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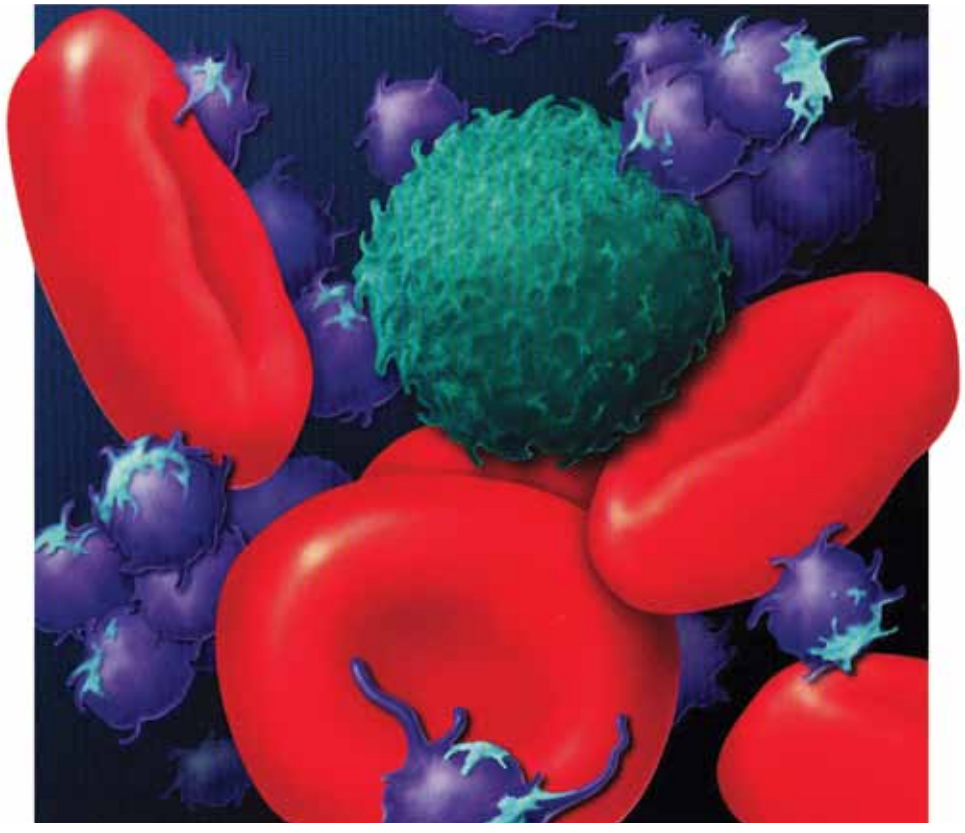
HEMATOLOGY
Board Review Manual



Transfusion Medicine

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

Transfusion Medicine

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Transfusion Medicine

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INTRODUCTION

Transfusion therapy is an essential part of hematology practice, allowing for curative therapy of diseases such as leukemia, aplastic anemia, and aggressive lymphomas. Nonetheless, transfusions are associated with significant risks, including transfusion-transmitted infections and transfusion-related reactions, and controversy remains about key issues in transfusion therapy, such as triggers for red cell transfusions. This article reviews the available blood products and indications for transfusion along with the associated risks and also discusses specific clinical situations, such as massive transfusion.

BLOOD PRODUCTS

WHOLE BLOOD

Whole blood is the product of 1 unit of donated blood plus anticoagulant/preservative, and by definition contains 1 unit of plasma and red cells. Whole blood can be stored for 5 weeks. Although it was the standard product in the past, currently whole blood is rarely used since 1 unit of donated blood can now be fractionated into 1 unit of red blood cells (RBC), 1 unit of platelets, and 1 unit of fresh frozen plasma (FFP). Thus, the use of whole blood for just a single transfusion represents a waste of resources. The one exception is autologous blood donations, which are whole blood units. A summary of available blood products is shown in **Table 1**.

PACKED RED CELLS

The remaining red cell mass after most of the plasma is removed is called the "packed" red cell unit (hematocrit = 70%–80%), and so red cells are often called "packed" red cells, or PRBC. To improve the flow of blood and to provide "nutrients" for the red cells, a preservative is added which reduces the hematocrit to about 60%. The volume of a red cell unit is about 340 mL. In the average adult, 1 unit of RBC raises the hematocrit by 3%. The indications for transfusion of red cells are to increase red cell mass, and thus oxygen delivery, in patients who are compromised by their anemia.

Several randomized trials have helped define the indications for red cell transfusions and justify lower hematocrit thresholds for initiating transfusion. The TRICC trial showed that in critical care patients (30-day mortality, 18.7%–23.3%), a conservative transfusion strategy of waiting until the hematocrit was below 21% had the same outcomes as transfusing at a threshold of 24%.[1] The TRACS trial showed that a hematocrit target of 24% had the same benefit as a target of 30% in patients after cardiac bypass surgery.[2] For patients suffering an acute myocardial infarction, the outcomes were worse with aggressive transfusion at hematocrit of 30% compared to 24%.[3] Finally, the FOCUS trial showed that in older patients (average age 80 years) after hip fracture surgery, transfusions based on symptoms and not a fixed trigger of 30% had the same outcomes but considerable savings in blood products.[4] Based on these trials, patients should be transfused for symptoms and not "numbers." Young patients, especially those with reversible anemias, can tolerate low blood counts and should not be transfused based on an arbitrary number.

PLATELETS

Several types of platelet products exist. One unit of *platelet concentrate* is derived from 1 unit of donor blood. Plateletpheresis from volunteer donors can be used to harvest platelets with the resulting product being called *plateletpheresis platelets.* One unit of single-donor (pheresis) platelets is equivalent to 6 platelet concentrates. Finally, *HLA-matched platelets* are single-donor pheresis units that are from an HLA-matched donor. This product should be ordered only if there is evidence of HLA antibodies (see "Platelet Alloimmunization" below).

The dose of platelets for the average patient is 6 units of platelet concentrate or 1 pheresis unit. In theory 1 unit of platelet concentrate can raise the count by 5 to 7 x 10^9/L, but often this response is blunted by concurrent illness or bleeding. In patients who appear to have a poor response, one can check a platelet count 15 minutes after platelet infusion. No rise or a minimal rise (<2 x 10^9/L) in the platelet

Table 1. Summary of Blood Products

Component	Content	Expected Response	Indications
Red cells	Red cells and preservative	1 unit to raise hematocrit by 3%	Hematocrit <21% Hematocrit <24% if • Acute coronary syndrome • Documented symptomatic anemia Rapid blood loss with >30%–40% of estimated blood volume (>1500–2000 mL) not responding to appropriate volume resuscitation, or with ongoing blood loss
Platelets	Concentrate— from 1 donor unit Pheresis—from 1 donor	1 unit of concentrate raises platelet count 5–10 x 10^9/L 1 pheresis raises platelet count 30–60 x 10^9/L	Platelet count of: <10 x 10^9/L—prophylaxis <20 x 10^9/L before minor procedures (eg, line placement) <50 x 10^9/L before major procedures or if bleeding
Fresh frozen plasma	All plasma proteins	Raises average coagulation factor levels by 5%	INR >1.5 prior to procedure or if bleeding Thrombotic thrombocytopenic purpura As part of therapy for massive transfusions Documented factor deficiency
Cryoprecipitate	Fibrinogen, factor VIII, von Willebrand factor	10 units raises fibrinogen by 100 mg/dL	Fibrinogen <100 mg/dL

count is suggestive of platelet refractoriness, while a good 15-minute response but poor 24-hour count is more suggestive of consumption—fever, sepsis, drug, or splenomegaly—and not refractoriness.

The indication for platelet transfusion depends on the clinical situation. For patients with immune thrombocytopenia, one should not transfuse platelets unless they are having severe bleeding. For stable patients with marrow aplasia from chemotherapy, a cut-off of a morning platelet count of less than 10 x 10^9/L has been shown to be as safe as higher levels for prophylactic transfusions.[5] For patients with active bleeding, the platelet count should be kept above 50 x 10^9/L. Patients with acquired or inherited platelet dysfunction may benefit from transfusion no matter the platelet count.

Platelet Alloimmunization

Patients exposed to transfused white cells with different HLA antigens can develop antibodies to these antigens.[6] Anti-HLA antibodies are common in patients who previously have received transfused blood that is not leukodepleted and in patients who have been pregnant. Since platelets carry class I HLA antigens, they will be rapidly destroyed by anti-HLA antibodies when transfused into these patients. In patients transfused for aplastic anemia or myelodysplasia, as many as 90% will become HLA-immunized. The incidence is lower in patients receiving chemotherapy but still can be as high as 60% to 90%.[7,8] Patients who have developed anti-HLA antibodies can respond to transfused platelets matched for HLA antigens. Unfortunately, some patients will either be a rare HLA type or be so heavily immunized that they will not respond to any platelet transfusion.

The significance of alloimmunization centers on 2 concepts: recognition and avoidance. Patients with HLA antibodies will fail to have an increment of their platelet counts with transfusions. Accordingly, patients who do not have an increase in their count 15 minutes after the transfusion may have HLA antibodies. One can test for the presence of anti-HLA antibodies, although some patients instead have specific antiplatelet antibodies that will not respond to HLA-matched platelets. In patients who have been pregnant or previously transfused and are scheduled to undergo transplant or aggressive chemotherapy, it is wise to test for anti-HLA antibodies in order to plan their transfusion needs. The evidence suggests that transfused white cells are responsible for initiating the anti-HLA response. Trials have shown that giving leukodepleted blood products may reduce the incidence of alloimmunization, so patients who are not HLA-alloimmunized should receive only leukodepleted products.[9]

A difficult problem is bleeding in patients who are refractory to platelet transfusion.[10,11] If patients are demonstrated to have anti-HLA antibodies, one can transfuse HLA-matched platelets.[12] Unfortunately, matched platelet transfusions are not effective in 20% to 70% of these patients. Also, since some loci are difficult to match, effective products may be unavailable. Finally, as many as 25% of patients have antiplatelet antibodies in which HLA-matched products will be ineffective. One can perform platelet cross-matching to find compatible units for these patients, but this may not always be successful. In the patient who is totally refractory to platelet transfusion, consider drugs as an etiology of antiplatelet antibodies (especially vancomycin).[13] Use of antifibrinolytic agents such as epsilon-aminocaproic acid or tranexamic acid may decrease the incidence of minor bleeding, but these are ineffective for major bleeding. "Platelet drips"—infusing either a platelet concentrate per hour or 1 plateletpheresis unit every 6 hours—may be given as a continuous infusion, but there is no evidence that this is helpful.[14]

FRESH FROZEN PLASMA

FFP is made from 1 unit of donated whole blood, with an average volume of 225 mL. One unit of FFP can raise coagulation factor levels by 5% and fibrinogen by 10 mg/dL in the average stable patient. It can take about 20 to 30 minutes to thaw FFP before use, so in situations where rapid FFP use is needed, the blood bank must be informed to "keep ahead" some units. Units of FFP that have been thawed but not used can be stored refrigerated for 5 days to prevent wasting blood products.

The indications for FFP are limited to several situations. These include a documented coagulation defect that can be corrected by a reasonable amount of FFP, such as factor V deficiency and factor XI deficiency, disseminated intravascular coagulation (DIC), reversal of warfarin, and massive transfusions. FFP is also used for the therapy of thrombotic thrombocytopenic purpura.

There is little justification for FFP transfusion in many of the clinical settings in which it is commonly used. For example, FFP is given for minor elevations of the INR in liver disease despite literature showing not only that the INR rise is not reflective of coagulation defects, but also that patients with liver disease may even be thrombophilic.[15] A recent review of FFP use found limited evidence-based indications for its use.[16] Also, several studies have shown that transfusion of FFP is not effective at reversing minor elevations of the INR (1.3–1.8).[17] In a meta-analysis, FFP was associated with increased lung injury and a trend toward increased mortality.[16]

CRYOPRECIPITATE

Cryoprecipitate is produced from 1 unit of FFP that is thawed at 4°C. The precipitate is resuspended with 10 mL of saline or FFP and refrozen for storage. One unit contains at least 150 mg of fibrinogen and 80 units of factor VIII, along with von Willebrand factor. Cryoprecipitate takes about 20 minutes to thaw.

Cryoprecipitate is used to raise the fibrinogen level in patients with DIC or massive transfusion with hemodilution. It is third-line therapy in the treatment of type 1 von Willebrand disease and is second-line therapy in the treatment of patients with other types of von Willebrand disease. Currently, von Willebrand factor concentrates are the preferred replacement product for von Willebrand disease. Cryoprecipitate can be used as a source for factor VIII for hemophiliacs, but the preferred product for these patients is the superpure factor VIII concentrates or recombinant products. Cryoprecipitate can also be used to shorten the bleeding time of uremic patients, but its effectiveness for this is controversial.

GRANULOCYTES

Granulocytes are harvested by leukopheresis of normal donors, with a target yield of 10^{10} granulocytes from each donor. To reach this target, the donors are often "stimulated" with neutrophil growth factors. The harvesting procedure can take 3 hours and is associated with some risks to the donor (eg, citrate toxicity).

The current indications for granulocytes are very limited since the advent of neutrophil growth factors and improved antimicrobials.[18] They can be useful in the neutropenic patient with a documented bacterial infection in whom the leukocyte count is not expected to recover in the near future. Given the difficulty of keeping the count up, these transfusions have been mainly used in treating small children.

SPECIAL BLOOD PRODUCTS

Irradiated Blood Products

Irradiation of blood is performed for only one reason: to prevent transfusion-related graft-versus-host disease (TGVHD) (**Table 2**).[19] The irradiation can be performed at the blood center or in the transfusion service of larger hospitals. The units are not radioactive and can be transfused safely to other patients. There is increased leakage of potassium in irradiated units of blood, so the units need to be transfused within 14 days, and in patients potentially sensitive to potassium (eg, neonates) within 24 hours. Patients undergoing stem cell transplant, those receiving either interuterine transfusions or products from relatives, any patient

Table 2. Situations Where Irradiated Blood Products Should Be Used

Absolutely	Probable
Stem cell transplant recipients	Hematologic malignancies other than Hodgkin disease
Congenital immune deficiencies	Patients receiving aggressive chemotherapy
Interuterine transfusion	
Transfusion from relatives	
Hodgkin disease (even in remission)	

with Hodgkin disease or receiving purine analogs or alemtuzumab, and patients with severe congenital immune deficiencies should receive irradiated blood. Most would also advocate that patients with hematologic malignances receiving chemotherapy receive irradiated products, but this is more controversial.

Leukodepleted Blood

White cells contaminating blood products are increasingly being recognized as a possible cause of adverse effects in transfused patients, including febrile transfusion reactions, inducing HLA alloimmunization, immunosuppression, disease transmission, and TGVHD. Reducing white cells can reduce the incidence of all of these except TGVHD. Currently, white cells are removed by infusion through filters that trap the cells. This can be done either at the bedside, in the blood bank, or at the donor center. The majority of red cells provided by blood centers in many areas of the country are already leukoreduced, eliminating the need for labor-intensive filtration at the transfusion center or bedside. Platelets collected by plateletpheresis methods can also be made leukopoor. The current indications for leukodepleted productions are:

1. Prevention of febrile transfusion reactions in patients with previous documented reactions
2. Prevention of HLA alloimmunization (ineffective if patient has received 1 or more blood products not leukodepleted or is already HLA immunized)
3. Prevention of cytomegalovirus (CMV) infection.

CMV-Negative Blood

CMV can be transmitted through any cellular blood product—red cells and platelets. For patients who are CMV-negative and receiving transplants, especially stem cell transplants, a new CMV infection can be devastating.[18] For years only blood from CMV-negative donors was use to transfuse CMV-negative patients. This policy is effective in preventing CMV infection, but because 50% of the population is positive for CMV antibodies, it may potentially lead to shortages of products that could be transfused to the patient. Currently, leukoreduced blood products are used since leukofiltration of the blood is just as effective as transfusion of CMV-negative blood in preventing infections and allows greater use of all blood products.[20]

COMPLICATIONS OF TRANSFUSIONS

HEMOLYTIC TRANSFUSION REACTION

Hemolytic reactions come in 2 forms—immediate and delayed. The immediate reaction is associated with fevers, hypotension, back pain, and oliguria. In severe cases, DIC and renal failure may occur. The immediate reaction is due to transfusion of blood that reacts with the recipient's preformed high-titer blood antigen antibodies, most often to ABO. This is fatal 2% of the time and occurs almost always as a result of errors in correct identification of the patient. Reactions are due to recipient antibodies attacking donated RBCs, resulting in release of hemoglobin and red cell membrane–antigen complexes. These complexes are believed to lead to the hypotension, fevers, chills, and renal damage associated with the hemolytic reaction. Treatment consists of immediately stopping the transfusion, notifying the blood bank, vigorous intravenous hydration to keep the urine output over 100 mL/hr, and supportive therapy.

The delayed reaction can range in severity from an abrupt drop in the hematocrit to normal response to transfusion but the patient developing a positive Coombs' test. The delayed response is due to an anamnestic response to blood-group antigens. When the patient is exposed to the same antigen, there is a rise in antibody titer leading to the reaction. Some alloantibodies can lead to a brisk reaction, most often anti-Kidd. The frequency with which delayed transfusion reactions occur is underestimated because mild reactions often do not get worked up or even discovered.

ALLERGIC REACTIONS

Allergic reactions are common (1%–3% of transfusions) and occur in patients having antibodies to proteins in donor blood which can lead to hives and itching with transfusions. Most of the time these allergic reactions are mild and can be treated with antihistamines. Prophylaxis with antihistamines is not indicated for future transfusions unless the reactions are frequent. Rarely these reactions can be associated with shock and hypotension. Patients who are immunoglobulin (Ig) A–deficient can develop anaphylactic reactions to IgA-containing blood products. Patients with severe allergic reactions need to have their IgA measured and, if deficient, receive only washed units or plasma from IgA-deficient donors to prevent future severe reactions.

FEBRILE REACTIONS

The most common transfusion reaction is a febrile reaction that occurs after the transfusion starts and that sometimes can be complicated by chills. This reaction often occurs due to the presence of leukocyte debris and cytokines in the donated blood. Therapy is supportive and involves stopping the transfusion and administering acetaminophen, but since hemolytic transfusion reactions can present with fever all patients need to be thoroughly evaluated. The incidence of reactions can be decreased by using leukodepleted blood and by using plateletpheresis platelets. Most patients do not benefit from receiving prophylactic acetaminophen for future transfusion unless they have multiple reactions.

TRANSFUSION-RELATED ACUTE LUNG INJURY

Once thought a rare complication, transfusion-related acute lung injury (TRALI) is increasingly being recognized, with an incidence of approximately 1:5000 patients; it is now the most frequent cause of transfusion-related death.[21] TRALI is noncardiac pulmonary edema and typically manifests clinically with hypoxemia, fever, bilateral infiltrates, and hypotension 2 to 6 hours after blood is given. Ventilatory support is often required. Recovery is usually rapid (24–48 hours) and complete. The etiology is complex. In many cases, transfused anti-HLA antibodies react with the recipient's white cells leading to pulmonary damage. Another theory is that transfusion of preformed cytokines leads to pulmonary damage. Because plasma products from multiparous women are most often associated with anti-HLA antibodies, the restricted use of blood products from women has decreased the incidence of lung damage.[22]

TRANSFUSION-RELATED GRAFT-VERSUS-HOST DISEASE

TGVHD is a rare reaction, but one that is most often fatal.[23] TGVHD occurs when donor lymphocytes attack the blood recipient's organs—skin, liver, intestines, and marrow. This is very rare in the normal blood recipient unless the donor and recipient share some HLA haplotypes.[24] In immunosuppressed patients, TGVHD can occur with lesser degrees of HLA similarity, with cases reported in blood recipients who are mainly patients with Hodgkin disease or acute leukemia undergoing chemotherapy, and in patients receiving purine analogs. TGVHD had not been reported in AIDS patients despite profound immunosuppression, perhaps because the milieu of the patient does not allow lymphocyte expansion. Symptoms of TGVHD are an erythematous rash that may progress to epidermal toxic necrolysis, liver dysfunction, diarrhea, and pancytopenia. TGVHD is prevented by radiating blood products given to at-risk patients with 2500 to 3500 rads. Directed blood donation from all blood relatives should also be radiated. TGVHD cannot be prevented by leukopoor blood because the minute amount of lymphocytes that are not filtered still can lead to these complications.

POST-TRANSFUSION PURPURA

Patients with post-transfusion purpura (PTP) develop severe thrombocytopenia ($<10 \times 10^9$/L) with often severe bleeding 1 to 2 weeks after receiving any type of blood product.[25] Patients who develop PTP most often lack platelet antigen PLA1 or other platelet antigens. For unknown reasons, exposure to the antigens from the transfusion leads to rapid destruction of the patient's own platelets. The diagnostic clue is thrombocytopenia in a patient, typically female, who has received a red cell or platelet blood product in the past 7 to 10 days. Treatment consists of intravenous immunoglobulin[26] and plasmapheresis to remove the offending antibody. If patients with a history of PTP require further transfusions, only PLA1-negative platelets should be given.

IRON OVERLOAD

Every transfusion of red cells delivers about 250 mg of iron to the recipient. Since there is no natural way of ridding the body of iron, heavily transfused patients are at risk of iron overload. This is most often seen in children heavily transfused for thalassemia. Starting in the second decade of life, they will develop endocrinolopathies due to iron overload, liver problems, and often fatal cardiomyopathies. Studies have shown that chelation of iron with deferoxamine can

be effective in preventing this fatal complication.[27] New oral iron chelators such as deferasirox and deferiprone are also effective. The risk of iron overload in heavily transfused patients with myelodysplasia is unclear, and uncertainty exists about the need for chelation.[28]

Young patients who face years of transfusions should be started on iron chelation to avoid iron overload. For older patients with transfusion-dependent anemia, iron chelation therapy should be considered if their life expectancy is long (years to decades) or special studies such as T2-weighted cardiac magnetic resonance imaging show iron overloading.[29]

INFECTIOUS COMPLICATIONS

Concern over transmission of HIV infection via blood products in the late 1980s led to both a reduction in blood product use and a greater awareness of infectious complications of transfusion and their prevention. However, no blood product can ever be assumed to be safe for 2 reasons. One is that blood products can transmit infections during a "window period"—the time before a contaminated product can be detected by testing. The second is that blood is not screened for all potential infections (eg, babesiosis or new infections such as West Nile virus at the start of the outbreak). Risk of infection is reduced in 2 ways: deferral of potential infectious donors and blood product testing.

As part of the donation process, potential blood donors are asked a series of questions to see if they have risk factors for infections (eg, recent travel to malarious areas, recent tattoos), and if they answer positive are deferred from donating blood. Then blood products are tested for infectious agents by a combination of methods including detection of viral antigen, antibody response to infections, and more recently polymerase chain reaction (PCR).[30] Current screening includes: syphilis testing; testing for antibodies to HIV, HTLV, hepatitis C virus (HCV), hepatitis B core antigen (HBcAg), hepatitis B surface antigen (HBsAg), and *Trypanosoma cruzi*, the cause of Chagas disease; and PCR for HIV, hepatitis B virus, HCV, and West Nile virus.

The numerically most common transfusion-related disease was hepatitis, first B and then C.[31] The first step in eliminating these infections was to stop paying donors for blood products. With the introduction of effective testing for hepatitis B and then C, the incidence of transfusion-related hepatitis has plummeted.[30] For example with the introduction of a diagnostic test for hepatitis C, the estimated risk has fallen from 5% to less than 1 per million. Currently, the most common hepatitis transmitted by blood is hepatitis B (1:277,000), due to the low titer of highly infectious virus early on in the infection. Although the infection patients still fear the most is HIV, the incidence is very low now, with the risk estimated at less than 1:2,000,000.

Despite this testing, blood transfusions can transmit a variety of infections, including malaria and babesiosis.[32] Any new blood-borne infection introduced into the population can get into the blood supply as well. For example at the start of the West Nile virus epidemic, there was a cluster of transfusion-transmitted cases that resulted in severe and sometimes fatal illness in immunosuppressed patients, but this issue has been addressed with the development of a PCR assay for screening blood.[33]

SPECIAL ISSUES

MASSIVE TRANSFUSIONS

Acutely bleeding patients can require large amounts of transfusion products. Early data showed high mortality rates with transfusion of over 20 units of blood,[34] but with modern blood banking techniques and improved laboratory testing, this rate has decreased dramatically, with survival rates of 43% to 70% in patients transfused with over 50 units of blood.[35]

The basic approach to massive transfusions is to first transfuse the patient to maintain hemodynamic stability while specific blood tests are being obtained, and then guide the rest of the resuscitation by the results of these early tests. An important component is the ability to rapidly deliver standard packages of red cells, usually 6 to 10 units at a time, to the bleeding patient. To avoid delay while the patient's blood is being typed, the first products delivered are blood group O Rh-positive units.[36] Given the shortage of Rh-negative blood, this should be reserved for only empiric therapy of women of child-bearing age. Once the blood type is known, the patient can be switched over to type-specific blood.

In the past few years, there has been a shift to increasing the amount of plasma given to massive transfusion patients. This change in strategy is based on 2 recent findings. First, modeling of coagulation changes in massive bleeding suggests the need for larger amounts of plasma to correct defects than have previously been used.[37] Second, in an analysis of resuscitation protocols used in military and civilian trauma centers, giving red cells and plasma units in a 1-to-1 ratio appeared to be associated with improved outcomes in trauma patients and those with ruptured

Table 3. Massive Transfusion Protocol

5 Basic Tests of Hemostasis
Hematocrit
Platelet count
Prothrombin time (PT/INR)
Activated partial thromboplastin time (aPTT)
Fibrinogen level
Management Guidelines
A. Platelets <50–75 x 10^9/L: give platelet concentrates or 6-pack of single donor platelets
B. Fibrinogen <125 mg/dL: give 10 units of cryoprecipitate
C. Hematocrit below 30%: give red cells
D. PT/INR >2.0 *and* aPTT abnormal: give 2 to 4 units of fresh frozen plasma

aneurysm.[38] Several studies have extended this concept to platelets, again suggesting improved survival with 1 unit of random donor platelets given 1-to-1 with red cells and plasma units.

However, there are concerns about the "1:1" concept. One is that all these studies are retrospective, with no attempt to specify the blood product ratio in advance. In fact, there are a variety of "ideal" ratios in the literature ranging from 1:1 to 3 units of red cells for every unit of plasma.[16] Second, there is concern about survivorship bias. Given that red cells can be instantly ready while plasma needs 20 to 30 minutes to thaw, patients who rapidly die of their injuries may only receive a few plasma products, while those destined to survive will live long enough for abundant plasma products to be thawed and transfused. Finally, the ability to give the patient plasma may reflect an organized massive transfusion protocol that is able to deliver products efficiently rather than any particular product ratio per se.[39]

The standard approach for laboratory testing is obtaining 5 tests: hematocrit, platelet count, INR/prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen.[40] Product selection is guided by these tests, and they are repeated at regular intervals during the massive transfusion. A typical protocol is shown in **Table 3**. It is important as part of any protocol to have a flow chart that records laboratory results and products given that any member of the team can easily view.

The transfusion threshold for a low hematocrit depends on the stability of the patient. If the hematocrit is below 30% and the patient is bleeding or hemodynamically unstable, one should transfuse packed red cells. Stable patients can tolerate lower hematocrits, and an aggressive transfusion policy may even be detrimental.[1,41]

If the patient is bleeding, has florid DIC, or has received platelet aggregation inhibitors, then keeping the platelet count above 50 x 10^9/L is reasonable. There are data regarding massive transfusion showing that keeping the platelet count above 50 x 10^9/L resulted in less microvascular bleeding.[42] The conventional dose of platelets is 6 to 8 platelet concentrates or 1 plateletpheresis unit.

While in the past fibrinogen targets of 50 to 100 mg/dL were recommended, recent data indicate that a target of 125 to 150 mg/dL or higher may be more appropriate.[43–45] In certain clinical situations such as brain injuries, hepatic trauma, or ischemic limb reperfusion, severe fibrinolysis may occur and the use of large amounts of cryoprecipitate can be anticipated.

In patients with an INR greater than 2 and an abnormal aPTT, one can give 2 to 4 units of FFP. For an aPTT greater than 1.5 times normal, 2 to 4 units of plasma should be given. Elevation of the aPTT above 1.8 times normal control is associated with microvascular bleeding in trauma patients.[46] Patients with marked abnormalities such as an aPTT more than 2 times normal may require aggressive therapy with at least 15 to 30 mL/kg (4–8 units for an average adult) of plasma.[47]

Recently there has been increasing interest in thromboelastrography (TEG) in massive transfusion.[48] This is a point-of-care assay performed on fresh whole blood that can assess multiple facets of hemostasis—coagulation, platelet function, and fibrinolysis.[38,49] TEG is performed by placing a 0.35 mL sample of whole blood into an oscillating container with a sensor pin that measures the force of thrombus formation. TEG measures 5 parameters:

- r time: time from starting TEG until clot formation
- K time: time between tracing going from 2 mm to 20 mm
- alpha angle: slope of tracing between r and K time
- MA: greatest amplitude of TEG tracing
- Whole blood lysis index: amplitude of tracing 60 minutes after MA.

Several centers have incorporated TEG into resuscitation protocols that include standardized strategies for responding to abnormalities. Data suggest that use of TEG may decrease the use of blood products, especially in cardiac surgery, but this has not been prospectively studied in massive transfusions.[50]

Complications of Massive Transfusions

Electrolyte abnormalities are unusual even in the massive transfusion patient.[51] Platelet concentrates and

plasma contain citrate that can chelate calcium. However, the citrate is rapidly metabolized, and it is rare to see clinically significant hypocalcemia. Although empiric calcium replacement is often recommended, one study suggests that this is associated with a worse outcome and should not be done.[52] If hypocalcemia is a clinical concern, then levels should be drawn to guide therapy. Stored blood is acidic, with a pH of 6.5 to 6.9. However, acidosis attributed solely to transfused blood is rare and most often is a reflection of the patient's stability. Empirical bicarbonate replacement has been associated with severe alkalosis and is not recommended.[53,54] Although potassium leaks out of stored red cells, even older units of blood contain only 8 mEq/L of potassium, so hyperkalemia is usually not a concern.

TRANSFUSING PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA

Patients with autoimmune hemolytic anemia can be difficult to transfuse.[55] The autoantibody can interfere with several aspects of the transfusion services evaluation. In some patients the autoantibody can be so strong that the patient's blood type cannot be determined. In most patients, the final step of the cross-match—mixing the donor blood with recipient plasma—will show noncompatibility due to the autoantibodies reacting with any red cells.

The first step when transfusing a patient with autoimmune hemolytic anemia is to draw several tubes of blood for the transfusion service before any potential transfusions. This allows the transfusion service to remove the autoantibodies so they can screen for underlying alloantibodies. Second, if the patient requires immediate transfusion, then type-specific or O-negative blood should be given. If the patient has not been recently (months) transfused, the incidence of a severe transfusion reaction is low. The first unit should be infused slowly with close observation of the patient. For patients who have been multiply transfused, the use of an *"in-vivo"* cross-match may be helpful. This is where the patient is slowly transfused 10 to 15 mL of blood over 15 minutes. Then the plasma and urine are assessed for signs of hemolysis and, if negative, the remaining product is given.

MANAGEMENT OF THE PATIENT WHO REFUSES BLOOD PRODUCTS

The initial step is to find out why the patient is refusing blood products. Many patients have an exaggerated fear of HIV and other infectious agents, so simple consoling can often resolve the situation. The most common reason for refusal of blood products is religious belief. Jehovah's Witness patients will refuse blood products due to their interpretation of the Bible.[56] All members will refuse red cells, plasma, and platelets. Decisions about use of "derived" blood products—products made by manipulation of the original donated units—are a matter of conscience. These include cryoprecipitate, intravenous gammaglobulin, and albumin.

In an elective situation, the first step is to discuss with the patient those products that are matter of conscience and clearly document this. The patient's blood count and iron stores should be assessed to identify any correctible causes of anemia or low iron stores before surgery. The use of erythropoietin to correct blood counts before surgery is controversial, as this may increase thrombosis risk and is contraindicated in curable tumors.

For patients with acute blood loss, use of intravenous iron combined with high-dose erythropoietin is the most common approach to raise the blood count. One recommended erythropoietin dose is 300 units/kg 3 times a week, dropping to 100 units/kg 3 times weekly until the goal hematocrit is reached.[57] Another often overlooked step is to consolidate and minimize laboratory testing. The most important step is to be respectful of the patient and their beliefs. Many larger cities have liaisons that can help with interactions between Jehovah's Witness patients and the health care system.

NON-TRANSFUSION THERAPIES FOR ACUTE BLEEDING

Desmopressin

Desmopressin (DDAVP) is a synthetic analog of antidiuretic hormone that raises the levels of both factor VIII and von Willebrand protein severalfold.[58] Desmopressin is effective in supporting hemostasis in patients with a wide variety of congenital and acquired bleeding disorders.[59–61] However, desmopressin does not reduce blood loss before routine surgery in a healthy patient and should not be used for this purpose.[62,63]

Antifibrinolytics

Aminocaproic acid and tranexamic acid are antifibrinolytic agents that block the binding of plasmin to fibrin.[64,65] These agents are useful in disorders that involve excessive fibrinolysis[66–70] or as adjunctive therapy for oral or dental procedures in patients with a bleeding diathesis. In patients with severe thrombocytopenia, the use of antifibrinolytic agents may reduce bleeding.[71,72]

Increasing data suggests that antifibrinolytics can prevent blood loss in a variety of surgeries including heart bypass, liver transplantation, and orthopedic surgery.[73–76] A recent study also showed the use of tranexamic acid significantly reduced mortality in trauma patients.[77]

Recombinant Factor VIIa

Recombinant factor VIIa (rVIIa) was originally developed as a "bypass" agent to support hemostasis in hemophiliacs.[78] However, the use of rVIIa for a wide array of bleeding disorders, including patients with factor VII and XI deficiency and Glanzmann thrombasthenia, has been reported.[79] Increasingly, rVIIa is being used as a "universal hemostatic agent" for patients with uncontrolled bleeding from any mechanism.[80] Multiple case reports have shown use of rVIIa for bleeding in cardiac surgery patients, obstetrical bleeding, reversal of anticoagulation, and trauma.[81] Unfortunately, little formal trial data exists to put these anecdotes into perspective, and formal review of clinical trial results has shown no benefit.[82,83] However, when used in older patients, especially those with vascular risk factors, the risk of arterial thrombosis appears to increase.[84] In the trials for intracranial hemorrhage, the thrombosis rate was 5% to 9%, and rates up to 10% for arterial events were seen in older patients in a review of all trials.[85–87] Given the lack of data but the evidence of risk, rVIIa use should be restricted to patients with documented bleeding disorders that have been shown to benefit by its use.

BOARD REVIEW QUESTIONS

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