TRANSFUSION THERAPY IN ACQUIRED COAGULOPATHIES

John E. Humphries, MD

Maintenance of hemostasis is a finely tuned balance involving blood vessels, vascular endothelial cells, platelets, and a large number of plasma proteins. Deficiency or dysfunction of any of the procoagulant mechanisms predisposes the patient to either spontaneous hemorrhage or excess blood loss associated with trauma or surgical procedures. Inherited disorders of hemostasis typically involve an abnormality of a single coagulation factor or an isolated platelet function defect. By contrast, acquired disorders of hemostasis are most often complex, involving the deficiency of multiple coagulation factors, as well as platelet function defects and thrombocytopenia. This review discusses transfusion therapy of the common acquired coagulopathies, including liver disease, uremia, acute disseminated intravascular coagulation, post-cardiopulmonary bypass, massive transfusion, and warfarin overdose.

BLOOD PRODUCTS

Over the years the menu of blood products available to the clinician to repair hemostatic disorders has expanded greatly. Where once whole blood was the product of choice, now the subdivision of whole blood into components, including packed red cells, plasma, cryoprecipitate, and concentrates of single coagulation factors, has permitted more efficient utilization of blood resources (Table 1). However, such subsetting requires that clinicians have greater knowledge of the specific contents of and appropriate uses of these components and also requires that the clinician understand each individual patient's specific defect or defects in hemostasis to prevent hemorrhage.

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From the Departments of Internal Medicine and Pathology, University of Virginia Health Sciences Center, Charlottesville, Virginia

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<table>
<thead>
<tr>
<th>Products</th>
<th>Red Blood Cells</th>
<th>Platelets</th>
<th>Fibrinogen</th>
<th>II</th>
<th>V</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
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*Each platelet concentrate made from whole blood also contains approximately 50 mL of plasma, and each single donor apheresis concentrate ordinarily contains 200–400 mL of plasma. This plasma contains normal amounts of fibrinogen and most coagulation factors. Some decrease in factors V and VIII will have occurred. + or – indicates whether a significant quantity of each of the listed components is (+) or is not (−) provided by the product.

Whole Blood

Whole blood, by definition, contains all the components of normal blood including the red cells, platelets, and coagulation factors. However, with storage of whole blood several functional components are lost. Most rapidly, within 1 to 2 days, platelet function becomes severely impaired, rendering the product less than optimal for the correction of complex coagulation disorders, such as occurs with von Willebrand disease, and providing inadequate support for correction of massive transfusion. Three days after 10 days of storage, the whole blood still retains up to 50% of factor V activity. After 10 days of storage, the whole blood has become an increasingly rare product in the blood banks in the United States, and therefore it is rarely available for the clinician to use. Whether whole blood is clinically useful in certain settings, such as post-cardiopulmonary bypass or massive transfusion remains controversial. 

Platelets

One unit of platelets is derived from a unit of whole blood by centrifugation. Platelet concentrates are stored at 2°C to 4°C for up to 5 days. An average intravascular platelet count of 5 to 6 x 10^9/L is required for an average intravascular platelet count of 5 to 6 x 10^9/L. An initial dose for an adult should be 1 unit per kg of body weight, with a maximum of 3 x 10^11/L. Each unit of platelets is equivalent to 1 unit of platelets obtained from 1 unit of whole blood, and contains a full therapeutic dose of platelets (greater than 3 x 10^11/L). The use of platelets in chronic anaemia is discussed by Dr. Koss in this issue.
for immunologic compatibility with an alloimmunized patient. Platelet concentrates are useful in the treatment of bleeding due to thrombocytopenia or platelet dysfunction. Guidelines for platelet transfusions are given in Table 2. Platelet transfusion therapy is discussed by Dr. Crowley elsewhere in this issue.

Plasma

Fresh frozen plasma is collected from a unit of whole blood after the red cells and platelets have been removed. This plasma is frozen at -18°C or below within 6 hours of collection and may be stored for up to 1 year. Although this product contains normal levels of all the procoagulants, these coagulation factors are not concentrated. Therefore, the ability of the clinician to use this product to increase the circulating levels of any given coagulation factor by more than 20% to 30% is limited by the risk of circulatory volume overload. Specific concentrates of coagulation factors have become available for the treatment of some of the inherited coagulation factor disorders, including factor VIII and factor IX. Concentrates of the vitamin K-dependent coagulation factors (II, VII, IX, and X) are also available, and factor VII and factor XI concentrates are under investigation.

<table>
<thead>
<tr>
<th>Table 2. GUIDELINES FOR BLOOD PRODUCT TRANSFUSION</th>
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<tr>
<td><strong>Fresh Frozen Plasma</strong></td>
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<tr>
<td>1. Multiple coagulation factor deficiencies with prothrombin time &gt; 16 to 18 seconds and/or aPTT &gt; 55 seconds and either active bleeding or planned surgical procedure*</td>
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<td>2. Previously documented deficiency of factor V or factor XI and either active bleeding or planned surgical procedure†</td>
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<td>3. Correction of warfarin anticoagulation with active bleeding or surgery planned within 6 hours*</td>
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<td>4. Thrombotic thrombocytopenic purpura or hemolytic uremic syndrome</td>
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**Cryoprecipitate**

- Documented deficiency of fibrinogen (< 100 mg/dL) and either active bleeding or planned surgical procedure
- Documented deficiency of factor XIII and either active bleeding or planned surgical procedure
- Active bleeding or a planned surgical procedure in a patient with uremia and a prolonged bleeding time§

**Platelets**

1. Prophylactic—platelet count < 5–20 x 10^9/L
2. Active bleeding or planned surgical procedure and either platelet count < 80 x 10^9/L or bleeding time > 7.5 minutes
3. Documented platelet function disorder and active bleeding or planned surgical procedure
4. Active bleeding with a platelet count < 100 x 10^9/L and either retinal or intracerebral hemorrhage or following cardiopulmonary bypass or following massive transfusion (> 1 blood volume transfused within 24 hours)

*Different reagents and coagulation instruments may have significantly different sensitivity to single or multiple factor deficiencies, so specific limits for prothrombin time or aPTT prolongation in terms of seconds or ratios of patient:control are only guidelines.
†Replacement of factors II, VII, and X, prothrombin concentrates or plasma may be used. For replacement of factor VIII or IX, specific single factor concentrates are available. Factor XI concentrates may become available in the near future.
§Platelet concentrates contain all the vitamin K-dependent factors and may be preferable to the administration of fresh frozen plasma.

**Side Effects of Blood Product Administration**

Blood product administration has been associated with a number of well-recognized adverse effects. These include the transmission of viruses, hemolytic reactions, and allergic reactions. Other potential risks include circulatory volume overload and hypothermia with massive transfusion, bacterial contamination, and graft-versus-host disease. With the routine screening of blood donors combined with testing for hepatitis and retroviruses, the risk of virus transmission has decreased greatly, but cases still occur. The introduction of solvent/detergent treated products may further decrease these risks. The danger of virus transmission combined with the risks of hemolytic transfusion reactions and allergic reactions mandates that clinicians continue to minimize patient exposure to blood products. The adverse effects of blood transfusion are discussed by several authors in Transfusion Medicine II.

**NONTRANSFUSIONAL HEMOSTATIC AGENTS**

Nontransfusional therapy of hemostatic defects has increased greatly in recent years (Table 3). These agents may often be sufficient to treat bleeding with...
Table 3. HEMOSTATIC DRUGS

<table>
<thead>
<tr>
<th>Desmopressin</th>
<th>Vitamin K</th>
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<tr>
<td>Epsilon-aminocaproic acid</td>
<td>Conjugated estrogens</td>
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<tr>
<td>Tranexamic acid</td>
<td>Erythropoietin</td>
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<td>Aprotinin</td>
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out the use of blood products or may be used as supplements to transfusion therapy.

Desmopressin Acetate (DDAVP)

1-Deamino-8-D-arginine vasopressin is a synthetic analog of vasopressin that has been shown to induce the release of stores of von Willebrand factor from vascular endothelial cells. Additional hemostatic mechanisms independent of von Willebrand factor release may be involved in the hemostatic effects of DDAVP, but these remain to be clarified. This agent has shown efficacy in the treatment or prevention of bleeding in patients with some types of von Willebrand disease, mild hemophilia A, and some types of inherited platelet function defects. Adverse effects attributed to DDAVP include facial flushing and minor alterations in the blood pressure. Uncommon events include significant hyponatremia and thrombosis. The use of DDAVP in congenital coagulopathies is discussed by Dr. Lusher in this issue.

Antifibrinolytic Agents

Tranexamic acid and epsilon-aminocaproic acid are analogues of lysine that are capable of inhibiting fibrinolysis in vivo. The proposed mechanism of action is the inhibition of plasminogen binding to fibrin. This prevents efficient activation of plasminogen to plasmin on the fibrin clot, thereby leading to delayed lysis of the thrombus. These agents have demonstrated efficacy in the prevention of bleeding in patients with hemophilia and von Willebrand disease undergoing dental extractions. There is also some evidence that they may decrease hemorrhagic risk in patients with severe thrombocytopenia. Side effects are usually minor and include gastrointestinal upset, diarrhea, and headache. Rarely, thrombosis has been reported.

Aprotinin

Aprotinin is a naturally occurring protease inhibitor purified from bovine lung. In vivo, it appears to have its greatest activity against plasmin, thereby inhibiting fibrinolysis, with a lesser inhibition of kallikrein. Kallikrein is involved in the intrinsic pathway of coagulation and may also directly activate plasminogen to plasmin. Aprotinin has been used extensively in cardiopulmonary bypass patients. The proposed effects of aprotinin in these patients include preservation of platelet function and inhibition of fibrinolysis. Its use in this setting has been associated with a significant decrease in post-bypass bleeding. The only significant adverse effect of aprotinin is a rare allergic reaction, occurring in fewer than 0.1% of patients.

Vitamin K

Vitamin K, one of the fat-soluble vitamins, serves as a cofactor for the intrahepatic modification of certain coagulation factors (II, VII, IX, and X). In the absence of vitamin K, these factors possess greatly decreased function. Hospitalized patients, particularly those whose oral nutrition intake is poor and are receiving antibiotics, are prone to develop clinically significant vitamin K deficiency, with decreases in the circulating levels of the vitamin K-dependent coagulation factors. Patients receiving warfarin therapy become similarly hypocoagulable. For either group of patients parenteral administration of vitamin K (5 to 10 mg) should lead to a shortening of the prothrombin time by 6 to 8 hours. Smaller doses may be given to patients over-anticoagulated to reduce their degree of anticoagulation, but without normalizing the prothrombin time. Rapid intravenous administration of vitamin K has been associated with hypertension and anaphylaxis; therefore, infusion should be given very slowly. Vitamin K may also be given subcutaneously, but it may produce significant skin reactions. Oral administration is associated with variable absorption and should not be relied on for emergent correction of vitamin K deficiency, but it may be useful for prophylaxis in hospitalized patients.

Conjugated Estrogens

Based on observations of improvements in hemostasis in women with von Willebrand disease receiving oral contraceptives, estrogens have been administered to patients with a variety of inherited and acquired hemostatic defects. Livio et al gave parenteral conjugated estrogens to patients with uremia and observed significant shortening of the bleeding time, which persisted for up to 14 days. The precise mechanism(s) of action remain unclear. Side effects of short courses of estrogens are minor and include nausea, vomiting, and hot flashes.

Erythropoietin

Erythropoietin is the hormone from the kidney critical to the production of red blood cells. Patients with chronic renal failure develop anemia predominantly owing to acquired erythropoietin deficiency. The anemia of renal failure appears to play an important role in the hemostatic defect observed in uremic patients. Erythrocytes may contribute to hemostasis by two different mechanisms: (1) by facilitation of margination of platelets to the surface of blood vessels, where they can participate in hemostasis; and (2) by contributing adenosine diphosphate, an important platelet agonist. The bleeding time as a measure of platelet function may become prolonged when the hematocrit falls below 26%. Correction of the hematocrit to 26% to 30% by either transfusion or administration of erythropoietin leads to a shortening of the bleeding time.

LIVER DISEASE

Hemostatic Disorder

The liver is the site of production of almost all coagulation factors and also serves to clear activated coagulation factors and fibrinolytic components from the
circulation. Depending on the severity and duration of liver disease, a patient may have an isolated deficiency of coagulation factors or may have a complex disorder including factor deficiencies, hyperfibrinolysis, thrombocytopenia, platelet dysfunction, and even disseminated intravascular coagulation. Therefore, laboratory assessment is essential for a patient with liver disease who presents with bleeding or in whom surgery is planned. The most commonly employed screening tests include the prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and bleeding time.

Significant decreases in the circulating levels of coagulation factors produce prolongations of both the PT and aPTT. Note that although much effort has been made in the development of a universal system for standardizing the PT system for the assessment of degree of oral anticoagulation, no such standardization exists for the understanding of PT or aPTT prolongations from any other cause, including liver disease. Therefore, caution must be exercised in the interpretation of published reports on the relation of a certain degree of PT or aPTT prolongation to the risk of bleeding. The international normalized ratio, as currently derived, is not an appropriate method for translating these published recommendations into general use. For example, in the study by McVay and Toy on the risk of bleeding with liver biopsy in patients with coagulation abnormalities owing to underlying liver disease, it is noted that liver biopsy may be safely performed in patients with PTs less than 1.5 times the midpoints of the normal range (approximately 18 seconds). However, the degree of PT prolongation observed in patients with liver disease will be very dependent on the reagents and machinery used to perform the PT, and a significant variation will likely exist between different laboratories and hospitals depending on the sensitivity of the reagents to coagulation factor deficiencies, analogous to the differences observed for warfarin-induced anticoagulation.

Patients with cirrhosis frequently have mild to moderate thrombocytopenia, mostly due to hypersplenism. Platelet function may also be impaired, although the specific etiology of the defect remains unclear. Evidence of increased fibrinolysis can often be detected in patients with cirrhosis. This may reflect primary fibrinolysis related to a decrease in the clearance of tissue-type plasminogen activator in combination with decreased hepatic synthesis of α1-antiplasmin, the primary inhibitor of plasmin. Alternatively, bleeding may occur owing to increased fibrinolysis secondary to low-grade disseminated intravascular coagulation.

Therapy

Patients with liver disease commonly have decreased circulating levels of coagulation factors. Because defective gamma carboxylation of the vitamin K-dependent factors (II, VII, IX, and X) may contribute to the coagulopathy, a trial of parenteral vitamin K (10 mg/day for 3 days) may produce some shortening of the PT and aPTT and should be considered before administration of blood products for the correction of the coagulopathy.

Few studies have been published on the optimal approach to the correction of coagulation factor deficiencies in patients with liver disease. Although the use of fresh-frozen plasma has been advocated for this purpose, the amount of plasma to be infused to provide a significant degree of PT correction is quite large, 15 to 20 mL/kg (4 to 8 units in an average adult). Even with large amounts of plasma, however, correction of the PT prolongation may not be achieved in all patients. In addition, correction of the PT is often very temporary owing to the short half-life of factor VII (5 to 6 hours), necessitating further plasma infusions in 4 to 6 hours. Volume overload may thus limit the efficacy of this therapeutic approach. Some have achieved greater correction of the PT using fresh-frozen plasma in combination with prothrombin complex concentrates (see Table 1) or factor VII–enriched prothrombin complex concentrates. Concern remains, however, regarding contamination of these concentrates with small amounts of activated factors II, VII, IX, and X, which might convey a risk of thrombosis or disseminated intravascular coagulation, particularly in patients with liver disease.

The routine provision of small amounts of fresh-frozen plasma (for example, 2 units) for minor bleeding or prior to procedures in patients with liver disease would not be expected to produce a significant increase in any of the depleted coagulation factors, and thus should not be expected to correct the PT or provide any improvement in hemostasis. In the absence of bleeding or a planned surgical or invasive procedure, correction of laboratory abnormalities is, of course, not indicated; however, the approach to patients requiring minor invasive procedures remains unclear. The recent retrospective study by McVay and Toy suggests that a moderate degree of deficiency of coagulation factors in patients with liver disease (PT up to 1.5 times the midpoint of the normal range) is not associated with increased bleeding after liver biopsy. Although this suggests that minor coagulation abnormalities need not be corrected prior to invasive procedures, definitive recommendations might best be made based upon prospective studies, which include determination of coagulation factor levels in addition to the PT and aPTT.

No studies have been published on the need for correction of the mild thrombocytopenia and platelet dysfunction often observed in patients with severe liver disease. However, in the patient with a platelet count less than 80 × 10^9/L or a prolonged bleeding time and platelet-type bleeding in whom a major operation is planned, use of platelet concentrates would appear reasonable. The expected increment in the postinfusion platelet count might be blunted in cirrhotic patients owing to hypersplenism and increased consumption related to low-grade disseminated intravascular coagulation. DDAVP, which has been shown to shorten the bleeding time in patients with cirrhosis, might also be considered.

Primary hyperfibrinolysis, owing to a decrease in the clearance of tissue-type plasminogen activator (t-PA) and decreased synthesis of the primary inhibitor of plasmin, α1-antiplasmin, is sometimes observed in patients with cirrhosis. Although plasma infusion might produce a small increase in α1-antiplasmin and plasminogen activator inhibitor-1, the primary inhibitor of t-PA, a more direct approach would be the administration of an antifibrinolytic drug, such as tranexamic acid or epsilon-aminocaproic acid. However, caution must be used if the patient has evidence of disseminated intravascular coagulation, because inhibition of fibrinolysis without attention to the ongoing activation of coagulation may lead to organ dysfunction related to microthrombus formation and persistence.

UREMIA

Hemostatic Disorder

Patients with significant renal failure commonly develop impaired hemostasis. The defect appears to be multifactorial and includes the compo-
Therapy

The platelet function defect appears to be primarily mediated by elevated levels of uremic retention products, such as guanidinosuccinic acid and phenols. Therefore, administration of platelet concentrates provides only very temporary assistance, because the infused platelets quickly become poisoned. Removal of these toxins by frequent hemodialysis (three or more times per week), however, does have a beneficial effect on platelet function, but correction of the hemorrhagic defect is incomplete. In addition, heparin administration during hemodialysis may increase the risk of bleeding, and it may lead to significant thrombocytopenia in uremic patients. In patients actively bleeding or at very high risk of bleeding, dialysis may be performed with citrate or prostacyclin, instead of heparin.

In 1980 Janson et al described correction of the bleeding time in eight patients with uremia following the infusion of cryoprecipitate. Since then, other case reports have documented similar improvement in hemostasis with cryoprecipitate. However, Triulzi and Blumberg showed in a retrospective review that responses to cryoprecipitate are variable, being absent in some and only partial in others. Therefore, the role of cryoprecipitate in the treatment or prevention of bleeding in uremic patients remains controversial.

Certain pharmacologic alternatives to blood products have been shown to be efficacious in the treatment and prevention of bleeding in uremia. In 1983 Mannucci et al demonstrated shortening of the bleeding time and improvement in hemostasis following the administration of DDAVP. The onset of action was rapid (within 2 hours) but short-lived, lasting no more than 12 hours. This finding has since been confirmed by others. The specific mechanism or mechanisms by which DDAVP improves hemostasis in uremia remains unclear and, unfortunately, the effects elicited by DDAVP are temporary; with repeated doses, its effects may become blunted. Thus, although it may be very useful in the treatment of acute bleeding, when more prolonged hemostasis is necessary it may be insufficient by itself. Conjugated estrogens have been administered to patients with uremia, with a resulting decrease in the bleeding time beginning as early as 6 hours after the first dose, and if given daily for 5 days, the effect may last up to 2 weeks. Therefore, given the risks involved in the administration of blood products such as cryoprecipitate, DDAVP and estrogens should be considered first-line therapies, and only if contraindications to these drugs are present or if they fail to achieve hemostasis should cryoprecipitate be administered.

Increasing the hematocrit with the administration of erythropoietin also improves hemostasis, but patients may require several weeks to respond. Therefore, infusion of packed red cells may be useful if this hemostatic effect is needed sooner.

In summary, the key elements in the prevention of bleeding in uremic patients are regular dialysis, maintenance of the hematocrit above 25% with erythropoietin, and avoidance of antiplatelet drugs. For the treatment of acute bleeding or in preparation for an invasive procedure, DDAVP should be given.

Cryoprecipitate may be used when DDAVP is ineffective or contraindicated. For situations in which hemostasis is required for more than 12 hours, a course of estrogens should be administered.

ACUTE DISSEMINATED INTRAVASCULAR COAGULATION

Hemostatic Disorder

Many years have passed since its initial description and numerous reviews of the topic, have been published, however, but disseminated intravascular coagulation (DIC) remains a confusing and complex disorder. Part of the confusion arises from the heterogeneity of diseases that may lead to DIC, from the rapidly changing laboratory parameters in individual patients with DIC and from the lack of definitive clinical trials on the optimal therapeutic approach to patients with DIC. This discussion focuses on acute DIC, which presents a combination of microthrombosis and diffuse microvascular bleeding, rather than on chronic or compensated DIC, which more often presents with predominantly thrombotic events.

The hemostatic disorder in patients with DIC is multifactorial. By definition, there is activation of coagulation with the generation of thrombin, either through the intrinsic or extrinsic coagulation pathways, leading to consumption of multiple procoagulant factors. Platelets also become activated and consumed leading to thrombocytopenia. Secondly, in response to the diffuse formation of fibrin, the fibrinolytic system is activated. The plasmin thus generated may digest not only fibrin, but also fibrinogen, factors V and VIII, and platelet surface receptors. This leads to further procoagulant factors, depletion, hypofibrinogenemia, and platelet dysfunction. In addition, large amounts of fibrin and fibrinogen degradation products generated may interfere with the formation of the normal fibrin clot and with platelet aggregation. In any given patient, the relative contributions of each of these possible defects may be different and may change rapidly over time during the course of the patient's illness. Therefore, frequent laboratory assessment of the PT, aPTT, fibrinogen level, and platelet count are needed to monitor the hemostatic defects and to monitor the efficacy of any interventions.

Table 4. CONTRIBUTORS TO IMPAIRED HEMOSTASIS IN UREIA

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<tr>
<th>Platelet function defects</th>
<th>Decreased adhesion</th>
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<tr>
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<td>Decreased platelet</td>
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<td></td>
<td>Membrane procoagulant</td>
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<tr>
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<td>Activity</td>
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<td>Decreased dense grain</td>
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<td>Thromboxane A2</td>
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<td>Generation</td>
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<td>Increased endothelial</td>
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<td>Cell Prostacyclin</td>
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<td>Increased endothelial</td>
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<tr>
<td></td>
<td>Derived Relaxing factor</td>
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<td>(Nitric oxide)</td>
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Anemia (hematocrit < 25%)  
Thrombocytopenia  
Coagulation factor deficiencies
**Therapy**

The most important interventions in the treatment of acute DIC do not involve specific hemostatic therapies, but rather the rapid and effective treatment of the disease underlying the development of DIC and prompt attention to intravascular volume repletion and maintenance of adequate oxygenation. In the patient with laboratory abnormalities of hemostasis, but without bleeding or any planned surgical intervention, correction of the laboratory abnormalities is not necessary, particularly if the underlying disease causing DIC is being successfully addressed. Should bleeding develop or if a surgical or invasive procedure is planned, however, some attempt at improving hemostasis is necessary. In the patient in whom the underlying disease is being effectively treated and the DIC laboratory parameters are stable or improving, correction of thrombocytopenia, hypofibrinogenemia, and coagulation factor deficits with platelet concentrates, fresh-frozen plasma, and cryoprecipitate is appropriate. By contrast, in the patient with active acute DIC with worsening laboratory abnormalities, many authors believe that the administration of blood products, particularly those containing fibrinogen, may "fuel the fire." No currently published prospective clinical trials exist to support or refute this recommendation, however. Because antithrombin III becomes depleted in patients with acute DIC, concentrates of antithrombin III have been administered. Preliminary reports suggest that normalization of the antithrombin III level using antithrombin III concentrates shortens the duration of DIC and may improve survival, however, further studies are needed.

**POST-CARDIOPULMONARY BYPASS**

**Hemostatic Disorder**

Patients having cardiac surgery are placed on cardiopulmonary bypass. The use of this extracorporeal circulation requires high-dose heparinization (3 to 4 U/mL) and introduces a decrease in both platelet number and function. In addition, owing to both hemodilution and consumption, there may be some decrease in the concentration of procoagulant factors. For a brief time during and immediately following bypass, evidence of increased fibrinogen can also be detected. In patients undergoing their first cardiac operation and having either coronary artery bypass grafting or single valve replacement, the frequency of postoperative bleeding is low, approximately 3% to 5%. Post-bypass diffuse microvascular bleeding occurs more frequently in patients having repeat or complex operations. The most common etiology appears to be a platelet function defect, although debate continues regarding the precise mechanism for this dysfunction. Proposed causes include plasmin-mediated degradation of platelet membrane receptors and partial platelet activation with alpha granule secretion during exposure to the extracorporeal circuit. Other potential contributors to platelet dysfunction are the drug-related effects of aspirin and heparin, and circulating fibrin degradation products. In addition, insufficient or possibly excess neutralization of heparin with protamine may aggravate the bleeding tendency.

**MASSIVE TRANSFUSION**

**Hemostatic Disorder**

Many patients who receive greater than 1 blood volume replacement within 24 hours may develop a laboratory as well as clinical coagulopathy. Provided the cause of massive blood loss requiring massive transfusion has been appropriately identified and repaired, it appears that most patients can tolerate the replacement...
of 1.5 to 2 blood volumes with crystalloid or colloid combined with red cells before a clinical hemostatic disorder manifests itself.98 Platelet number and coagulation factor concentrations both decrease during this massive transfusion; however, only a portion of these decreases may be attributable to the expected hemodilution.21, 24, 56 Duration of shock or hypotension appear to be important determinants of the development of coagulation abnormalities and bleeding in patients receiving massive transfusion.58 Other factors, such as physiologic consumption, DIC, and hypothermia, may also contribute.36 Pre-existing liver or kidney dysfunction will aggravate the coagulopathy.

Typically, patients who receive massive transfusion will become thrombocytopenic; they will have a decreased fibrinogen level and show prolongation of the PT and aPTT.97, 102 Most often, bleeding appears to be related to thrombocytopenia (less than 50 x 10^9/L).21, 24, 85 Less often, bleeding may be caused by coagulation factor deficiencies, such as fibrinogen less than 50 mg/dL or the PT or aPTT greater than 1.5 to 1.8 times the control or mean of the normal range.21, 97 Unfortunately, the correlation between lesser prolongations of the PT and aPTT with bleeding is poor.137

Therapy

In patients with shock owing to massive blood loss, the immediate goals are to restore circulating blood volume and oxygen-carrying capacity. These aims can be met with large volumes of crystalloids or colloids, combined with packed red cells, once the hematocrit drops below 25%. Most patients tolerate the replacement of up to 1½ to 2 times their blood volume without the development of a clinical hemostatic disorder.98 In the past, the administration of fresh whole blood or stored whole blood has been advocated.23, 120 The former product is very difficult to obtain in large quantities on short notice, and the latter product contains dysfunctional platelets and decreased levels of factors V and VIII. All attempts to create formulas for the supplementation of packed red cell transfusions with either platelet concentrates or fresh-frozen plasma have failed to demonstrate any efficacy. Therefore, prophylactic addition of plasma, platelets, or cryoprecipitate with any number of red cell products in the course of massive transfusion does not appear to be warranted.24, 54, 80, 97, 109 Should a patient develop bleeding, then the laboratory assessment, including PT, aPTT, fibrinogen, bleeding time, and platelet count, should provide useful information for guiding therapeutic intervention.85, 110, 135

Because the disorders leading to the requirement for massive transfusion are varied, no universal guidelines can be given for the treatment of all patients. Thrombocytopenia is the most common cause of bleeding following massive transfusion; therefore, in an emergency, administration of platelet concentrates would be appropriate first-line treatment.85, 94, 102 Such therapy also provides some coagulation factor replacement owing to the infusion of plasma in which the platelets have been stored. Remember that acute DIC owing to shock or sepsis may also develop in this very ill patient population.

WARFARIN OVERDOSE

Hemostatic Disorder

Warfarin administration leads to depletion of functional levels of the vitamin K-dependent coagulation factors (II, VII, IX, and X). This is detected by a pro-longed PT or elevated international normalized ratio. The aPTT may also be prolonged. The platelet count and bleeding time should be normal. The degree of anticoagulation at which an individual patient becomes at excess risk of hemorrhage only partially depends on the PT or international normalized ratio. Other important variables include patient age, history of stroke or gastrointestinal bleeding, and severe anemia.76

Therapy

Patients receiving warfarin may become over-anticoagulated for a variety of reasons. Should this lead to hemorrhage, then prompt reversal of anticoagulation becomes necessary. Patients on warfarin, but within the therapeutic range, may need correction of the PT when bleeding develops or if emergency major surgery is planned. Simple excess prolongation of the PT or elevation of the international normalized ratio without bleeding and without any planned surgical or invasive procedures may be treated by simply withholding warfarin. If the patient has additional risk factors for hemorrhage or mild bleeding symptoms, parenteral vitamin K should be administered. Depending on the degree of anticoagulation, doses of vitamin K may range from 0.5 to 5 mg.121 Correction of the PT using vitamin K requires at least 4 to 6 hours.14 Therefore, if significant bleeding is present or a surgical or invasive procedure is planned within 6 hours in a patient receiving warfarin, then prompt reversal of anticoagulation is needed. In addition to the parenteral administration of vitamin K (5 to 10 mg), it will be necessary to replenish the vitamin K-dependent coagulation factors to hemostatic levels (exceeding 20% to 30%) by using blood products.

The only blood products currently available that contain all the vitamin K-dependent coagulation factors are plasma (either fresh-frozen or single donor) and prothrombin complex concentrates.14, 43 A rather large volume of plasma, 1 to 2 L, may be required to increase the levels of vitamin K-dependent coagulation factors to safe hemostatic levels. Also, it will be necessary to follow the PT and international normalized ratio, because correction may be only temporary and treatment may need to be repeated. This may lead to problems with volume overload. The prothrombin complex concentrates permit increasing the concentration of all vitamin K-dependent factors to safe hemostatic levels, without these volume considerations. However, these concentrates often are standardized for their factor IX content and contain variable amounts of the other vitamin K-dependent coagulation factors. In patients with liver disease or a history of prior thromboembolism, there remains some concern regarding the contamination of these concentrates with very small amounts of activated coagulation factors.81 This conveys a small risk of inducing thrombosis or DIC.81 The addition of a small amount of heparin (such as 0.1 to 0.3 unit heparin/unit coagulation factor IX) to the concentrate prior to administration appears to decrease these risks.

SUMMARY

Acquired coagulopathies, such as are observed in patients with liver disease, uremia, and acute disseminated intravascular coagulation, are complex disorders usually involving a combination of deficiency of multiple coagulation factors, platelet dysfunction, and thrombocytopenia. Transfusion of specific blood products, such as fresh-frozen plasma, platelets, and cryoprecipitate, may be effective.
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