Conclusion

The studies discussed illustrate some very important facts about the data that are avail-

able on oxygen-carrying solutions. First, there is virtually no published data on use of any of these products in humans for resuscitation from hemorrhage shock. Second, much of the evidence for the oxygen-carrying solutions currently under study in humans undergoing Phase 2 and Phase 3 trials to obtain FDA approval is proprietary. As a result, the data in the literature may not be scientifically valid, as adverse effects may be minimized. Third, there are interspecies variations, so that toxicities or benefit seen with a product in animal studies may not translate into reality in human studies. Fourth, endothelial interactions are still not completely understood and could result in adverse reactions to oxygen-carrying solutions that preclude their use in shock. Fifth, mediators released during reperfusion or conditions that develop in hemorrhagic shock may accentuate the toxicities of hemoglobin-based oxygen-carrying solutions, since administration of similar quantities of one hemoglobin-based oxygen-carrying solution (PHP) to animals not in shock does not result in coagulopathy or mortality. Sixth, minor changes among several potential modifications can significantly alter the toxicities of oxygen-carrying solutions.

What then is the future of hemoglobin and perfluorocarbon-based oxygen-carrying solution? From news through the proprietary grapevine, it appears that an equivalent of a two-unit transfusion of oxygen-carrying solution is well tolerated by the majority of individuals when given in elective surgical circumstances. The side effects are relatively minor, including gastrointestinal upset, musculoskeletal aches, and headache. One worrisome side effect that is rumored has been the development of pancreatitis or signs of pancreatic changes seen in a very few individuals receiving some hemoglobin-based oxygen-carrying solutions. Another worrisome issue was the indefinite postponement of a Phase 3 trial of a hemoglobin-based oxygen solution in patients with trauma and hemorrhagic shock, presumably because of increased mortality in the study group (*Wall Street Journal*, February 6, 1998). The data that led to the action have not been made public to date.

Other potential future uses include management of ischemic disease and angioplasty. The acellular oxygen-carrying fluids have very favorable rheologic properties and enhance mitochondrial oxygenation. In some tumors, radiosensitivity is increased by means of increased oxygen levels. A further potential use of oxygen-carrying solutions is as an adjunct to radiation therapy for certain tumors. In sickle cell crisis, perfusion and oxygenation may be improved with oxygen-carrying solutions and hematopoietic stimulation may be a result of infusion of a hemoglobin-based oxygen-carrying solution. Because of the ability to carry oxygen, these solutions may also be useful for organ preservation, extracorporeal

real organ perfusion, and cardioplegia. Potential future uses also include transfusion alternative in patients with red cell incompatibilities. For Jehovah's Witnesses, perfluorocarbon, but not hemoglobin-based oxygen-carrying solutions, are an acceptable alternative to blood transfusion.

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15 Hemoglobin Therapeutics, Blood Substitutes, and High Volume Blood Loss

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Definitions

Technically, a blood substitute is a substance that can effectively replace most functions of human blood. However, oxygen-carrying modified hemoglobin solutions and perfluorocarbons have been referred to as "blood substitutes." Since these recently developed solutions can only carry out selected functions of blood, they are more accurately referred to as "oxygen-carrying volume expanders."

Hemoglobin-based oxygen carriers (HBOCs) are modified hemoglobin solutions or hemoglobin packaged into liposomes, which are able to deliver oxygen to tissues. A hemoglobin therapeutic is a hemoglobin solution optimized through chemical modification to bring about certain pharmacologic and therapeutic effects. Hemoglobin therapeutics may possess a combination of therapeutically active properties such as oxygen-carrying capacity, favorable rheologic properties, and pressor action.

Need for Blood Substitutes

Although blood transfusions represent a life-saving measure for many medical and surgical patients, there are still problems with homologous blood transfusions in the United

States. Oxygen-carrying volume expanders may be particularly helpful in situations where blood is not available (remote areas; difficult cross match; rare blood type, etc.). Furthermore, a national blood shortage is predicted with the aging of America, since the over-65 age group has a high demand for blood. This age group represents 12.5% of the population but receives 50% of all blood transfusions. The risk of infection from blood has decreased dramatically, but potentially could be eliminated with blood substitutes (although it is recognized that prions and other agents appear to resist sterilization). Allogeneic blood also is associated with a higher surgical infection rate, presumably related to the immunosuppressive effects of white blood cells contained in non-leuko-depleted blood.

Desirable "blood substitutes" have a long shelf life, a long circulation half-life, good oxygen carrying capacity and tissue oxygen delivery, few side effects, and reasonable cost. Furthermore, their use should not interfere with diagnostic tests or the clinical diagnosis of serious disease processes.

Hemoglobin-Based Oxygen Carriers Structure and Design

Free, unmodified human tetrameric hemoglobin rapidly dissociates into dimers and monomers when removed from its normal environment inside the erythrocyte. Dissociation into hemoglobin fragments leads to renal toxicity and greatly increased oxygen affinity, precluding effective tissue oxygen delivery.

Manufacturers of HBOCs therefore have

undertaken a variety of strategies to modify the native hemoglobin molecule in order to stabilize it, extend intravascular residence time, and return its oxygen-unloading properties into the range of erythrocyte-based hemoglobin. One such method is intramolecular cross-linking between alpha and beta chains. Other methods involve polymerization, pyridoxylation, or conjugation to larger molecules, including polyethylene glycol (PEG). Encapsulation of hemoglobin into a liposome or polymer structure has also been pursued. There is a dilemma in the trade-off between desirable properties: Larger hemoglobins and liposomes may have longer half-lives and are less active in scavenging nitric oxide (NO) from the endothelium (which limits their hypertensive properties). Unfortunately, they also undergo accelerated auto-oxidation, hemoglobin peroxidation, and heme loss.¹ On the other hand, smaller species are less antigenic but can be filtered by the kidneys, are more oncotically active, and have shorter vascular residence times.

Such "designer" modifications stabilize the molecule's tetrameric structure and affect molecular size, renal filtration, P50 (defined as the oxygen tension at which hemoglobin oxygen saturation is 50%), affinity to NO binding, circulation half life, and more. The raw material for hemoglobin solutions can be human red blood cells, bovine red blood cells, or recombinant *Escherichia coli* bacteria. To date, no hemoglobin solution has been approved for human use, although several are being investigated for safety and efficacy (Table 1).

Table 1. Hemoglobin Solutions Undergoing Clinical Testing

HBOC	Raw Material	Structure for Stabilization	Size (kD)	T1/2 (hr)	Oncotic Pressure (mmHg)	Viscosity vs. blood	P50* (mmHg)
Hemassist (DCLHb™; Baxter)†	Human RBC	Alpha-alpha cross-linked	64	4-16‡	42	50%	32
Optro (Baxter-Somatogen)	Recombinant <i>E coli</i>	Alpha-alpha cross-linked; Hb Presbyterian mutation	64	12-24	<20	50%	33
Hemopure (HBOC-201; Biopure)	Bovine RBC	Glutaraldehyde-polymerized	>150	8-17§	17	30%	34
Hemosol (Fresenius)	Human RBC	o-Raffinose cross-linked polymerized	>150	10-11	24	25%	34
Polyheme (Northfield)	Human RBC	Polymerized Hb; pyridoxylated 2,3-DPG site	>150	24	20	30%-40%	28-30

*Normal human P50 = 28 mmHg

†Baxter has discontinued the DCLHb program in favor of developing a second-generation hemoglobin.

‡Varies directly with dose (0.1-1.0 g/kg)

§Dose = 0.2-0.6 g/kg

Properties

Although there are product-specific variations, the P-50s of HBOC solutions are generally similar to those of fresh blood but higher than those of stored blood. Circulation half-lives are measured in hours (4–24 hours, often dose dependent) rather than days, as would be the case for red blood cells.

All currently investigated hemoglobins elevate systemic and pulmonary vascular resistance, resulting in a mild reduction in cardiac index. For example, diaspirin cross-linked hemoglobin (DCLHb™), an alpha-alpha cross-linked tetramer, produces a predictable, rapid, and sustained rise in mean arterial pressure (MAP) and in systemic and pulmonary vascular resistance.² At the microcirculatory level, functional capillary density is reduced.³ The pressor response is dose dependent and pharmacologically reversible and exhibits a “ceiling effect.”^{4,5} In human volunteers, 100 mg/kg DCLHb™ raised median systolic BP maximally by no more than 10 mmHg and diastolic BP by no more than about 15 mmHg.⁶ Biopure’s HBOC-201 raised MAP by about 10 mmHg when a dose of 0.6 g/kg was administered to healthy volunteers,⁷ but it had no significant effect on blood pressure when given to surgical patients.⁸ In the author’s clinical investigative experience with 1g/kg DCLHb™ administered to patients undergoing major orthopedic and urologic surgery, MAP was elevated by an average of about 20 mmHg, the hypertensive effect persisting for 24 to 30 hours after administration.⁹ Although HBOC-associated hypertension has not been associated with adverse cardiac events, selected patients are likely to require treatment of hemoglobin-induced systemic and pulmonary hypertension.

The mechanisms thought to account for this pressor effect are the scavenging of NO from vascular endothelium, facilitation of endothelin production and, possibly, a sympathomimetic effect. The smaller the hemoglobin molecule the more effectively it interacts with the endothelium, penetrating it and scavenging endothelial NO to form met-hemoglobin and NO-hemoglobin.¹⁰

In the operative setting, several factors may blunt HBOC-associated hypertensive tendencies. The hypotensive action of surgical hemorrhage,¹¹ as well as volume depletion,^{12,13} may diminish hypertension. Furthermore, halothane and propofol, but not isoflurane, have been shown to decrease the hypertensive action of DCLHb™ on pulmonary vein rings.¹⁴

Hemoglobin solutions have colloidal properties (Table 1), are highly purified, generally do not affect coagulation, and are only weakly antigenic. Modified molecular hemoglobin undergoes oxidation to methemoglobin and leaves the circulation primarily through the reticuloendothelial system. Pre-clinical and clinical studies indicate that modified hemoglobins can mildly increase the concentrations of plasma CPK (but not MB fraction), hepatic enzymes, reticulocyte count, bi-

lirubin, and amylase.^{15–17} In a study of patients undergoing high-blood-loss (approximately half of an adult’s blood volume) surgical procedures, 1 g/kg DCLHb™ was associated with transient elevations in serum LDH, AST, total bilirubin, CK, BUN, and amylase; a high incidence of yellow skin discoloration; and asymptomatic hemoglobinuria.⁹

Gastrointestinal side effects include flatulence, nausea, vomiting,^{6,7} and possibly pancreatitis. However, pancreatitis occurs frequently after major abdominal surgery^{18–20} even in the absence of HBOC administration. The gastrointestinal side effects of DCLHb™ may be related to its ability to interfere with NO production and signaling,²¹ thus possibly affecting gastrointestinal and biliary motility. Judging from preclinical studies^{22,23} of intestinal and portal system blood flow after administration of DCLHb™, gastrointestinal side effects are unlikely the result of tissue ischemia.

Toxicity

Toxicity of hemoglobin solutions has historically been related to impurities such as RBC membrane residues, endotoxin, free dimers, and monomers. With vastly improved purification procedures, concern over toxicity from impurities is waning. In particular, the issue of renal toxicity appears to have been overcome. In rats, 0.4 g/kg DCLHb™ did not affect renal blood flow.²³ Creatinine clearance was neither decreased by 0.1 g/kg DCLHb™⁴ nor by 0.32 g recombinant hemoglobin²⁴ in human volunteers. It was similarly unaffected by up to 0.7 g/kg in critically ill patients with sepsis syndrome²⁵ by 750 ml DCLHb™ in cardiac patients,²⁶ and by 1.0 g/kg DCLHb™ in patients undergoing high-blood-loss surgery, despite the occurrence of hemoglobinuria at the higher doses.⁹ Neither was renal toxicity observed with polymerized hemoglobin.²⁷

Free hemoglobin, then directly applied to central nervous system tissue, is neurotoxic. It stimulates leukocyte migration and vascular adherence. Hemoglobin also activates platelets, promoting aggregation.²⁸ Circulating ferrous hemoglobin, even when highly purified, undergoes a number of reactions that may contribute to toxicity.²⁹ Ferrous hemoglobin binds NO about 3,000 times more tightly than carbon monoxide and therefore effectively removes any NO in its vicinity, accounting for the vasoactive properties. Free hemoglobin is converted to methemoglobin at a rate as fast as 4% per hour; this reaction can lead to the generation of free radicals. Hemoglobin also has a number of “pseudo-enzymatic” properties, which could lead to oxygenation, lipid peroxidation, and cytotoxicity. Further possibilities for toxicity arise from the degradation products of hemoglobin’s heme moiety such as hemin. Red blood cells contain antioxidant enzymes such as catalase and superoxide dismutase, which may help limit ischemia reperfusion injury. It has been speculated that the administration of pure hemoglobin (i.e.,

without antioxidants) may lead to a potentially higher risk of reperfusion injury.³⁰

Although many early trials indicate that some HBOCs have not been associated with severe toxicity, more study in a wide variety of clinical situations is required before their side effects are fully known. Investigation into the effects of HBOCs on the gastrointestinal system, pulmonary vasculature, and organ function during hemorrhagic and other stress is particularly needed. Furthermore, the characteristics of HBOC-assisted oxygen delivery and tissue oxygen availability during supply-dependent conditions need additional investigation.

Perfluorocarbons (PFCs)

Perfluorocarbons are inert aromatic or aliphatic chemicals that can dissolve oxygen and carry it in solution throughout the body. They typically carry 4 to 50 vol% at a PaO₂ of 160 mmHg; their ability to carry oxygen is directly proportional to their concentration in blood and, importantly, to the partial pressure of oxygen. The first fluorocarbon to be approved for clinical use (during percutaneous transluminal coronary angioplasty) was fluosol DA-20, which contains 20% emulsified fluorocarbon. When used as an oxygen-carrying volume expander, fluosol DA was associated with a number of limitations, including low oxygen-carrying capacity, short shelf life, temperature instability, and serious side effects. Second-generation perfluorocarbons, such as perfluoro-octylbromide (PFOB; Alliance Pharmaceuticals), are being investigated and show promise because of a much higher oxygen-carrying capacity, a 2- to 4-year refrigerated shelf life, low viscosity, and less interference with normal pulmonary surfactant mechanisms.³¹

Since PFCs are not metabolized, but excreted unchanged via the lungs, their potential for cytotoxicity is thought to be limited. There is no antigenicity. However, since PFCs are taken up avidly by the reticuloendothelial system, they increase liver enzymes and result in hepatosplenomegaly. Because of the extensive uptake in the reticuloendothelial system and impairment of neutrophil function, they may interfere with host defense mechanisms. Monocyte and macrophage activation may lead to release of prostaglandins, endoperoxides, and cytokines, which probably accounts for the symptoms of flushing, backache, fever, chills, headaches, and nausea observed in clinical trials. Platelet count decreases by as much as 40% due to increased platelet clearance from PFC-induced modification of platelet surfaces.³² PFCs also may prolong the effects of certain drugs, including barbiturates.

Potential Clinical Uses and Effectiveness of HBOCs Major Surgical Bleeding and Hemorrhagic Shock

Fluid therapy for the acutely bleeding patient can be accomplished initially with either crystalloid or colloid solutions. Blood transfusion is begun when, despite volume resuscita-

tion with non-oxygen carrying solutions, there is evidence of tissue ischemia and resultant organ dysfunction. Accumulation of base deficit and serum lactate and low central venous oxygen concentration are all indices of tissue ischemia, which should be taken into consideration in the transfusion decision.³³ Alternatively, blood is transfused when organ ischemia can be anticipated, given the extent and rapidity of ongoing bleeding.

Hemoglobin solutions are as effective as whole blood in restoring MAP in animals³⁴⁻³⁶ and humans.¹² In contrast to typical catecholamine effects, the pressor response of DCLHb™ is associated with an increase in perfusion (as indicated by organ flow measurements) in both top-load and hemorrhagic, hypovolemic, animal models.³⁶⁻⁴⁰ DCLHb™, compared with non-oxygen-containing crystalloid or colloid solutions, resulted in substantially better survival from experimental hemorrhagic shock.^{37,38} This salutary effect may be related to DCLHb™'s effect on tissue perfusion and peripheral oxygenation. For example, tissue oxygenation, measured directly by a fluorescence-quenching optode, was restored more effectively in a rat hemorrhagic shock model treated with DCLHb™ compared with lactated Ringer's solution and albumin.⁴¹ Despite increased total peripheral vascular resistance, rat coronary blood flow²³ was augmented after DCLHb™ and human cerebral blood flow was unchanged after infusion of polymerized hemoglobin.⁴²

Despite their vasoconstrictive properties, HBOCs may counteract tissue hypoperfusion with added blood oxygen-carrying capacity and better rheologic properties. In spontaneously hypertensive rats subjected to middle cerebral artery occlusion, hemodilution with DCLHb™ (to hematocrits of 30, 16, or 9%) resulted in a significant dose-dependent reduction in the extent of brain injury and cerebral edema.⁴³ The most effective reductions in ischemic injury occurred in those animals in which the inherent hypertensive response to DCLHb™ was not inhibited.

The effect of HBOCs on cardiac index is more controversial, with some studies reporting a slight decrease,⁴⁴ others no change.²⁵ Calculated oxygen delivery generally follows cardiac output, thus accounting for the slight decreases reported. However, increased tissue-diffusing capacity has been shown.⁷ Furthermore, the equivalent or enhanced oxygen-unloading capacity of HBOCs compared with blood should allow favorable tissue oxygen delivery, or at least counteract vasoconstrictive effects of free hemoglobins. Therefore, their use in trauma patients and in those with substantial surgical bleeding would seem reasonable. Table 2 suggests potential uses of HBOCs for therapy of patients suffering large blood losses.

However, because of their short half-lives, current hemoglobin solutions are likely to be used essentially as a "bridge to transfusion." For example, the half-life of DCLHb™ administered to patients undergoing high-blood-loss

Table 2.
Use of Hemoglobin-Based Oxygen Carriers in Patients with High Blood Loss

Emergency administration

- Trauma, especially penetrating
- Unexpected surgical bleeding
- Unexpected bleeding from disease (e.g., gastrointestinal tract)
- Difficult cross-match

Elective administration

- Acute normovolemic hemodilution*
- Acute hypervolemic hemodilution*
- Replacing blood transfusion during expected active surgical bleeding
- Replacing blood transfusion postoperatively

*Especially in patients presenting with low initial hematocrit

them over" a limited period of intraoperative or postoperative bleeding, after which autologous or allogeneic blood would be administered if still needed. Furthermore, volume replacement with HBOCs (compared with crystalloid or colloid) during ANH for autologous collection would likely result in a greater yield of pheresed blood components.

Caveats Regarding the Use of HBOCs for Major Blood Loss (Table 3)

The safety of large-scale and rapid transfusion of HBOCs in human traumatic injury remains to be demonstrated. While the author's small series of patients undergoing high-blood-loss elective surgery tolerated up to 1g/kg DCLHb™ relatively well,⁹ a phase III trial of DCLHb™ for resuscitation of traumatically injured patients was halted among concerns about increased mortality in the study group.

Because HBOCs are associated with systemic hypertension, concern has been raised over a potential for increased blood loss in hemorrhage. This concern could not be corroborated in preclinical⁴⁰ or clinical studies⁹ conducted in a setting of hemorrhage, but the issue has yet to be clarified in the setting of penetrating trauma.

The clinical use of HBOCs with relatively short half-lives must take into account their tendency for transvascular migration and their rapid clearance through the reticuloendothelial system. Although the initial effect of transfusion may be an immediate increase in vascular volume (enhanced by some HBOCs' colloidal properties) and blood pressure (mediated by the HBOCs' NO-scavenging effect), rapid dissipation of the HBOC requires care-

surgery was approximately 10 hours.⁴⁵ Administration of DCLHb™ after bypass spared nearly 20% of cardiac patients from allogeneic transfusion.⁴⁶ Nevertheless, there is also concern that the administration of modified hemoglobins merely delays blood transfusion rather than truly substituting for it.

Preoperative acute normovolemic hemodilution (ANH) is likely to become more attractive with the use of modified hemoglobins as a diluent. The short half-life of HBOCs does not present a significant liability for this clinical application. Patients with low preoperative hematocrit might receive an infusion of HBOC to "tide

Table 3. Caveats and Potential Remedies in the Clinical Use of HBOCs

Caveats	Remedies
Hypertensive tendency; cardiac afterload stress	Co-administration of nitroglycerin, other vasodilator
Pulmonary hypertension, right ventricular dysfunction	Co-administration of pulmonary vasodilator
Short intravascular residence time; recurrence of hypovolemia	More frequent assessment and adjustment of intravascular volume
Interference with diagnostic blood tests	Avoidance of photospectrometric methods; removal of free hemoglobin from specimens; other correction algorithms
Hemoglobinuria interfering with diagnosis of transfusion reaction	Special pre-arranged testing protocol
Immune depression as larger Hb species overwhelm the reticuloendothelial system	Unknown
Possible NO-related gastrointestinal or other organ injury	Co-supply NO donor or precursor; redesign molecule

NO, nitric oxide; Hb, hemoglobin

ful and frequent monitoring of circulatory adequacy, since hypovolemia may re-manifest rather quickly.²⁸

At least within the first 24 to 36 hours of administration, free hemoglobins can interfere with the photospectrometric methods used in a variety of clinical laboratory tests. Interference with laboratory testing constitutes an important limitation for the potential clinical use of artificial hemoglobin species.

Other Uses: Hemoglobin Therapeutics?

Since NO plays a part in the pathogenesis of septic shock, modified hemoglobins may become useful in the treatment or prevention of severe septic shock. Artificial oxygen carriers also may be used for oxygen delivery to ischemic tissues (as in stroke or intestinal ischemia) and tumor cells to improve their susceptibility to radiation and chemotherapy. Because iron is one of the breakdown products of hemoglobin metabolism, hemoglobin therapy may stimulate erythropoiesis under certain circumstances. These and other potentially salutary effects of HBOCs, which transcend basic oxygen-carrying properties, have led to an emerging interest in the area of "hemoglobin therapeutics."

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CME Questions

This monograph can be used to earn 15 AMA category 1 credit hours.

The International Trauma Anesthesia and Critical Care Society (ITACCS) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials. ITACCS designates this CME activity for 15 credit hours in Category 1 of the Physicians Recognition Award of the American Medical Association.

Educational Objectives

This activity is designed to provide trauma care professionals interested in the treatment of critically ill trauma patients with a regular overview and critical analysis of the most current, clinically useful information available, covering strategies and advances in the diagnosis of traumatic injuries and the treatment of trauma patients. Controversies, advantages, and disadvantages of diagnosis and treatment plans are emphasized. There are no prerequisites for participation in this activity.

After reading this document, participants should have a working familiarity with the most significant information and perspectives presented and be able to apply what they have learned promptly in clinical practice.

Accreditation Statement

This activity is planned and produced in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of the International Trauma An-

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pleted disclosure forms are on file in the managing editor's office.

INSTRUCTIONS

- Print the answer form and the evaluation form on page 51.
- Complete both forms. On the answer form, circle only one response next to each number.
- Sign and date the certification statement on page 51.
- Write a check for \$150 (or \$75 accompanied by verification of current ITACCS membership), payable to the International Trauma Anesthesia and Critical Care Society.
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- The completed text will be accepted for grading if received by January 31, 2004.
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1. The most sensitive measure of acute blood loss is
 - a. blood pressure.
 - b. urine output.
 - c. heart rate.
 - d. mixed venous oxygen saturation.
2. High-risk elderly patients require invasive hemodynamic monitoring
 - a. only if they have a history of coronary artery disease.
 - b. as early as possible, following emergency department admission.
 - c. once they are evaluated for injuries.
 - d. if they have evidence of hypotension and tachycardia.
3. The relationship between serum lactate and base deficit remains constant for how long following resuscitation?
 - a. 12 hours
 - b. 24 hours
 - c. 36 hours
 - d. 48 hours
4. Which of the following is the most accurate predictor of survival following injury?
 - a. serial blood pressure determination
 - b. adequacy of urine output
 - c. ability to clear lactate to normal
 - d. resolution of tachycardia
5. Interventional radiologic techniques can be useful in which body area?
 - a. Zone 3 of the neck
 - b. Zone 2, the thoracic outlet
 - c. deep in the pelvis
 - d. all of the above
6. Stages of traumatic shock include all of the following *except*
 - a. subacute irreversible shock.
 - b. compensated shock.
 - c. decompensated shock.
 - d. cardiogenic shock.
 - e. acute irreversible shock.

7. Of the following organ systems, the one most directly affected by decreased blood flow in traumatic shock is
- cardiac.
 - intestinal.
 - pulmonary.
 - central nervous.
 - skeletal muscle.
8. Which of the following statements is correct?
- In compensated shock, the body is not developing an oxygen debt.
 - In subacute irreversible shock, normal hemodynamics are never achieved.
 - In neurogenic shock, ischemia is caused by decreased oxygen-carrying capacity.
 - Traumatic shock is the same as hemorrhagic shock.
 - Decompensated shock is a stable clinical state that can persist for many days.
9. Which of the following is not an inflammatory mediator produced by ischemic cells?
- Prostacyclin
 - Tumor necrosis factor
 - Complement
 - Thromboxane
 - Angiotensin II
10. Acute irreversible shock includes all of the following clinical signs *except*
- hyperthermia.
 - coagulopathy.
 - hypotension not responsive to fluids.
 - hypotension not responsive to inotropes.
 - diffuse edema.
11. The first response of the body to obtain hemostasis is
- initiation of the coagulation cascade.
 - platelet aggregation.
 - initiation of fibrinolysis.
 - platelet release reaction.
 - vasoconstriction.
12. Concerning platelets and hemostasis:
- Exposure of platelets to subendothelial collagen leads to adherence between platelets and the blood vessel wall.
 - Platelet release reaction refers to the liberation of platelets sequestered in the spleen.
 - The intrinsic coagulation pathway is the predominant pathway in the coagulation cascade.
 - The intrinsic and extrinsic pathways merge with the activation of Factor IX.
 - Fibrinolysis occurs only after the clotting mechanism is completed.
13. The ideal topical hemostatic agent possesses which of the following properties:
- Rapid time to hemostasis
 - Easily applied and manipulated
 - Holds sutures
 - Low infectious risk and minimal tissue reaction
 - All of the above
14. Concerning topical hemostatic agents:
- Collagen sponges are unique in that they are bactericidal.
 - Denatured gelatin (Gelfoam®)
- possesses clotting activity similar to collagen preparations.
- Thrombin is effective only if combined with a carrier such as Gelfoam®.
 - Fibrin glue has been shown to be effective as either the primary hemostatic agent or as an adjunct to conventional suture repair in patients with hepatic or splenic trauma.
 - In vitro* testing reveals that oxidized regenerated cellulose (Surgicel®) is more effective than collagen preparations for inducing platelet aggregation and clotting.
15. Severely injured patients
- have been shown to have elevated serum fibrin degradation products (FDP).
 - may exhibit thrombocytopenia.
 - may progress to death if FDP and platelet assays trend in an abnormal manner.
 - benefit from prophylactic transfusion of fresh frozen plasma and platelets even in the absence of pathologic bleeding.
 - a, b, c
16. Risk factors for DVT in trauma patients include
- spinal cord injury.
 - prolonged bed rest.
 - hypercoagulability.
 - lower extremity fractures.
 - all of the above.
17. The most common inborn metabolic error that causes thrombophilia is
- activated protein C resistance.
 - protein C deficiency.
 - protein S deficiency.
 - hypohomocysteinemia.
 - serum porciline deficiency.
18. Physical examination is the most accurate method of diagnosing DVT.
- True
 - False
19. The primary reason to provide prophylactic treatment to prevent DVT in trauma patients is to
- prevent leg swelling.
 - enhance fracture healing.
 - prevent fatal pulmonary embolism.
 - increase billable services.
 - decrease length of hospitalization.
20. Epidural analgesia in the patient receiving LMWH
- is absolutely contraindicated.
 - is associated with epidural abscesses.
 - is no problem.
 - may be performed at least 12 hours after the last dose.
 - is not associated with problems of catheter removal.
21. Management priorities in the acutely bleeding trauma patient include all of the following *except*:
- Measurement of BP
 - Securing the airway and verifying adequacy of ventilation and oxygenation
 - Insertion of a pulmonary artery catheter
 - Placement of the ECG
 - Obtaining large-bore venous access
22. Appropriate intraoperative fluid management for a 70-kg multiple blunt trauma patient in class 4 hemorrhagic shock includes which of the following:
- Hestastarch, 2.5-L bolus
 - Lactated Ringer's, 5 L
 - 7.5% saline, 1.5 L
 - Two units type-specific uncrossmatched red blood cells and 3 L normal saline
 - Four units of fresh frozen plasma
23. Resuscitation endpoints after major trauma include which of the following:
- Resolution of lactic acidosis and base deficit
 - Mixed venous oxygen saturation 45%
 - Normalization of ventilation-perfusion mismatch
 - All of the above
 - a and c
24. The differential diagnosis of hypotension in the setting of massive transfusion after major blunt trauma includes all of the following *except*:
- Hypocalcemia
 - Transfusion reaction
 - Hypovolemia
 - Tension pneumothorax
 - All of the above
25. Which of the following products carries the highest risk of infection?
- 5 units packed red blood cells
 - 2 units fresh frozen plasma
 - 6 units platelets
 - 3 units whole blood
 - 2 L 0.9% saline
26. Is there an exact transfusion trigger HCT at which all patients should be transfused:
- Yes
 - No
27. Can hepatitis C be transmitted via blood transfusion?
- Yes
 - No
28. Does transfusion result in immunosuppression of the recipient?
- Yes
 - No
29. In general, will patients with histories of impaired cardiac function or cardiac ischemia require transfusion at higher or lower HCT levels?
- Higher
 - Lower
30. Is there a relationship between the number of units of blood transfused and infection in trauma patients?
- Yes
 - No
31. Complications of subclavian and internal jugular catheterization include
- air embolism
 - hemotorax
 - pneumothorax
 - sepsis
 - all of the above

32. In a patient with multiple stab wounds to the abdomen, which of the following would provide adequate venous access?
- a large-bore femoral catheter
 - two upper extremity 14-gauge IV catheters
 - a saphenous cutdown
 - a right internal jugular triple lumen
 - none of the above
33. Choose the incorrect statement regarding venous access in the trauma patient:
- Venous cutdowns provide rapid, secure, large-bore venous access.
 - Two large-bore percutaneous catheters should be placed immediately.
 - A central line should be inserted in all trauma patients.
 - Main complications of venous cutdown are nerve injury and infection.
 - The major complications of internal jugular cannulation are pneumothorax and carotid puncture.
34. Choose the incorrect statement:
- Long, large-bore IV catheters should be used for rapid IV fluid infusion.
 - Thrombosis of femoral catheters occurs more often than with subclavian catheters.
 - Subclavian catheterization should be attempted in the side of injury in a patient with a chest wound.
 - Strict aseptic technique should always be used in central line placement.
 - Venous air embolism is often a fatal complication.
35. Intraosseous catheters
- are recommended only in children.
 - should be considered after two unsuccessful percutaneous IV attempts in the pediatric trauma patient.
 - do not provide adequate venous access for fluid administration.
 - should be used only as a last resort in a trauma patient.
 - none of the above.
36. Regarding the impact of rapidly infusing unwarmed IV fluids in a 70-kg anesthetized patient:
- 4.5 L of 21°C crystalloid will result in ~1.0-1.5°C decrease in mean body temperature.
 - 4 units of 4°C red cells diluted in 0.9% saline will result in ~1.0-1.5°C decrease in mean body temperature.
 - Red cells may be warmed safely to a maximum temperature of 42°C.
 - Gas embolism may occur, especially with the use of constant pressurized infusion devices.
 - All of the above
- For questions 37-40, match the fluid/blood warmer with the one best answer.
Answers may be used only once.
- Hotline
 - Flotem IIe
 - Level 1- H1000
 - Alton Dean/Mallinkrodt FW537 or FW538
 - Coiled IV tubing immersed in a water bath
 - Aluminum tube in tube countercurrent heat exchanger combined with heated patient line
 - Metal foil countercurrent heat exchange
 - IV tubing sandwiched between aluminum heating plates in a serpentine fashion—dry heat technology
 - Countercurrent heated patient line to insure delivery of 37°C fluid at flow rates of 5–80 ml/min (300–5,000 ml/hr)
 - Infusion rates of up to 1,500 cc/min can be achieved.
 - 100-cc and/or 500-cc boluses over 1 minute can be infused periodically.
 - All forms of blood components may be infused through it.
41. When a critically injured patient enters the operating room for emergency surgical therapy, which of the following should be the anesthesiologist's #1 priority?
- TEE probe insertion
 - Pulmonary artery catheter insertion
 - ECG monitoring
 - Blood pressure measurement
 - Evaluation and management of the airway, oxygenation, and administration
42. Which of the following is not ideal as a route for fluid administration in trauma?
- Use of two peripheral intravenous catheters in the upper extremities
 - Use of the internal jugular vein with a short, large-bore IV catheter
 - Use of the femoral vein with a large-bore IV catheter in a patient with a gunshot wound in the neck
 - Use of the femoral vein with a large-bore IV catheter in a patient with suspected cervical spine, abdominal, and pelvic injuries
43. Which of the following is a known storage lesion for PRBCs?
- decreased pH
 - hemolysis
 - increased concentration of potassium
 - decreased 2,3-DPG
 - all of the above
44. The following are true regarding sodium citrate *except*
- Calcium chloride should always be given when more than 2 units of blood are transfused to an adult trauma patient.
 - Sodium citrate transiently decreases ionized calcium.
 - Hypocalcemia can cause hypotension.
 - Hypocalcemia can cause a prolonged QT interval.
 - Hypocalcemia can cause biventricular cardiac dysfunction.
45. Which of the following infection is the most frequently associated with blood transfusion in the United States?
- HIV
 - Hepatitis B
 - Hepatitis C
 - HTLV 1
 - HTLV 2
46. True statements regarding the Rapid Infusion System (Haemonetics Corporation) include all of the following *except*
- It features a roller pump mechanism.
 - Fluids are pumped from a 3-liter hard shell reservoir.
47. True statements regarding the i-STAT Portable Clinical Analyzer (i-STAT Corp., Princeton, NJ) include all of the following *except*:
- It is a hand-held unit.
 - It utilizes a "thin film" biosensor requiring 2 to 3 drops of blood in order to give results over a variety of laboratory parameters.
 - Coagulation studies available include PT, PTT, and fibrinogen levels.
 - Blood chemistry results are obtained within 2 minutes.
 - Various laboratory results can be obtained, depending on the particular cartridge inserted into the unit.
48. Current guidelines regarding quality control in laboratory testing are mandated through
- The National Committee for Clinical Laboratory Standards
 - The Health Care Financing Administration
 - The clinical director of an individual laboratory facility
 - The 1988 Amendment to the Clinical Laboratory Improvement Law of 1967
 - The Department of Health and Human Services
49. In the massive transfusion scenario, true statements regarding banked red blood cells include all of the following *except*
- Pre-washing RBCs removes a significant proportion of citrate that may be present in the infused blood.
 - May be indicated in patients with a history of renal insufficiency.
 - Pre-washing RBCs decreases K+ concentration of blood administered to the patient.
 - K+ concentration is unrelated to the length of time a unit of blood has been stored.
 - The risk of untoward effects of massive transfusion of banked red blood cells increases with rapidity of transfusion.
50. Key points of the rapid infusion strategy employed by anesthesia personnel at the Elvis Presley Memorial Trauma Center include all of the following *except*
- Transfusion of blood products through the Rapid Infusion System in units of 10 units PRBCS, 4 units fresh frozen plasma, and 7 units pooled platelets.
 - Dilution of each unit of red blood cells with 500 cc of normal saline.
 - Maintenance of relative normotension.
 - Communication with surgeons, the blood bank, and lab personnel regarding use of the RIS.
 - Infusion of fluids through the RIS at 1,500 cc/min until hemostasis is achieved.

CME ANSWER FORM

Answer Form: Please circle the *one* best answer for each question.

Massive Transfusion Monograph — 1999/2002

1. a	b	c	d	18. a	b				35. a	b	c	d	e
2. a	b	c	d	19. a	b	c	d	e	36. a	b	c	d	e
3. a	b	c	d	20. a	b	c	d	e	37. a	b	c	d	e
4. a	b	c	d	21. a	b	c	d	e	38. a	b	c	d	e
5. a	b	c	d	22. a	b	c	d	e	39. a	b	c	d	e
6. a	b	c	d	23. a	b	c	d	e	40. a	b	c	d	e
7. a	b	c	d	24. a	b	c	d	e	41. a	b	c	d	e
8. a	b	c	d	25. a	b	c	d	e	42. a	b	c	d	e
9. a	b	c	d	26. a	b				43. a	b	c	d	e
10. a	b	c	d	27. a	b				44. a	b	c	d	e
11. a	b	c	d	28. a	b				45. a	b	c	d	e
12. a	b	c	d	29. a	b				46. a	b	c	d	e
13. a	b	c	d	30. a	b				47. a	b	c	d	e
14. a	b	c	d	31. a	b	c	d	e	48. a	b	c	d	e
15. a	b	c	d	32. a	b	c	d	e	49. a	b	c	d	e
16. a	b	c	d	33. a	b	c	d	e	50. a	b	c	d	e
17. a	b	c	d	34. a	b	c	d	e					

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