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Surgical Bleeding: Bleeding Disorders, Hypercoagulable States, and Replacement Therapy in the Surgical Patient

Hollis W. Merrick Ill, Jared M. Huston, Timothy A. Pritts, Carlos Ramirez Tanchez, and Mary R. Smith

Bleeding may occur during surgical procedures. Although the volume of blood lost is usually not large enough to create a major problem, certain operations are invariably associated with large blood losses that may impair the normal hemostatic process. Additionally, some patients with congenital or acquired disorders of hemostasis require elective or emergency surgery. Therefore, surgeons must be prepared for significant blood losses that may have an adverse effect on patient recovery, and they must be able to manage blood loss in their patients. Careful screening for bleeding risks can detect bleeding disorders before surgery and allow for correction to avoid major bleeding problems during and after surgery (Table 4-1). In addition, surgeons must be knowledgeable about common bleeding disorders and causes of hypercoagulable states, the components of blood replacement, and the problems associated with the transfusion of blood products.

TABLE 4-1 Preoperative Evaluation for Bleeding and Clotting Disorders

Study	When Performed
History	In all patients as part ofroutine preoperative evaluation
Physical examination	As part ofroutine preoperative evaluation
Laboratory studies: aPTT, PT, bleeding time (less commonly used) or whole blood platelet function, thrombin	In patients with evidence ofbleeding disorders or in whom excessive bleeding is anticipated because ofthe nature ofthe surgery time

aPTT, activatedpartial thromboplastin time; PT,prothrombin time.

CAUSES OF EXCESSIVE SURGICAL BLEEDING

Most patients are hemostatically normal before they enter the operating room. However, in some patients with large blood losses, generalized oozing is noted after a period of time. In addition, some operations (e.g., cardiopulmonary bypass, aortic surgery, liver transplant surgery, prostate surgery, construction of portacaval shunts, trauma) are frequently associated with large blood losses.

Preexisting Hemostatic Defects

Preexisting hemostatic defects should be suspected when a prior history of bleeding exists or when abnormal bleeding begins within the first 30 minutes of the operative period. Bleeding disorders may be congenital (Table 4-2) or acquired (Table 4-3).

TABLE 4-2 Congenital Bleeding Disorders

	Hemophilia A	Von Willebrand Disease
Incidence	25 per 100,000 in the United States	1% ofU.S. population
Pathophysiolow	Reduced or absent factor VIII activity. Factor VIII molecule is present.	Reduced factor VIII activity and von Willebrand activity
Site ofbleeding	Joints and intramuscular	Mucocutaneo us
Inheritance	X-Iinked	Autosomal dominant
Patients	Only males	Males and females
Laboratory studies	Prolonged aPTT	Prolonged aPTT
	Normal PT	Normal PT
	Normal platelet function	Abnormal platelet function

aPTT, activatedpartial thromboplastin time; PT,prothrombin time.

TABLE 4-3 Causes of Acquired Bleeding Disorders

Advanced liver disease
Anticoagulationtherapy
Acquired thrombocytopenia
Platelet-inhibiting drugs
Uremia
Over-the-counter medications, e.g., herbal supplements
DIC
Primary/secondary fibrinolysis

DIC, disseminated intravascular coagulation.

All anticoagulants and platelet-inhibiting drugs carry the risk of inducing bleeding in any patient. The most common anticoagulants that are currently in use include the vitamin K antagonist warfarin and heparins, both unfractionated and low molecular weight. A new class of anticoagulants, direct factor Xa inhibitors (e.g., fondaparinux [Arixtra]), are being used in specific settings but are likely to have expanded uses in the future. Direct thrombin inhibitors, such as argatroban (Acova) and bivalirudin (Angiomax), have limited indications; in particular, these drugs are used to treat patients with heparin-induced thrombocytopenia. The most commonly used platelet-inhibiting drugs are aspirin and clopidogrel (Plavix), both of which cause irreversible inhibition of platelet function. Because of the increased risk of bleeding associated with all anticoagulants and platelet-inhibiting drugs, great care must be exercised in the use of these drugs (Table 4-4).

TABLE 4-4 Mechanism of Action and Monitoring of Anticoagulants

Mechanism ofAction	Anticoagulant	Laboratory Monitoring
Xa inhibition and thrombin inhibition	Unfractionated heparin	aPTT or anti-Xa activity
Xa inhibition	Low—molecular-weight heparin (Lovenox), apixaban (Eliquis), edoxaban (Lixiana), rivaroxaban (Xarelto), fondaparinux (Arixtra)	Anti-Xa activity
Production ofinactive vitamin K—dependent clotting factors rx, X, Vll, 11 (1972)	Warfarin (Coumadin)	PT, INR
Thrombin inhibition	Argatroban (Acova), dabigatran (Pradaxa), bivalirudin (Angiomax)	aPTT, TCT

aPTT, activatedpartial thromboplastin time; INR, international normalized ratio; PT,prothrombin time; TCT, thrombin clotting time.

Intraoperative Complications

Several common conditions contribute to bleeding during a surgical procedure. Shock may cause or aggravate consumptive coagulopathy. Massive transfusion of stored packed red blood cells (PRBCs) alone may lead to bleeding. For this reason, standard of care has become the administration of a balanced, 1:1:1 transfusion of PRBCs, platelets, and plasma, along with cryoprecipitate and calcium for patients receiving massive transfusion of red blood cells.

Acute hemolytic blood transfusion reactions may lead to disseminated intravascular coagulation (DIC). [A]Nhen a patient is under general anesthesia, there may be no clues that incompatible blood has been infused until the onset of generalized bleeding as a result of DIC. The usual symptoms of an incompatible blood transfusion (e.g., agitation, back pain) are not apparent under general anesthesia. Hemoglobinuria and oliguria provide additional clinical evidence of DIC.

Intraoperative bleeding from needle holes, vascular suture lines, or extensive tissue dissection can often be controlled through the use of local hemostatic agents. These include gelatin sponge (e.g., Gelfoam), oxidized cellulose (Surgicel), collagen sponge (Helistat), microfibrillar collagen (Avitene, Hemotene), topical thrombin (with or without topical cryoprecipitate), topical E-aminocaproic acid (EACA), and topical aprotinin.

Massive Hemorrhage and Damage-Control Resuscitation

Massive hemorrhage following injury is defined as bleeding requiring a transfusion of 10 or more units of PRBCs in 24 hours or more than 4 units in 1 hour, replacement of a patient's entire blood volume in 24 hours or >50% in 4 hours, or a rate of blood loss > 150 mL/minute with hemodynamic instability. Early recognition and treatment of patients with massive hemorrhage is critical to survival. Predictors of massive transfusion requirements include emergency room systolic blood pressure mm Hg, heart rate ž120 beats/minute, positive Focused Assessment with Sonography for Trauma scan, and penetrating injury.

Treatment of massive hemorrhage has evolved dramatically over the past 10 to 15 years. The impetus for this change is a better understanding of acute traumatic coagulopathy (ATC), also known as trauma-induced coagulopathy. ATC is present on admission in approximately 25% of major trauma patients, occurs independently of injury severity, and is associated with a 4-fold higher mortality rate. ATC results from inadequate tissue perfusion, not excessive consumption of circulating clotting factors. Elevated plasma thrombomodulin (a marker of endothelial damage) and decreased protein C concentrations result in hyperfibrinolysis.

Damage-control resuscitation (DCR) is a comprehensive strategy to guide the care of critically injured bleeding trauma patients. Its main objective is to minimize blood loss until definitive hemostasis is achieved. Essential principles of DCR include early hemorrhage control during transport and avoidance of delays in surgical or angiographic hemostasis. Damage-control surgery involves an abbreviated initial operation to stop bleeding and ongoing bacterial contamination, followed by a more definitive procedure after resuscitation and stabilization in the intensive care unit. This approach is the current standard of care for patients with severe abdominal, thoracic, pelvic, and extremity injuries, and it results in significantly improved survival. Other important principles include delayed aggressive volume resuscitation and targeted low-normal blood pressure (permissive hypotension), which can help avoid hypothermia and hemodilution stemming from excess crystalloid administration.

Massive transfusion protocols (MTPs) are perhaps the most widely studied DCR intervention. The optimal ratio of plasma, platelets, and PRBCs to achieve hemostasis and prevent death from exsanguination is 1:1:1. Supplementary calcium should be given with every 2 units of PRBCs. Evidence suggests that the implementation of MTPs improves patient survival, reduces blood product usage, and reduces treatment costs. Adjuncts to MTPs include recombinant factor Vlla (rVIIa) to augment clot formation, tranexamic acid (TXA) to inhibit fibrinolysis, and functional laboratory measures of coagulation to guide resuscitation, such as thromboelastography. Administration of rVIIa may reduce the need for massive transfusions, but there is no significant mortality benefit. Because of a favorable side effect profile when used within 3 hours after injury, TXA is conditionally recommended for severely bleeding adult trauma patients.

TXA competitively inhibits the activation of plasminogen to plasmin, resulting in its antiflbrinolytic activity. It is indicated for use as a treatment or prophylaxis for profuse bleeding in traumas, major surgeries, and dental extractions in hemophiliacs.

Postoperative Bleeding

Fifty percent of postoperative bleeding is caused by inadequate hemostasis during surgery. Residual heparin that remains after cardiopulmonary or peripheral vascular bypass surgery can cause significant oozing or overt bleeding. Shock due to any cause that results in consumptive coagulopathy can lead to significant postoperative bleeding. Altered liver function after partial hepatectomy is often associated with bleeding. If a large portion of the liver is removed, the remaining liver may need 3 to 5 days to increase its production of clotting factors sufficiently to support hemostasis. Acquired deficiency of the vitamin K—dependent clotting factors (Il, VII, IX, and X) can develop in patients who are poorly nourished and are receiving antibiotics. Supplementation with vitamin K in postoperative patients who are not able to adequately nourish themselves is essential to avoid the development of these clotting factor deficiencies. Factor XIII deficiency is an uncommon disorder but must be considered as a possible cause for delayed postoperative bleeding. In this case, bleeding occurs 3 to 5 days after surgery. The diagnosis of this deficiency is confirmed by a factor XIII assay.

Disseminated Intravascular Coagulation

In any patient with postoperative bleeding, the possibility of DIC must be considered as a possible cause. This is particularly true if there is severe infection or shock. DIC is characterized by intravascular coagulation and thrombosis that is diffuse rather than localized at the site of injury. This process results in the systemic deposition of platelet—fibrin microthrombi that cause diffuse tissue injury. Some clotting factors may be consumed in sufficient amounts to eventually lead to diffuse bleeding. DIC may be acute or clinically asymptomatic and chronic. The etiology of DIC may be any of the following: (1) the release of tissue debris into the bloodstream after trauma or an obstetrical catastrophe; (2) the introduction of intravascular aggregations of platelets as a result of activation by various materials, including ADP and thrombin (which may explain the occurrence of DIC in patients with severe septicemia or immune complex disease); (3) extensive endothelial damage, which denudes the vascular wall and stimulates coagulation and platelet adhesion (as seen in patients with widespread burns or vasculitis); (4) hypotension that leads to stasis and prevents the normal circulating inhibitors of coagulation from reaching the sites of the microthrombi; (5) blockage of the reticuloendothelial system; (6) some types of operations that involve the prostate, lung, or malignant tumors; (7) severe liver disease; and (8) brain trauma or surgery because the brain is rich in thromboplastin, which activates clotting if released into the circulation.

The diagnosis of DIC is established by the detection of diminished levels of coagulation factors and platelets. The following laboratory results may be useful in diagnosing DIC: (1) prolonged activated partial thromboplastin time (aPTT); (2) prolonged prothrombin time (PT); (3) hypofibrinogenemia; (4) thrombocytopenia; and (5) the presence of fibrin and fibrinogen split products and positive D-dimers. The presence of fibrin and fibrinogen split products is caused by activation of the fibrinolytic pathway in response to activation of the clotting pathway. The D-dimer is a product of fibrin digestion by the fibrinolytic process.

The most important aspect of the treatment of DIC is to remove the precipitating factors (e.g., treating septicemia). If DIC is severe, replacement of coagulation factors is required to correct the coagulation defect. Cryoprecipitate is the best method for replacement of a profound fibrinogen deficit. Platelet transfusions may also be required. Fresh frozen plasma (FFP) is useful for replacing other deficits that are identified, but it must be used judiciously if volume overload is a potential problem.

Bleeding Disorders Caused by Increased Fibrinolysis

Postsurgical bleeding may also be caused by disorders leading to increased fibrinolysis.

Primary fibrinolysis is a disorder that occurs when the fibrinolytic pathway is activated, leading to the production of plasmin without antecedent activation of the coagulation pathways. Most commonly, primary fibrinolysis occurs after fibrinolytic therapy with drugs such as tissue plasminogen activator, which are used to lyse coronary artery or peripheral artery thromboses. Primary fibrinolysis is also seen in conjunction with surgical procedures on the prostate, which is rich in urokinase. It also occurs in patients with severe liver failure. Very rare disorders of inhibitors of the fibrinolytic pathway (e.g., congenital deficiencies of Chantiplasmin) can also cause primary fibrinolysis. The treatment of these disorders is best accomplished by eliminating the precipitating cause, such as discontinuing lytic therapy. Because the half-life of lytic agents is short (in minutes), bleeding usually stops rapidly.

If primary fibrinolysis becomes severe, EACA can be used for therapy. This drug must be used cautiously because it blocks the fibrinolytic pathway and may predispose the patient to thrombotic events.

Secondary fibrinolysis is most often seen in response to DIC. The coagulation pathways are activated, followed by the fibrinolytic pathway. Manifestations of this activation in laboratory tests include hypofibrinogenemia and the presence of fibrin split products and positive D-dimers. As the DIC is corrected, the secondary fibrinolysis resolves.

Hypercoagulable States in the Surgical Patient

Thromboembolism may occur for a number of reasons during the course of surgery and in the postoperative period (Table 4-5). Both congenital and acquired disorders can put surgical patients at risk for venous thromboembolism (VTE). The evaluation of patients for surgery must include an assessment of the degree of risk the patient has for a VTE event. Virtually all surgery carries varying degrees of risk for VTE, from minimal to highly significant. A number of steps are essential in the assessment of the degree of risk in a patient.

TABLE 4-5 Differential Diagnosis of Hypercoagulable States by Site ofThrombosis

Arterial Thrombosis (e.g., Myocardial Infarction)	Venous Thrombosis (e.g., VTE)
Common: Antiphospholipid syndrome	Common: Factor V Leiden
Prothrombin 20210 mutation	Prothrombin 20210
HIT Syndrome	Protein C deficiency
Uncommon: Elevated PAI-I activity	Protein S deficiency
Hyperhomocysteinemia (strokes in children)	Antithrombin deficiency
tPA Deficiency	Uncommon: Hyperhomocysteinemia (uremic patients)

Anomalous coronary arteries	Factor XII deficiency
Vasculitis	Trauma
	Immobilization
	Pregnancy, oral contraceptive therapy, or hormone replacement therapy

HIT, heparin-induced thrombocytopenia; PA" Plasminogen activator inhibitor; tPA, tissuePlasminogen activator; VTE, venous thromboembolism.

The most important first step in the assessment of VTE risk is the medical history of the patient. The information to be obtained should address the following points: Has the patient suffered a VTE event before the age of 40 or had an unprovoked VTE event at any age? A recurrent VTE event at any age can be a harbinger of a hypercoagulable state, as can a thrombosis occurring at an unusual site (e.g., mesenteric vein thrombosis). Perhaps one of the most important points in the history is the family history, which can provide helpful clues about the risks for VTE in any patient. A significant positive family history can guide one to evaluate patients for inherited hypercoagulable risk factors.

A positive history for thrombosis associated with pregnancy, oral contraceptives, or hormone replacement therapy should alert practitioners to the possibility of an underlying hypercoagulable state. The specific complications of pregnancy that one must address in the history include recurrent fetal loss, fetal growth retardation, preeclampsia, or eclampsia. Each of these disorders can be an indicator of any underlying hypercoagulable state.

Management of Hypercoagulable States

Therapy for hypercoagulable states is primarily directed at (1) interfering with the coagulation pathways (with heparin, warfarin, or both) and (2) interfering with platelet function (with aspirin, clopidogrel, or other platelet-inhibiting drugs). Therapy must be individualized both to the patient and to the site and severity of the thromboembolism. Great caution must be exercised when using warfarin in patients with protein C deficiency. These patients may develop "Coumadin-induced skin necrosis" if a long overlap period with heparin is not performed. This long overlap allows the metabolism of all vitamin K—dependent proteins to reach a steady state. The duration of anticoagulation therapy requires careful consideration, and the risks and benefits of protracted anticoagulation therapy must be weighed against potential benefits.

During the perioperative period, therapy for patients with a history of thromboembolism and a documented hypercoagulable state must be planned carefully by both the surgeon and the hematologist. Lowdose heparin (5,000 international units), subcutaneously administered, provides adequate protection from thromboembolism for short periods without compromising surgical hemostasis. Alternatively, low—molecularweight heparin prophylaxis may be used. For patients with a documented hematologic risk factor for thrombosis who have never had a thromboembolic event, prophylaxis with pneumatic compression boots or low-dose heparin is adequate. Deep vein thrombosis prophylaxis is also covered in detail in Chapter 1, Perioperative Evaluation and Management of Surgical Patients.

Special Populations

Several subgroups of commonly encountered patients have unique needs with regard to bleeding and clotting. Pregnant females experience an expansion of circulating blood volume with a relative anemia, but elevated levels of factor VIII, fibrinogen, and other clotting factors. Clotting and pulmonary embolism are

the leading causes of death in pregnant females. This risk is highest during the third trimester and after delivery. Low— molecular-weight and unfractionated heparins are the preferred modalities of anticoagulation therapy in pregnant women.

Physiologically, healthy children and adolescents differ little from their adult counterparts.

Aging does not bring about any major changes to the hemostatic system; however, it is associated with increasing disease burden and decreased physiologic reserves. For this reason, when hemorrhage and coagulopathy do occur in elderly persons, the event is typically more serious and associated with worse outcomes.

Patient with cirrhosis, acute liver failure (including "shock liver" and hepatitis), and other liver dysfunctions have a metabolic coagulopathy as a result of decreased protein production. The international normalized ratio (INR) test is the modality of choice for measuring synthetic liver function. Bilirubin, ammonia, and transaminase levels are not useful measurements in determining coagulopathy for patients with liver disease. Paradoxically, patients with liver disease may experience inappropriate bleeding or clotting, or even both simultaneously, because of a derangement of both anticoagulant and procoagulant processes.

Patients with renal failure are more prone to bleeding events primarily because of platelet malfunction secondary to uremia. Anticoagulants used during the dialysis process, a buildup of medications because of decreased renal drug elimination, and dilutional anemia also play a role in the increased risk of bleeding for these patients. Dialysis may help correct these issues but cannot ultimately eliminate them. Patients on dialysis are also at risk for thrombotic events because of chronic platelet activation caused by platelet contact with synthetic surfaces within the dialysis machine or the surgical graft for venous access.

BLOOD COMPONENT THERAPY

Typing and Cross-Matching of Blood Components

There are over 600 known red blood cell antigens organized into 22 blood group systems. Only two groups have immunologic relevance: the ABO and Rhesus groups. An individual must receive ABO/Rh-matched blood. ABO incompatibilities are the most common cause of fatal transfusion reactions.

Cross-matching is performed after ABO/Rh typing. It is a process whereby serum from the recipient is mixed with the red blood cells from the donor. Antibodies to donor red cells present in recipient serum will cause a positive crossmatch and preclude transfusion of those donor cells to this recipient.

Transfusion of Red Blood Cells

Red blood cell transfusions are available as (1) whole blood, (2) PRBCs, (3) washed red blood cells, (4) leukoreduced red blood cells, and (5) divided or pediatric unit red blood cells. There are no firm current indications for the transfusion of whole blood, with the exception of the need for massive transfusion or the need for lifesaving transfusion when component therapy is not available. Washed and leukoreduced red-cell preparations are used to transfuse red cells to patients who have had hypersensitivity or nonhemolytic febrile transfusion reactions to ordinary PRBCs, and for transplant patients. Transfusion of PRBCs is indicated when the red blood cell mass is decreased (as reflected in the hemoglobin concentration and/or

hematocrit level) with a subsequent compromise of oxygen delivery to tissues and organs. The decision to transfuse, and the amount of blood to be transfused, is multifactorial and must be individualized on the basis of a number of factors, including (1) the reason for anemia; (2) the degree and acuity/chronicity of anemia; (3) underlying medical conditions, particularly cardiac, pulmonary, and renal disease; (4) anticipated future transfusion requirements; and (5) hemodynamic instability.

PRBCs are typically stored between I ^{O}C and 6^{0}C. The red blood cells have a shelf life of approximately 42 days. One unit of PRBCs contains about 200 ml. of red cells and 30 ml-J of plasma in a total volume of about 310 mL. The hematocrit of a typical unit ofPRBCs is approximately 57%. Transfusion of one unit of PRBC into an average 70-kg person can be expected to raise the hematocrit by 3% and the hemoglobin concentration by 1 g/dL.

Transfusion Triggers

It is important to note that anemia alone is not an indication for transfusion in most populations; rather, the symptoms related to the anemia may trigger the decision to transfuse. Numerous retrospective studies in a variety of patient populations have found an association between blood transfusion and poor patient outcome. At its core, blood product transfusions are a tissue transplant, with all of the attendant immune problems. The decision to transfuse must be made on the basis of individual physiologic need and clinical circumstances. Patients who are actively bleeding should receive balanced transfusion on the basis of their hemodynamic state and coagulation profile.

Transfusion of Fresh Frozen Plasma

Indications for transfusion of FFP include patients with laboratory evidence of multiple coagulation factor deficiency (e.g., abnormally elevated PT or aPTT) with clinical bleeding or the need for an invasive procedure. Coagulation factor deficiencies can result from dilutional coagulopathy following massive transfusion or resuscitation, congenital synthesis defects, anticoagulant medications such as warfarin or heparin, liver disease, malnutrition, and other acquired disorders.

Transfusion of Platelets

Platelet transfusion is indicated for patients who have clinical bleeding, and either an absolute thrombocytopenia or a relative thrombocytopenia due to platelet dysfunction. Platelet dysfunction often occurs as a result of medical conditions, such as renal failure, or as a result of medications such as nonsteroidal anti-inflammatory drugs and clopidogrel (Plavix). Patients with normal platelet function typically do not experience clinical bleeding until the absolute platelet count drops to 30,000 to 50,000 platelets/UL and often even lower than this. In contrast, patients with dysfunctional platelets will often manifest clinical bleeding with platelet counts in the normal range. Additional information regarding the need for platelet transfusion can be obtained from a whole blood platelet function testing. Platelet suspensions contain some plasma and few red blood cells or leukocytes. The therapeutic effect of platelet transfusion depends upon the patient's pathologic state, existing platelet count, level of platelet function, weight of the patient, and the number of platelet concentrates transfused. The absolute rise in platelet count is also variable. A typical transfusion of six platelet concentrates can be expected to raise the platelet count by approximately 50,000 to 100,000 platelets/

Clinical Use ofActivated Recombinant Factor VII

Evidence is growing in support of rFVIIa use to correct some factor deficiencies and clinical bleeding caused by consumptive coagulopathies, such as those associated with massive transfusions in association with trauma and surgery.

Complications of Blood Component Therapy

Transfusion of blood and blood components is safe and efficacious when used for the correct indications. However, transfusion is not without risk. There are multiple potential side effects associated with transfusion. These can be divided into (1) metabolic derangements, (2) immunologic reactions, (3) infectious complications, (4) volume overload, and (5) pulmonary complications. There are also special considerations for transfusion of large amounts of blood products over a short period of time, such as in massive transfusion.

Metabolic Derangements

Metabolic complications of transfusion therapy are typically seen in the context of transfusion of large amounts of blood products, or transfusion of older blood products, or both. Most common are hypocalcemia,

hyperkalemia, hypokalemia, and hypothermia.

The lethal triad (Figure 4-1) consists of the interrelation of acidosis, hypothermia, and coagulopathy, and has been recognized as a significant cause of death for patients with trauma and/or massive blood loss. Successful resuscitation depends on breaking the cycle. Hypothermia, defined as core temperature $<35^0$C, is a constant problem in trauma, and may be present in a patient with otherwise normal vital signs. Hypothermia is seen in 50% of trauma patients at initial presentation. Some populations are more susceptible to hypothermia, particularly elderly patients, frail patients, pediatric patients, burn patients, diabetics, and those with thyroid dysfunction. Hypothermia results in impaired platelet function, inhibition of clotting factors, and inappropriate activation of clot breakdown. Among other rewarming strategies, warmers for fluids and blood products being infused are important, because room temperature fluids contribute significantly to hypothermia.

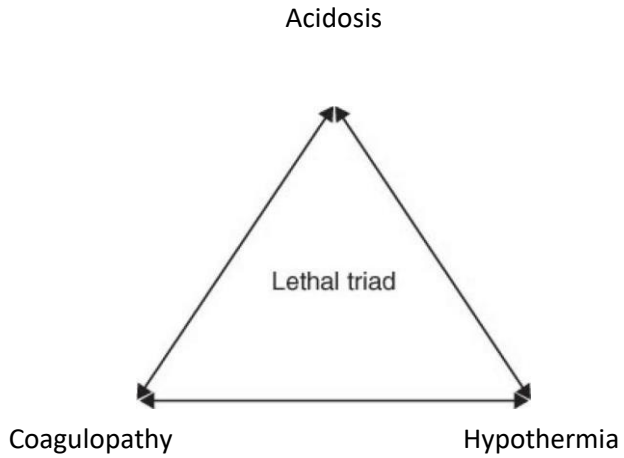

Figure 4-1 The Lethal Triad.

Acidosis, pH < 7.35, results in poor tissue perfusion because of decreased cardiac output. Decreased cardiac output is already present in bleeding trauma patients, independent of acidosis, from decreased preload (due to blood loss) and peripheral vasoconstriction. Decreased cardiac output results in overall tissue hypoperfusion and anaerobic metabolism, resulting in more lactic acid production and a further decrease in the pH.

Multiple factors affect coagulopathy: ongoing blood loss, cofactor consumption, dilutional coagulopathy due to intravenous (IV) fluid administration, and inadequate replacement of clotting factors. Additionally, coagulation cofactors are progressively inhibited by decreasing pH and hypothermia. Coagulopathy results in continued bleeding in trauma patients and is associated with a 4-fold increase in mortality.

The lethal triad begins and ends with bleeding, so the first step is to apply direct pressure to sites of bleeding. Take steps to maintain euthermia, and be aware that exposed patients are constantly losing heat. Resuscitate bleeding patients in a balanced fashion with blood products. Crystalloid solutions are low in pH (5.5 for normal" saline), contribute to dilutional coagulopathy, and are often administered cold. Thus, crystalloid use should be minimized and infused through a warmer whenever possible. By addressing all three factors in the lethal triad simultaneously, the cycle can be broken and the patient salvaged.

Immunologic Transfusion Reactions

Although ABO and Rh compatibility testing and cross-matching can obviate some of the more serious transfusion reactions, minor untested and unidentified antigens and antibodies can still precipitate immunologic reactions (Table 4-6). Immunologic transfusion reactions are (1) febrile reactions, (2) acute and delayed hemolytic transfusion reactions, (3) thrombocytopenia, (4) anaphylactic shock, (5) urticaria, (6) graftversus-host disease, and (7) immune suppression.

TABLE 4-6 Management of Transfusion Reactions

Reaction		Management
Minor transfusion reaction	Fever, rash, urticaria	Observation, antihistamines
Major transfusion reaction	Fever, chills, hypotension, bleeding in previously dry areas, hemoglobinuria, decreased urine output	Immediate cessation oftransfusion; the unit ofblood should be sent back to the blood bank for recrossmatch, volume expanders, pressors (mannitol, Lasix)

Febrile reactions are the most common immunologic transfusion reactions. These reactions typically occur as a result of antileukocyte antibodies. Symptoms and signs include fever, chills, and tachycardia. Hemodynamic instability can occur in severe cases. Patients with minor reactions can be managed expectantly, and the therapy is largely supportive. The transfusion should be stopped. Pretreatment with aspirin, antipyretics, and antihistamines can prevent future reactions. Alternatively, transfusion of leukocyte-reduced red cells can also be effective.

Acute hemolytic reactions can vary in severity from minor to catastrophic. Most hemolytic reactions occur as a result of a clerical error and transfusion of ABO-mismatched blood. They can begin quickly with administration of as little as 50 ml. of donor blood. Symptoms include sensation of hot or cold, flushing, chest pain, and low back pain. Signs include fever, hypotension, tachycardia, hematuria, hemoglobinuria, bleeding, and possibly acute renal failure. Successful management of hemolytic transfusion reactions rests on early diagnosis and prompt intervention. The transfusion must be immediately stopped. The remaining transfusion blood and a sample of the patient's blood are returned to the laboratory for retyping and cross-matching. Transfused and patient blood is also sent for culture to differentiate from contamination. Care is primarily supportive. Hemodynamic instability is treated with volume expansion and pressors, if necessary. Some clinicians recommend administration of mannitol and/or loop diuretics, such as furosemide, to maintain urine output. Severe renal failure may require hemodialysis.

Graft-versus-host disease occurs when immunosuppressed patients receive donor leukocytes in blood component therapy. These cells are unrecognized as foreign cells by the recipient, and they mount an immune response against recipient tissues. Onset of symptoms is often delayed for weeks and includes fever, rash, liver dysfunction, and diarrhea. This can be prevented by using leukocyte-reduced red cells and/or irradiated red cells.

Transmission of Infectious Agents

Transmission of infectious agents following transfusion is rare but not zero. Blood can transmit infections caused by bacteria, viruses, and parasites.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) occurs in about 1 out of every 5,000 transfusions. It can occur with transfusion of any blood component, but is most common with transfusions that contain plasma, such as FFP or platelets. TRALI is characterized by noncardiogenic pulmonary edema following transfusion. The inciting event in TRALI is unknown, but likely immunologic. Onset of pulmonary edema and respiratory insufficiency is generally within 1 to 2 hours of beginning the transfusion, but it can happen up to 6 hours after a transfusion. Recently, a delayed TRALI syndrome has been recognized, in which onset may be delayed up to 72 hours after transfusion. Treatment ofTRALI is supportive.

SUGGESTED READINGS

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Sample Questions

Questions

Choose the best answer for each question.

1. A 21-year-old male patient arrives to the trauma bay with multiple gunshot wounds. After initial resuscitation, the patient is taken to the operating room for exploratory laparotomy. Within the next 4 hours, the patient receives more than 10 units of packed RBCs and 2 g of IV calcium. The patient continues to have diffuse oozing from surgical sites and venous access sites. Labs are remarkable for an aPTT of 100 sec, INR of 5, and a platelet count of 20,000. What is the MOST likely cause of this patient coagulopathy?

   A. Acute hemolytic transfusion reaction

   B. Dilutional coagulopathy

   c. Antiplatelet medication use at home

   D. Citrate-induced hypocalcemia

   E. Von Willebrand disease

2. A 55-year-old woman is scheduled for a craniotomy to remove a brain tumor. She has a history of hypertension and hypercholesterolemia, and she underwent coronary artery angioplasty with a stent placed 6 months ago. Current medications include enalapril, pravastatin, and clopidogrel. [A]Nhich one of the following tests would most likely be prolonged?