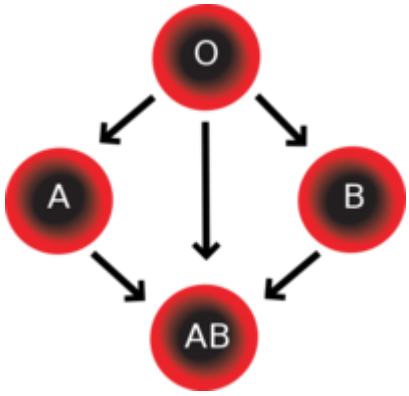
I. Blood Component Therapy

Introduction to RBC Use



Blood Compatibility for Red Cell Transfusions

Major cross matching occurs when the donor erythrocytes are mixed with the recipient's plasma (minor cross matching mixes the donor plasma with recipient erythrocytes). In an urgent situation, one can do a partial cross match (in which macroscopic agglutination is looked for) in < 5 minutes. In truly urgent situations, give type-specific non-cross-matched blood. O-negative should be the last option because it can contain high levels of anti-A and anti-B antibodies. Screening simply analyzes donor blood for common antibodies. The risk of a significant hemolytic reaction following screening in type-specific blood is 1:10,000 units. [Stoelting RK. Basics of Anesthesia, 5th ed. Elsevier (China) p. 356, 2007]

Stored at 4° C in an anticoagulated preservative that contains citrate, phosphate, and dextrose (CPD). Citrate binds calcium and anticoagulates. Phosphate retards breakdown of 2,3-DPG, and dextrose serves as fuel. In these conditions, RBCs are viable for at least 21 days. That said, 2,3-DPG declines with age, which may have adverse effects – A study of 63 trauma patients who received 6-20 units of blood identified mean age of blood, number of units older than 14 days, and number of units older than 21 days as independent risk factors for MOF. [Zallen G et. al. Am J Surg 178: 570, 1999]

PRBCs can be combined with saline through a Y-connector to give approximately equal amounts as in whole blood, but be sure not to use LR as

the solvent because it contains calcium which will clot the PRBCs [Am Assoc Blood Banks Tech. Manual p. 341, 1990]. RBCs are usually passed through filters which can impede the flow of blood – they should be changed after ~ 4 units of blood. Smaller filters (< 170 microns) may reduce pulmonary complications of RBC transfusions but this is unproven [Ann Emerg Med 17: 327, 1988]. Warming blood has two effects – the first and most important is prevention of hypothermia [Transfusion 31: 558, 1991], but also reduction in viscosity with increases in flow rates of up to 50%

Blood Bank Concepts

Some authors (Miller's Anesthesia, 6th edition, Chapter 55) have questioned whether or not a cross match is really needed. They cite the following statistics – only 1% of previously transfused or pregnant patients (i.e. some prior exposure to non-native red blood cell antigens) will have any non-A or non-B antibodies. Many of these are not reactive at temperatures above 30C. If anti-Rh(D) is accounted for, only 0.1% of these patients will have reactive (A, B, D) antibodies. Thus, a **simple ABO-Rh type reduces the risk of a transfusion reaction to 99.8%**. Screening lowers this risk to 99.94%, and crossmatching lowers it to 99.95% [Polesky HF, Walker RH, ed. Safety and Transfusion Practices, Skokie, IL: College of American Pathologists p. 79, 1982]. Is the crossmatch worth this extra 0.01% of risk (i.e. 1:10,000)?

Type and Cross

What does a "type and cross" actually mean? As always, both the recipient and donor cells are ABO-Rh typed – this alone reduces the risk of a transfusion reaction to 0.2%. In order to further decrease this risk, a small sample of donor blood can be mixed with the recipient's serum. In the first phase (**immediate phase**, 1-5 mins, room temp), ABO errors antibodies and MN, P, and Lewis system antibodies are sought. In the second phase (**incubation phase**, 10-20 minutes), the first phase reactants are heated to 37C in salt solution (or for 30-45 minutes in albumin), additional antibodies (mostly to Rh, but also partial or incomplete Ab) are detected, as the salt solution and/or albumin can facilitate agglutination. In the last phase, (**antiglobulin phase**), antiglobulin sera are added, further increasing the ability of the crossmatch to detect incomplete antibodies (ex. Rh, Kell, Kidd, Duffy). This third step is not essential.

Type and Screen

In a type and screen, as in a type and cross, the recipient and donor cells are ABO-Rh typed (risk of transfusion reaction 0.2% after simply doing an ABO-Rh type). Subsequently, “standard” blood cells (with known, significant non-ABO-Rh-antibodies) are added to the patient’s serum. The major advantage of the type and screen is that it can be performed prior to the operation (ex. a patient’s blood and serum can be typed and screened well in advance of the day of surgery), and, if negative, a 99.94% transfusion risk is assured with ABO-Rh-matched blood. If an antibody is found, the blood bank can then give donor blood negative for the identified antibody, although the blood bank may choose to crossmatch the donor’s blood with the recipient’s serum. An important point is that while typing and screening cannot eliminate all potential transfusion reactions (clinically insignificant reactions may still approach 1%), the *vast majority* of transfusion reactions following a type and screen are benign – in fact, in a study of 13,950 patients, Oberman et al. found only eight “clinically significant” antibodies that were detected by complete crossmatch but not during antibody screening [Oberman et al.] (thus, **the risk of hemodynamically significant transfusion reactions after a negative type and screen is approximately 0.057%**).

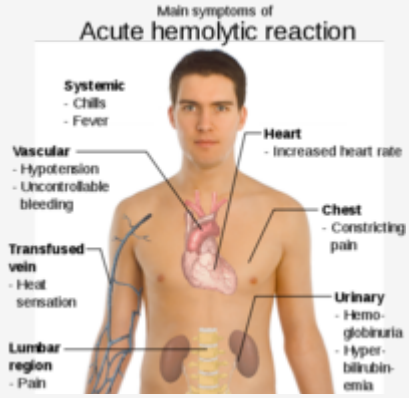
II. Adverse Reactions

Risks of Homologous Blood Transfusion

Complication	Frequency
Immune	
Fever, chills, urticaria	1:100
Hemolysis	1:6000
Fatal hemolysis	1:100,000
Anaphylaxis	1:500,000
Infectious	
Bacterial contamination	1:25,000
Hepatitis B	1:250,000
Hepatitis C	1:1,000,000
HIV	1:2,000,000

(Acute lung injury 1:5000 – < 10% fatality, leading cause of death)

Transfusion Reactions



Acute hemolytic reaction

- Definition: When antibodies to a particular blood antigen already exist. Can be delayed if there is an amnestic response to a transfused RBC antigen to which the recipient is already sensitized.
- Causes: Usually the result of ABO incompatibility and technical errors made during the collection of blood.
- Risks: The risk of acute hemolytic transfusion reaction due to incompatible blood is 1:4 per 1 million units transfused and has a high fatality rate.

Most of the transfused cells are destroyed which can activate the coagulation system with DIC and release of anaphylotoxins and other vasoactive amines. Patients might present with back pain, pain at site of transfusion, headache, change in vital signs, pulmonary edema, bleeding, new/worsening renal failure. Hemolysis, spontaneous hemorrhage, complement activation, and renal failure are possible . This error is usually clerical]. Severe reactions can occur with as little as 10 mL of blood [World J Surg 11: 25, 1987] – common initial signs include fever, dyspnea, chest pain, and low back pain. Hypotension can develop very suddenly. Hypotension is the only obvious sign under general anesthesia, thus always maintain a high level of suspicion. Severe reactions are accompanied by a consumptive coagulopathy and MOD. Acute renal failure occurs in 5 – 10% of cases]. Treat by immediately discontinuing the transfusion, and consider fluid resuscitation with the addition of mannitol or furosemide. Bicarbonate has not been proven to be helpful

Treatment of Acute Hemolytic Reactions
1. Stop the transfusion
2. Check blood pressure

- If BP dropping, give volume
- If BP dropping, start vasopressors (no data as to which are superior)

Once the patient is stabilized…
3. Obtain a blood sample and inspect plasma for pink/red hue of hemoglobin
4. Obtain a fresh urine specimen and dipstick for blood
5. Send blood for direct Coomb's

Transfusion rxn – Lab findings

Definition

Transfusion reactions can be broadly categorized into three categories: **Hemolytic, Delayed Hemolytic, and Nonhemolytic** transfusion reactions. Typical signs and symptoms of a hemolytic transfusion reaction include chest and flank pain, nausea, and chills. These can be masked while under general anesthesia and so, more useful indicators include fever, hypotension, or red colored urine (a result of hemoglobinuria – not frank RBC's in the urine). If a hemolytic transfusion reaction is suspected, in addition to immediately terminating the transfusion and providing the appropriate supportive treatment, it is necessary to perform a laboratory investigation in the form of the following:

Direct antiglobulin test (Coombs Test): Should be performed on patient's post-transfusion serum, if the test is positive and with a negative DAT on a pre-transfusion sample, then a hemolytic transfusion reaction may have occurred. Of note, a negative DAT on a post-transfusion sample does not preclude a hemolytic transfusion reaction, as if most or all of the transfused donor cells have been destroyed by intravascular hemolysis. In this event the test would be a false negative.

Repeat Crossmatching: Repeat ABO typing, Rh typing, and antibody screen of patient's pre/post transfusion samples as well as donor unit samples. If both pretransfusion and posttransfusion blood samples return incompatible, then a pre-transfusion clerical error may be at fault. Of note, the post-transfusion antibody screen may result in a false negative if most of the patient's antibody is bound to donor cells.

Urine Free Hemoglobin: Hemolysis will result in hemoglobinuria and thus a positive urine hemoglobin; however, the presence of intact RBC's indicates bleeding into the urinary tract, NOT hemolysis.

Serum bilirubin: Bilirubin (unconjugated) can be elevated as a byproduct of hemolysis. It is important to note that these levels will peak within 5-7 hours after transfusion, and will return to baseline within 24 hours in the setting of normal renal function.

Serum haptoglobin: Best performed when comparing both pretransfusion and posttransfusion samples, a decrease in serum haptoglobin can indicate hemolysis as haptoglobin binds hemoglobin that is liberated from red blood cells during hemolysis. It is important to note that haptoglobin is an acute phase protein and can be increased in any inflammatory condition including surgery.

Acute Lung Injury

Acute lung injury is possible, but only occurs in 1:5000 transfusions [Intensive Care Med 14: 654, 1988]. The theory is that donor antileukocyte antibodies bind host granulocytes, sequestering them in the pulmonary microcirculation and leading to ARDS. Unlike most cases of ARDS, this variety is fatal in < 10% [Crit Care Med 34S: S114, 2006]. Dyspnea and/or hypoxemia may arise within a few hours, and CXR may show diffuse infiltrates. You CANNOT get pulmonary edema from PRBC because the osmotic pressure is too high – if you see what you think is edema, it's TRALI/ARDS. The process generally resolves within a week. Stop the transfusion and manage as you would ARDS.

Infectious Disease

Highest risk of viral transmission is hepatitis B (1:220,000). < 10 fatalities per year in United States from bacterial infections

TRALI

TRALI is an acute syndrome of dyspnea, hypoxemia, and non-cardiogenic pulmonary edema usually occurring within 6 hours of transfusion and is now the leading cause of mortality following blood transfusion (as of 2005). Stop all

transfusions if ongoing, and if possible consider suctioning fluid from the endotracheal tube to send for protein count.

Immunomodulation

Allogenic transfusions suppress cell-mediated immunity, and may place patients at risk for post-operative infection.

III.

Delayed Hemolytic Transfusion Reaction

- Also known as extravascular hemolysis
- Generally mild and caused by antibodies to non-D antigens of the Rh system or to foreign alleles in other systems such as the Kell, Duffy, or Kidd antigens
- Following an ABO and Rh D-compatible transfusion, patients have a 1-1.6% chance of forming antibodies directed against foreign antigens in other systems. By the time significant amounts of the antibodies have formed, the donor RBCs have been cleared from circulation. Subsequently, the titers of these antibodies decrease over a period of time. A second exposure to these antigens with a subsequent transfusion triggers an anamnestic response against the foreign antigen. This response takes about 2 to 21 days after transfusion to reach significant levels hence why it is referred to as a delayed hemolytic transfusion reaction.
- Symptoms: malaise, jaundice, fever, Hct fails to rise, increased serum unconjugated bilirubin (as a result of Hbg breakdown)
- Diagnosis may be facilitated by the antiglobulin (Coombs) test
- Direct Coombs test detects the presence of antibodies on the membrane of red cells
- *however, this test cannot distinguish between recipient antibodies coated on donor RBCs and donor antibodies coated on recipient RBCs
- Treatment is primarily supportive
- Frequency: 1:12,000 transfusions

IgA deficiency and transfusion

Definition

- Anti-IgA antibodies have been identified in severely IgA deficient patients who experienced infusion reactions to blood products containing small amounts of IgA, typically in plasma, including the following: whole blood, RBCs, plts, FFP, cryoprecipitate, granulocytes, IVIG
- It is suggested that screening for anti-IgA antibodies in all patients with severe IgA deficiency and for patients with partial IgA deficiency who have received blood products in the past and experienced an infusion reaction.
- In patients who have anti-IgA antibodies, it is suggested that repeat testing be done before each administration of plasma-containing blood products (except immune globulin).
- All blood products should be used with caution in IgA deficient patients, and appropriate staff and medication should be available to treat anaphylaxis
- Patients can receive cells that have been washed to remove as much of the contaminating IgA as possible. Desensitization to blood products is another management approach

Febrile transfusion reaction mechanism

Occur in 0.5% of RBC transfusions and 30% of platelet transfusions**.**

Febrile reaction may occur without hemolysis. **Recipient antibodies directed against HLA antigens on donor WBCs or platelets** are the most common cause, although **cytokines released from WBCs of stored products (particularly platelets) may also be a cause.** Relatively common in multitransfused or multiparous patients.

Clinically, febrile reactions consist of a temperature increase of ≥ 1° C, chills, and sometimes headache and back pain. This can take up to 2 hours to manifest. Simultaneous symptoms of allergic reaction are common. Because fever and chills also herald a severe hemolytic transfusion reaction, all febrile reactions must be investigated as with any transfusion reaction.

Most febrile reactions are treated successfully with **acetaminophen** and, if necessary, **diphenhydramine**. Patients should also be treated (eg, with acetaminophen before future transfusions. If a recipient has experienced more

than one febrile reaction, special **leukoreduction filters** are used during future transfusions; many hospitals use prestorage, leukoreduced blood components .

Allergic Reactions

Allergic reactions (rash, anaphylaxis) are a result of sensitivity to donor plasma proteins, usually beginning with urticaria and possibly with fever. Mild urticaria does not require intervention in the absence of fever, however it is common practice to stop the transfusion and give diphenhydramine 25-50 mg PO or IM q6h – the only benefit is relief of pruritus. If the patient has true anaphylaxis, treat it as such (also test these patients for IgA deficiency and avoid future transfusions if at all possible).

Transfusion, leukoreduction

Definition

Although leukocytes are a normal inclusion with whole blood collection they are actually considered a contaminant of the other blood components such as PRBC's and platelets. **They have increasingly been recognized as the cause or contributors to many transfusion reactions such as immunologically-mediated effects, infectious disease transmission (CMV) and reperfusion injury.** Of these reactions the immunological mediated effects are the most common and include febrile non-hemolytic reactions, platelet refractoriness, and transplant rejection. Also included in this group are graft versus host disease (GVHD), immunosuppression and reactivation of viral disease.

Each unit of whole blood contains about 2 to 5 x 109 leukocytes (2 to 5 billion). With leukocyte filtering a 99.9% reduction can be obtained, leaving residual leukocyte counts below 5 x 106. If it were not for cost leukoreduction would likely be performed on all transfusion components. Currently it is recommended that chronically transfused patients, potential transplant recipients, patients with acute leukemia, patients with previous transfusion reactions, CMV seronegative at-risk patients, and patients undergoing

cardiac surgery or oncology surgery should receive leukoreduced blood components