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TRANSFUSION THERAPY

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CHAPTER 6

1. How would knowledge of oxygen delivery impact the decision to transfuse?

A transfusion would be indicated when oxygen delivery falls to a critical level (DO_{2crit}) and oxygen consumption (VO_2) needs are not met. Recall that DO_2 is a function of cardiac output (CO) and the arterial oxygen content (CaO_2). Arterial oxygen content is a function of arterial oxygen saturation, the oxygen-carrying capacity of hemoglobin, the hemoglobin concentration, and, for the amount of oxygen dissolved in blood (unbound to hemoglobin), the partial pressure of oxygen.

Ordinarily DO_2 exceeds VO_2 by a factor of four (800 to 1200 ml/min vs. 200 to 300 ml/min). Thus the extraction ratio ($O_2ER = VO_2/DO_2$) is 20% to 30%. As long as DO_2 exceeds VO_2, VO_2 is "supply independent." However, below DO_{2crit} VO_2 becomes "supply dependent," and VO_2 decreases as DO_2 decreases, creating a situation in which end-organs are at risk for ischemia. It is at this point that a transfusion is clearly indicated.

2. At what point is DO_{2crit} reached? What are our surrogate measures for DO_{2crit}?

As long as the patient is euvolemic, DO_{2crit} is not reached until hemoglobin decreases to about 3.5 g/dl. This also requires that pulmonary function is intact since it requires full hemoglobin oxygen saturation and oxygen dissolved in blood (not bound to hemoglobin). It should be noted that at this hemoglobin level the oxygen dissolved in blood becomes a major contributor (almost 75%) to the oxygen delivered. It should also be mentioned that the DO_{2crit} is modified by the patient's oxygen requirements above baseline (e.g., catabolic states such as sepsis, burns) and the presence of end-organ disease such as coronary artery disease.

Given that in the course of normal operating room conditions, DO_{2crit} is unavailable, other variables are used to determine whether the patient is transfused. These include hypotension, tachycardia, urine output, the presence of lactic acidosis, signs of myocardial ischemia (new ST-segment depression >0.1 mV, new ST-segment elevation >0.2 mV, regional wall motion abnormalities by echocardiography), and low mixed venous oxygen saturation ($<50\%$, requires pulmonary artery catheterization to determine).

3. What are the physiologic adaptations to acute normovolemic anemia?

During surgery acute blood loss is usually replaced with crystalloid solutions and, if in sufficient volume, results in acute normovolemic hemodilution. Compensatory changes include sympathetic stimulation, resulting in tachycardia and increased cardiac output. Decreased viscosity reduces afterload, increases preload, and improves flow at the capillary level. Since capillary flow is not maximal under resting conditions, capillary recruitment is an adaptive mechanism as well. In addition, there is redistribution of blood to the tissues that are oxygen supply dependent (e.g., heart and brain) and oxygen extraction is increased.

It is important to note that myocardial oxygen extraction is high under normal circumstances; thus the reserve is less. The brain has greater extraction reserve than the heart. Thus the heart is more dependent on increasing blood flow to increase oxygen delivery; the significance of this becomes clear in coronary artery disease. A failure for acute normovolemic anemia to deliver oxygen in excess of consumption is another argument in favor of blood transfusion.

4. Historically, a hemoglobin level of 10 g/dl (hematocrit of 30) was used as a transfusion trigger. Why is this is no longer an accepted practice?

In patients with coronary artery disease having signs of myocardial ischemia, this level of hemoglobin might be appropriate. Otherwise it has come to be viewed as a liberal transfusion trigger. Recall that in an otherwise normal situation, DO_{2crit} has not been reached until hemoglobin decreases to 3.5 g/dl. Although no clinician probably pushes a patient to this extreme (unless the patient requests no transfusion based on religious reasons and the like), the less likely a transfusion is really indicated, the more the risks of transfusion negatively impact the risk/benefit ratio.

It is also interesting to note that men and women tend to be treated equally when the decision to transfuse is made, despite the fact that normal women are anemic relative to men. Using the same transfusion triggers hardly seems rational. Finally there is a concern that a transfusion might not substantially increase oxygen delivery (see discussion of blood storage lesions in question 8). These are strong arguments for closely scrutinizing the consideration to transfuse.

5. What are the risks of transfusion?

The risks include contracting an infectious disease through transfusion, transfusion reactions, and the immunomodulatory effects of transfusion.

6. What infectious diseases can be contracted from a transfusion and how significant is that risk?

At this point in time, the blood supply is as safe as it as ever been, with risks of contracting hepatitis or human immunodeficiency virus (HIV) in a developed nation estimated at 1 in 2.4 million units transfused. Donated blood is tested for hepatitis B (hepatitis B core antigen), hepatitis C (hepatitis C antibody), syphilis, HIV, human T cell lymphotropic virus, West Nile virus, and cytomegalovirus. Because of improvments in testing, the window between donation and seroconversion is becoming increasingly narrow.

However, there are new infectious risks, including contracting prion-mediated diseases (variant Creutzfeldt-Jakob disease (vCJD), parasitic disease (Chagas disease, malaria), and avian flu. There are concerns that severe acute respiratory syndrome will eventually be spread through the blood supply. The risks of these diseases vary with the geographic locality. For instance, malaria is a greater risk in undeveloped countries (as is HIV); the only known cases of contraction of vCJD through transfusion are in the United Kingdom.

Because platelets are stored at a higher temperature (20 to 22° C) than red blood cells (4° C) or other blood products, platelets are the blood component at greatest risk for bacterial infection. However, testing for sepsis in platelet units is improving, and the risk will likely decrease over time.

7. Review the major transfusion-related reactions.

- **Hemolytic transfusion reactions** caused by ABO incompatibility are most commonly caused by clerical errors and transfusion of the wrong unit. Mistransfusion is thought to occur with a frequency between 1:14,000 and 1:18,000. Most reactions occur during or shortly after a transfusion. Clinical manifestations include fever; chills; chest, flank, and back pain; hypotension; nausea; flushing; diffuse bleeding; oliguria or anuria; and hemoglobinuria. General anesthesia may mask some of the clinical manifestations, and hypotension, hemoglobinuria, and diffuse bleeding may be the only signs. It should be noted that the signs of a severe hemolytic reaction might be missed while the patient is under general anesthesia or attributed to another cause.
- **Anaphylactic reactions** are caused by binding of IgE; present with bronchospasm, edema, redness, and hypotension; and require urgent treatment with epinephrine, fluid infusions, corticosteroids and antihistamines, and other therapies as indicated by severity and progression of symptoms.

- **Febrile reactions** may be an early sign of hemolytic transfusion reaction (but other symptoms should be present) or bacterial contamination of the blood product. Febrile nonhemolytic transfusion reactions usually occur in patients who have had prior transfusions; headache, nausea, and malaise are associated symptoms. The reaction is caused by leukocyte antibodies, and leukocyte-depleted red blood cells may be indicated for these patients. Antipyretics may decrease the symptoms if given before the transfusion; meperidine may decrease the severity of chills.
- **Transfusion-related acute lung injury (TRALI)** is in the top three of transfusion-related deaths, having a mortality of 50%. A form of noncardiogenic pulmonary edema, TRALI is also immune related and is usually noted within 6 to 12 hours after transfusion. Symptoms include hypoxia, dyspnea, fever, and pulmonary edema; treatment is supportive.
- **Urticarial reactions** secondary to mast cell degranulation do not require that the transfusion be stopped; antihistamines may be given.
- These transfusion reactions are compared in Table 6-1.

TABLE 6-1. DIFFERENTIAL DIAGNOSIS OF TRANSFUSION-RELATED ACUTE LUNG INJURY*

Diagnostic Entity	Onset	Major Signs and Symptoms	Differentiating Features
Transfusion-related acute lung injury	Minutes to hours	Dyspnea, respiratory distress, hypoxemia, cyanosis, pulmonary edema, fever, tachycardia	Noncardiogenic pulmonary edema, frequent fever
Anaphylactic or anaphylactoid reaction	Minutes to hours	Bronchospasm, respiratory distress, hypotension, cyanosis, generalized erythema and urticaria, mucous membrane edema	Rash, urticaria, and edema present; hypotension and bronchospasm prominent
Bacterial contamination of blood products	Minutes	Fever, rigors, hypotension, and vascular collapse	Fever, rigors, and vascular collapse predominant; most common with platelets
Hemolytic transfusion reaction	Minutes	Fever, rigors, hypotension, hemoglobinuria, disseminated intravascular coagulation	Usually with red blood cell transfusion, hemolysis

*Symptoms may be missed while under general anesthesia, and differential diagnosis should be expanded to include common intraoperative problems. (Permission from Boskkov LK: Transfusion-related acute lung injury and the ICU, *Crit Care Clin* 21:479-495, 2005.)

8. What are the current standards for the length of storage of blood? What is a blood storage lesion?

Federal regulation requires that at least 70% of transfused red blood cells survive 24 hours after CPDA-1 and for 42 days when AS-1 (Adsol) or AS-3 (Nutrice) is added.

Changes in stored blood that reduce post-transfusion viability are known as *storage lesions*. They include reduction in red cell deformability; altered red cell adhesiveness; depletion of adenosine triphosphate stores; and reduction in 2,3-diphosphoglycerate (2,3-DPG) which decreases the ability of the hemoglobin dissociation curve to shift to the right, which enhances peripheral oxygen release. Proinflammatory cytokines accumulate and, even after 2 weeks, are capable of significantly priming neutrophils for an exacerbated inflammatory response.

9. Is there convincing evidence that the effect of a transfusion on immune function is harmful?

Much of the evidence for immune modulation and infection related to transfusion is retrospective in nature and as such suffers from a failure to control for confounding variables. There are insufficient numbers of randomized, controlled studies of sufficient power, and the studies that do exist have been conducted on critically ill patients, not in the perioperative setting (perhaps with the exception of patients having coronary bypass). As such, definitive recommendations await. However, a few points are worthy of discussion.

The Transfusion Requirements in Critical Care trial was sufficiently powered to evaluate the impact of transfusion on outcome. The groups under study were divided into a restrictive transfusion (hemoglobin trigger of 7 g/dl, targeting a hemoglobin level between 7 and 9 g/dl) and a liberal transfusion group (hemoglobin transfusion trigger of 10 g/dl, targeting a hemoglobin level of 10 to 12 g/dl). Thirty-day mortality was lower in the restrictive transfusion group, although a statistical significance of $p<0.05$ was not met. However, if the patients were subdivided by acuity of illness, fewer acutely ill patients in the restrictive transfusion group had lower 30-day mortality.

Other prospective studies are less convincing in their findings, but there are overlapping transfusion triggers, and the patient populations differ. Some but not all observational studies have found that the number of transfused units is an independent risk factor for mortality and increased length of stay. Overall it must be said that the final word on the impact of transfusion on mortality has yet to be written. It should be noted that many countries now routinely perform leukoreduction on donated blood out of concern for the impact of transfusion on the recipient's immune function.

10. Review the features of transfusion-related acute lung injury.

Recently TRALI has been identified as the leading cause of transfusion-related deaths in the United States. It is estimated that 1 in 5000 transfusions will result in TRALI. All blood components have resulted in TRALI, including packed erythrocytes, random donor platelets, single donor (apheresis) platelets, fresh frozen plasma, and cryoprecipitate. However, the cellular components have a greater association with TRALI. Even autologous blood has resulted in TRALI, suggesting that there may be some storage lesion contributing to its etiology.

Although donor antibodies have been shown to be present in many TRALI series, their presence is neither necessary nor sufficient to result in TRALI. It is now believed that TRALI is multifactorial and a two-event subtype of acute lung injury. Because of some associated conditions, the recipient has a high level of inflammatory mediators (e.g., cytokines), primed white blood cells, and pulmonary endothelium. The administered blood product provides the second event, through classic antibody-antigen coupling or the lipid products or other cytokines generated during storage of the blood products. The primed white blood cells are activated to release substances such as superoxides that damage the pulmonary endothelium.

11. What conditions may predispose a patient to transfusion-related acute lung injury?

Some conditions that have been associated with TRALI include sepsis, organ ischemia, massive transfusion, extracorporeal circulation, malignancies, recent surgical procedures, aspiration of gastric contents, near-drowning, pneumonia, long-bone fractures, burns, pulmonary contusion, and disseminated intravascular coagulation. Obviously the patient must be ill enough to require a transfusion.

12. Discuss the criteria for diagnosis of transfusion-related acute lung injury.

- Acute onset: often occurring in less than 2 hours after a transfusion, but usually less than 6 hours
- Pulmonary arterial occlusion pressure $\leq$18 mm Hg or lack of clinical evidence of left atrial overload (i.e., the problem is noncardiogenic pulmonary edema)
- Bilateral infiltrates observed on chest radiograph
- Hypoxemia with a ratio of PaO_2/FiO_2 $\leq$300 mm Hg regardlesss of the level of positive end-expiratory pressure, or oxygen saturation $\leq$90% on room air
- No acute lung injury existed prior to transfusion

13. What treatments are available for transfusion-related acute lung injury?

If the patient experiences deterioration in oxygenation during transfusion, the transfusion should be discontinued, and the remainder of the transfused blood returned to the laboratory for analysis. Of course, some other form of transfusion injury besides TRALI may be taking place.

Therapy is supportive, continuing to treat the patient's other medical problems (which may have been the priming event for TRALI) and aggressive pulmonary support. If further transfusions are needed, it is wise to use blood products that have a reduced likelihood of having inflammatory mediators, including leukoreduced packed erythrocytes, packed units less than 14 days old, washed erythrocytes, or, in the case of platelets, apheresis units less than 3 days old.

14. Review the ABO and Rh blood genotypes and the associated antibody patterns.

Blood type is determined by two alleles of three types: O, A, and B. A and B refer to antigens on the red blood cell surface. An individual can have either A or B, both A and B, or neither (blood type O). If an individual does not have the type A antigen, over time anti-A antibodies (also known as *agglutinins*) form. A patient with type AB blood has both antigens and will form no agglutinins. Individuals with type O blood have no antigen and develop both A and B antibodies (Table 6-2). The antibodies are primarily immunoglobulin (Ig)M or IgG. Acute hemolytic reactions are caused by complement activation and release of proteolytic enzymes that digest the red cell membrane.

TABLE 6–2. BLOOD TYPES AND THEIR CONSTITUENT ANTIGENS AND ANTIBODIES

Blood Genotypes	Blood Type	Antigens (Agglutinogens)	Antibodies (Agglutinins)
OO	O	None*	Anti-A and Anti-B
OA or AA	A	A	Anti-B
OB or BB	B	B	Anti-A
AB	AB	A and B	None†

*The absence of agglutinogens makes the O-packed cells the universal packed cells donor.
†The absence of agglutinins makes AB plasma the universal plasma donor.

People with type O blood have neither A nor B antigens (agglutinogens) on their cell surface. These cells cannot be agglutinated by antibodies (agglutinins) that may be present in a transfusion recipient's blood. Thus type O blood is known as the *universal donor* for red blood cells. Patients with type AB blood have both classes of antigens (agglutinogens) and therefore do not form A or B antibodies (agglutinins). Because there are no antibodies in the plasma, type AB patients are universal donors for plasma.

There are six common antigens in the Rh system; the presence of the *D* antigen is what is most commonly referred to as *Rh positive*. The Rh blood type system is slightly different because Rh agglutinins rarely form spontaneously. Usually massive exposure, as from a prior transfusion, is necessary to stimulate their formation. An Rh-negative patient can receive Rh-positive blood in an emergency situation, although antibodies will form in some patients, and there may be a delayed, usually mild, hemolytic transfusion reaction. But now the patient is Rh sensitized and can have a more significant transfusion reaction if exposed to Rh-positive blood at a later date.

15. What is the difference between a type and screen and a crossmatch?

The patient's blood is typed for ABO and Rh group by placing his or her red cells with commercially available anti-A and anti-B reagents and reverse typing the patient's serum against A and B reagent cells. A screen for antibodies involves placing the patient's serum with specially selected red cells containing all relevant blood group antigens. In a crossmatch the patient's serum is also incubated with a small quantity of red cells from the proposed donor unit to verify in vitro compatibility. A crossmatch also detects more unique antibodies (Table 6-3).

TABLE 6-3. CROSSMATCH AND COMPATIBILITY

Degree of Crossmatch	Chance of Compatible Transfusion
ABO-Rh type only	99.8%
ABO-Rh type + antibody screen	99.94%
ABO-Rh type + antibody screen crossmatch	99.95%

16. What type of blood should be used in an emergency situation?

Transfusions in emergency situations do not allow time for a complete crossmatch. Under these circumstances the fastest choice is to use type O, Rh-negative (or Rh positive in males), uncrossmatched blood. If more than two units of type O blood are given to patients who are type A or B, because of the anti-A and anti-B antibodies in type O blood, type O blood should continue to be administered until complete testing of the patient's blood has ensured that hemolysis of his or her native cells will not take place. Type-specific, uncrossmatched blood would be the next choice, followed by type-specific, partially crossmatched blood and finally fully crossmatched blood.

17. What are some of the complications of massive blood transfusion?

Massive transfusion is defined as the administration of more than one blood volume within several hours. Complications include:

- Coagulopathy secondary to dilutional thrombocytopenia, lack of labile coagulation factors V and VIII, and disseminated intravascular coagulation
- Metabolic disturbances associated with banked blood, including hyperkalemia, hypocalcemia (citrate toxicity), acidosis, and impaired oxygen delivery caused by reduced 2,3-DPG

- Hypothermia. Interestingly, a meta-analysis (Rajagopalan et al, 2008) found that mild hypothermia (34° to 36° C) increases blood loss by 16% and increases the relative risk for transfusion by 22%. Hypothermia impairs platelet function and proteins of the coagulation cascade.

18. If suspected, how should a major transfusion reaction be managed?

- Stop the transfusion immediately and remove the blood tubing.
- Alert the blood bank and send a recipient and donor blood specimen for compatibility testing.
- Treat hypotension aggressively with intravenous fluids and pressor agents.
- Maintain urine output with intravenous hydration. Mannitol and loop diuretics are used on occasion.
- Massive hemolysis can result in hyperkalemia. Follow serum potassium levels and continuously monitor the electrocardiogram for electrocardiographic signs of hyperkalemia.
- Disseminated intravascular coagulation may occur. The best treatment is identifying and treating the underlying cause. Follow prothrombin, partial thromboplastin, fibrinogen, and D-dimer levels.
- Check urine and plasma hemoglobin levels and verify hemolysis with direct antiglobulin (Coombs') test, bilirubin, and plasma haptoglobin levels.
- The availability of thromboelastography is increasing and is very useful for assessing coagulation disturbances.

19. What alternatives are there to transfusion of donor blood?

- Autologous transfusion (the collection and reinfusion of the patient's own blood). It should be noted that only about 55% of predonated units are returned to the patient. The patient scheduled to autologous transfusion still runs the risk of clerical errors and bacterial infection. There is also a report of a patient who received an autologous transfusion developing TRALI.
- Preoperative use of erythropoietin to stimulate erythrocyte production. Erythropoietin stimulates erythrocyte production in 5 to 7 days and has been shown to reduce use of allogeneic blood in patients with renal insufficiency and anemia of chronic disease and when transfusion is refused.
- Intraoperative collection and reinfusion of blood lost during surgery
- Intraoperative isovolemic hemodilution (the reduction of hematocrit or hemoglobin by withdrawal of blood and simultaneous intravascular replacement with crystalloid)
- Use of hemoglobin solutions

20. What are the limitations, advantages, and disadvantages of alternative hemoglobin solutions?

The benefits of alternatives to erythrocyte transfusion include a lack of antigenicity, possible unlimited availability, no disease transmission risk, long storage life, and better rheologic properties. Two types of oxygen-carrying solutions have been developed:

- Perfluorocarbon emulsions that have a high gas-dissolving capacity for oxygen
- Hemoglobin-based oxygen carriers.

This discussion focuses on the latter. Such compounds are manufactured from human recombinant hemoglobin, outdated human blood, or bovine blood. The stromal components of erythrocytes are removed, and the hemoglobin molecule polymerized or liposome encapsulated to prevent rapid renal excretion and nephrotoxicity. Cell-free hemoglobin solutions have two major problems. First, they have low concentrations of 2,3-DPG. The lack of 2,3-DPG shifts the oxyhemoglobin dissociation curve to the left, the affinity of hemoglobin for oxygen increases, and oxygen cannot be off-loaded at the tissue level. Second, they are nitric oxide scavengers and produce excessive vasoconstriction. Pulmonary hypertension and myocardial ischemia are risks; in fact, reports of death from myocardial infarction have delayed release of these solutions for general use. These solutions also result in platelet activation; release of proinflammatory mediators; methemoglobinemia; and, because of their color, interference with laboratory tests.

KEY POINTS: TRANSFUSION THERAPY

1. There is no set hemoglobin/hematocrit level at which transfusion is required. The decision should be individualized to the clinical situation, taking into consideration the patient's health status.
2. If blood is needed in an emergency, type O–packed cells and/or type-specific blood may be used.
3. There are numerous tranfusion-related reactions, and vigilance while administering under anesthesia is a must because many of the classic signs and symptoms might be missed in a draped patient under general anesthesia.

WEBSITE

American Society of Anesthesiologists
http://www.asahq.org

SUGGESTED READINGS

1. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusions. Practice guidelines for perioperative blood transfusion and adjuvant therapies. Anesthesiology 105:198–208, 2006.
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