Blood Transfusion: Friend and Foe

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INTRODUCTION AND BRIEF HISTORY

Blood transfusion is an art as well as a science, though we tend to focus on studying the science of transfusion, and the conditions for which it is useful. Transfusion practices have evolved greatly, and despite its many risks, transfusion continues to be an important life-saving tool.

It is worth recalling that for centuries, blood-letting was used liberally for countless illnesses, and excessive use is considered to have been a major factor in the death of George Washington in 1799. The first documented human-to-human transfusion was performed in 1818 by Dr. James Blundell, who successfully transfused 227 ml of blood into a woman with postpartum hemorrhage. He later said: “she felt as if life were infused into her body.”

Even before then, animal-to-animal and human-to-animal transfusions had been performed. Blundell established that blood could safely be transfused from one dog to another dog,* but blood from one species to another was fatal. There is even documentation from 1667 of a transfusion from animal-to-human by Dr. J. Denis (Phil Trans. 1667. p.557). Blood transfusion could be life saving but only in some instances, and it often led to unfortunate consequences, including death.

In the early 1900’s Karl Landsteiner made the important discovery of four blood types, A, B, O, and AB. If the types could be matched between donor and recipient, the outcome would almost always be positive. In the 1940’s it was widely accepted that blood from group O donors could be transfused to a person of any blood type. Landsteiner discovered the Rh factor, which made a significant impact by enhancing the compatibility between recipient and donor.

The International Society of Blood Transfusion (ISBT) recognizes 29 blood group systems with 302 specifcations. The Rh system alone has 56 antigens and with the increasing technologies available in molecular and genetic testing, new antigens are being discovered at a rapid rate. These variations from individual to individual can make compatibility testing extremely difficult in certain patients. Predominantly only the A and B antibodies are naturally occurring, meaning that in order for a patient to develop other antibodies they must have been exposed to blood either by an earlier transfusion or by pregnancy. Some patients are more prone to developing antibodies. Also, not all of the antibodies are clinically significant and will cause a hemolytic transfusion reaction.

The process of storing blood has also evolved. Great progress was made during times of war when the need for treating soldiers on the battlefield pushed the ingenuity of blood bankers to devise ways of accommodating these patients. Red cells currently can be refrigerated and stored for 35 days in citrate-phosphate-dextrose-adenine (CPDA-1) or stored for 42 days when an additive such as Optisol is used, which contains saline, mannitol, additional dextrose, and adenine.

RISKS OF BLOOD TRANSFUSION

The life-saving benefits of blood transfusion are balanced by its risks. Compatibility is the principal issue and it can be very complex. Matching a unit to the correct patient is paramount, hence the meticulous identification process from careful collection and identification of the blood sample, to the intense scrutiny needed to identify the patient and corresponding unit of blood at the bedside by two individuals. ABO incompatibility is a preventable, potentially deadly consequence of blood transfusion with an incidence of 1:38,000-1:70,000, with some estimates as high as 1:14,000. (Some administrative errors may lead to a

* Interestingly, although dogs do have at least six and possibly more blood “types” due to different erythrocyte surface antigens, they do not have clinically significant antibodies, and can usually tolerate a first transfusion even if grossly mismatched.
specific unit going to the wrong patient, but some units are nevertheless compatible by chance, so mismatching may not inevitably result in a hemolytic transfusion reaction.) Many other complications can occur which include febrile reactions, urticarial and anaphylactic reactions, transfusion related acute lung injury and circulatory overload (please refer to Table 1). Delayed reactions include alloimmunization to RBC antigens and HLA antigens, delayed hemolytic transfusion reactions, graft vs host disease, post transfusion purpura, immunomodulatory effects, and iron overload.6

Transfusion-related acute lung injury (TRALI) occurs during or after transfusion, generally within six hours. It is associated with white blood cell antibodies in the donor reacting with WBCs in the recipient (or occasionally vice versa), leading to microaggregation in pulmonary capillaries. These microaggregates prevent adequate oxygen exchange which in turn leads to dyspnea to a degree requiring oxygen by nasal cannula or even ventilatory assistance. If a patient has pre-existing congestive heart failure or other respiratory illness, the diagnosis of a transfusion reaction is difficult, since simple fluid overload as the cause of symptoms cannot be entirely excluded. The diagnosis can only be definitively made if an HLA or neutrophilic antigen is identified on the recipient’s WBCs for which a corresponding antibody is found in the donor’s plasma. Since most antibodies in plasma are found in donors who have either received blood transfusions or have had multiple pregnancies, multiparous women and previously transfused blood donors have been excluded from donating plasma and platelets in the United States since November 2008 (November 2007 at LGH). This strategy has reduced the risk of TRALI worldwide.7,8

Infectious disease testing is a major part of blood banking and has perhaps received the most public attention. Since the 1940’s, as transfusion became more widespread, the concern for infections transmitted by blood transfusion has been acute, beginning with concern about Hepatitis B, followed by HIV, Hepatitis C, West Nile virus (WNV), new variant CJD (Creutzfeldt-Jakob disease), sepsis associated with blood transfusion, Chagas disease, and Babesiosis. Table 2 includes a timeline of blood donor testing as it has evolved.3,9 Table 3 lists the current infectious disease risks of blood transfusion.5

With the advent of nucleic amplification testing, the risk of HIV, HCV, WNV and now HBV have been reduced substantially, though not to zero. And despite some initial studies of manufacturing universal donor red cells from stem cells, there will most likely never be zero risk. The safest transfusion is avoidance of transfusion, followed by autologous transfusion which can still carry the risk of bacterial contamination, fluid overload, or hemolytic transfusion reaction if misidentification of the blood or the patient occurs at the time of administration of the blood component.

Table 1. Non-Infectious Complications of Blood Transfusion

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Etiology</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic</td>
<td>1:38,000-1:70,000</td>
<td>Red cell Incompatibility</td>
<td>Chills, fever, hemoglobinuria, hypotension, renal failure, DIC, back pain</td>
</tr>
<tr>
<td>Febrile</td>
<td>About 1:100</td>
<td>Antibody to donor WBCs or accumulated cytokines in platelet unit</td>
<td>Fever, chills, rigors, headache, vomiting</td>
</tr>
<tr>
<td>Urticarial</td>
<td>About 1:100</td>
<td>Antibody to donor plasma proteins</td>
<td>Urticaria, pruritis, flushing</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>1:20,000 to 1:50,000</td>
<td>Antibody to donor plasma proteins (includes IgA)</td>
<td>Hypotension, urticaria, bronchospasm, local edema, anxiety</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury</td>
<td>1:5,000 to 1:190,000</td>
<td>WBC antibodies in donor (occasionally in recipient)</td>
<td>Hypoxemia, respiratory failure, hypotension, fever, bilateral pulmonary edema</td>
</tr>
<tr>
<td>Transfusion-associated sepsis</td>
<td>Varies by component (more common with platelets)</td>
<td>Bacterial contamination</td>
<td>Fever, chills, hypotension</td>
</tr>
<tr>
<td>Circulatory overload</td>
<td>&lt;1%</td>
<td>Volume overload</td>
<td>Dyspnea, orthopnea, cough, tachycardia, hypertension, headache</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Dependent on clinical setting</td>
<td>Rapid infusion of cold blood</td>
<td>Cardiac arrhythmia</td>
</tr>
</tbody>
</table>

Blood Transfusion: Friend or Foe

RECENT INFECTIOUS DISEASE CONCERNS

It is appropriate to comment briefly on the more recent infectious disease concerns including West Nile Virus, Chagas disease, and Babesiosis. WNV first appeared in the US in 1999 and has become endemic especially in the warmer months of the year. It is mostly transmitted between birds and mosquitoes but has infected humans. In 2003, Nucleic Acid Technology (NAT), an unlicensed test under an Investigational New Drug application (IND), became available and recently became licensed. LGH participated in the IND for HIV NAT and HCV NAT, and we also participated in the WNV study. In 2002 there were 23 confirmed cases of WNV transmitted via blood transfusion nationwide. Since implementation of NAT testing, there were 3 transmissions between 2004 and 2006. Since that time additional precautions have been added such as changing from pooled donor testing to single donor testing when incidence is high in a region.

Chagas disease has been a concern for a couple of decades, generally in specific areas of the country where there is a high influx of people emigrating from Mexico, Central, and South America. As the country becomes more diverse there is concern even of possible transmission from person to person within the United States. In the past, donors who have lived outside of the U.S. for a period of time were tested for Chagas disease. As of July 2011 all donors are tested for Trypanosoma cruzi. Other travel-based risks include malaria exposure and new-variant Creutzfeldt-Jakob disease (mad cow disease). Several cases of transmission of vCJD by blood products have occurred in the United Kingdom.

Babesiosis is another parasitic infection that can be transmitted by blood transfusion, which has occurred in more than 70 cases in the US with at least 12 deaths. Babesia microti is tick borne as is Borrelia burgdorferi which causes Lyme disease. Babesia is most common in the northeast and upper Midwest. There is no FDA licensed blood donor screening test for Babesia or Borrelia.

Bacterial contamination of blood products is also a major concern. Platelets, because they are stored at room temperature, are the most likely product to be affected. Bacterial testing of all platelets is currently being performed on leukoreduced as well as non-leukoreduced platelet products.

IMMUNOMODULATORY EFFECTS

Perhaps the most prevalent risk is one that is often not considered by clinicians. More and more information is being presented about transfusion

Table 2. Timeline of Blood Donor Testing

<table>
<thead>
<tr>
<th>Year</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940's</td>
<td>Syphilis testing of blood donors</td>
</tr>
<tr>
<td>1971</td>
<td>HIV antibody testing</td>
</tr>
<tr>
<td>1985</td>
<td>Hepatitis B surface antigen testing</td>
</tr>
<tr>
<td>1987</td>
<td>Hepatitis B core antibody and ALT</td>
</tr>
<tr>
<td>1989</td>
<td>HTLV I antibody testing</td>
</tr>
<tr>
<td>1990</td>
<td>First HCV antibody testing</td>
</tr>
<tr>
<td>1991</td>
<td>Second generation HCV antibody testing</td>
</tr>
<tr>
<td>1992</td>
<td>HIV-1 and HIV-2 antibody testing</td>
</tr>
<tr>
<td>1996</td>
<td>HIV p24 antigen testing</td>
</tr>
<tr>
<td>1999 and 2000</td>
<td>Investigational use of HCV and HIV NAT tests</td>
</tr>
<tr>
<td>2003</td>
<td>Investigational use of WNV NAT testing</td>
</tr>
<tr>
<td>2003</td>
<td>Licensure of NAT for HIV and HCV</td>
</tr>
<tr>
<td>2007</td>
<td>Licensure of NAT for WNV</td>
</tr>
<tr>
<td>2011</td>
<td>Bacterial testing of all platelet products</td>
</tr>
<tr>
<td>2011</td>
<td>Chagas disease testing required</td>
</tr>
</tbody>
</table>

Table 3. Infectious Disease Complications of Blood Transfusion

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Estimated Risk per Unit Transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV1 and 2</td>
<td>1:1,400,000 to 1:2,400,000</td>
</tr>
<tr>
<td>HTLV I and II</td>
<td>1:256,000 to 1:2,000,000</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1:1,000,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1:137,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1:872,000 to 1:1,700,000</td>
</tr>
<tr>
<td>B19 parvovirus</td>
<td>1:3,300 to 1:40,000</td>
</tr>
<tr>
<td>Bacteria</td>
<td>RBCs&lt;1:1,000</td>
</tr>
<tr>
<td></td>
<td>Platelets screened by pH and glucose&lt;1:2000</td>
</tr>
<tr>
<td></td>
<td>Platelets screened by aerobic culture&lt;1:10,000</td>
</tr>
<tr>
<td>Babesia and malaria</td>
<td>&lt;1:1,000,000</td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>unknown</td>
</tr>
</tbody>
</table>

causing immunomodulation which presents itself as increased risk of infection and longer hospital stays. There are dramatic differences in practices nationally and internationally in terms of the trigger levels used to initiate transfusion. The US transfuses 44% more blood per capita than Canada and more per capita than the UK and Europe. Many patient populations have been shown to do better with hemoglobins of 7 vs 10 and there appears to be a dose relationship between number of units of blood given and infection rates.\textsuperscript{15,17} The cost of blood is skyrocketing even as the dollars allotted to medical care are being reduced. The average cost of a unit of blood is $250, but there is the additional cost of administering the blood and monitoring the patient. A potential four-fold increase in cost for increased infection rates and longer hospital stays is added to the overall cost of a blood transfusion. These are important facts to weigh when making the decision to transfuse or not to transfuse.

Leukoreduced products are considered safer and are the only products provided by most major blood centers including the American Red Cross. Leukoreduction is known to reduce the risk of febrile reactions, decrease alloimmunization and reduce risk of becoming refractory to platelet transfusions. It also removes WBC’s that may be carrying viruses, such as CMV. Some experts believe leukoreduction also decreases or slows the process of red cell storage injury which would perhaps decrease some of the immunomodulatory effects of transfusion.\textsuperscript{17} At LGH most red cells and platelets are leukoreduced prior to storage. Almost 100% leukoreduction is anticipated in the near future as we accomplish technical upgrades in our cell separator apheresis blood collection. Another limiting factor is that pre-storage leukoreduction must occur within 8 hours of collection if platelets are also to be made from a whole blood collection. As we have lengthened the storage time of blood, there are also concerns that older blood may be more harmful to patients.\textsuperscript{16} Close to 90% of the blood transfused at LGH is less than 14 days old.

Although blood transfusion has unquestionable benefit in certain situations, its use should be conservative. Figure 2 lists the indications for transfusion at LGH. Approximately 75% of red cell units go to patients with Hb > 7.0, an experience we hope to change. The blood order form currently used at LGH is demonstrated in figure 1 which also lists the indications. When ordering blood, not only should the physician include what product and how much of it should be given, but also the indication for transfusion.

LGH currently transfuses an average of 1014 units of red cells, 191 units of FFP, and 110 platelet pools or single donor platelets per month. Transfusion complications were primarily pyrogenic, allergic or urticarial, or related to fluid overload with no documented TRALI related complications in the last year. There have been no reported transmissions of hepatitis or HIV in many years (since 1991 for HIV). We currently collect about 76% of our transfusion needs. Our goal for the next fiscal year is to increase collection to 87% of our needs and to reduce usage by 10%.

CONCLUSION

Making the decision to transfuse blood should not be done lightly. While many of the infectious disease risks have decreased, more recent literature focuses on the immunomodulatory effects of blood transfusion. Conservative use of blood products with weighing of the risks and benefits and careful consideration of the individual patient’s clinical status can provide enhanced care and benefit to the patient, combining both the science and the art of blood transfusion therapy.
**Lancaster General Hospital**

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**Physician Orders**

**Adult Blood Product Order Form**

Current Armband R# ________________________ (filled in by Nursing)

1. **Diagnostic Labs**
   - [ ] Hold Blood Bank Specimen (No testing performed)
   - [ ] Type and Screen (No product order)
   - [ ] RED BLOOD CELLS TYPE & CROSSMATCH:
     - [ ] Type and Crossmatch _______ units
     - Comments: [ ] Autologous [ ] Directed
     - [ ] Hold 72 Hours (New order is needed for blood transfusion)
     - [ ] Preop for surgery (date)
     - [ ] Open Heart Surgery (OHS) (date)

2. **Transfusion/Administration**
   - [ ] No Specific Requirements / Leukoreduced if available
   - [ ] Washed
   - [ ] Irradiated (Required if possible Ventricular Assist Device)

   - [ ] CMV Negative
   - [ ] Leukoreduced (Required Open Heart Surgery)
   - [ ] Sickle Negative (Indicated for Sickle Cell Anemia)

**Product Requirements**
- [ ] Hold Blood Bank Specimen (No testing performed)
- [ ] Type and Screen (No product order)
- [ ] Irradiated (Required if possible Ventricular Assist Device)
- [ ] CMV Negative
- [ ] Leukoreduced (Required Open Heart Surgery)
- [ ] Sickle Negative (Indicated for Sickle Cell Anemia)

**PHYSICIAN STAMP / PRINTED NAME**

**PHYSICIAN SIGNATURE**

**DATE/TIME**

2. **Transfusion/Administration**
   - [ ] STAT [ ] Today Date to be Administered: ____________
   - [ ] Hold Blood Bank Specimen (No testing performed)
   - [ ] Type and Screen (No product order)
   - [ ] Irradiated (Required if possible Ventricular Assist Device)
   - [ ] CMV Negative
   - [ ] Leukoreduced (Required Open Heart Surgery)
   - [ ] Sickle Negative (Indicated for Sickle Cell Anemia)

**Product Requirements**
- [ ] Hold Blood Bank Specimen (No testing performed)
- [ ] Type and Screen (No product order)
- [ ] Irradiated (Required if possible Ventricular Assist Device)
- [ ] CMV Negative
- [ ] Leukoreduced (Required Open Heart Surgery)
- [ ] Sickle Negative (Indicated for Sickle Cell Anemia)

**PHYSICIAN STAMP / PRINTED NAME**

**PHYSICIAN SIGNATURE**

**DATE/TIME**

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**Fig. 1**

**Blood Transfusion: Friend or Foe**

- **Rapid Blood Loss with**
  - [ ] Presumed Rapid Blood Loss with greater than 30-40% of estimated blood volume (greater than 1500-2000mL) not responding to appropriate volume resuscitation, OR
  - [ ] With ongoing blood loss

**Fresh Frozen Plasma**
- Transfuse _______ units
  - **Checkmark indication for transfusion below.**
    - [ ] Abnormal coagulation studies and significant hemorrhage
    - [ ] Post Cardiac/Vascular procedure coagulopathy
    - [ ] Emergent reversal of Coumadin/Warfarin

**Platelets**
- Transfuse _______ units
  - **Checkmark indication for transfusion below.**
    - [ ] Platelet count less than 10,000/eq3 prophylactically in a patient with failure of platelet production
    - [ ] Platelet count less than 20,000/eq3 and signs of hemorrhagic diathesis (petechiae, mucosal bleeding)
    - [ ] Active hemorrhage
    - [ ] Invasive procedure (recent, in-progress, planned)

**Cryoprecipitate**
- Transfuse _______ units
  - **Checkmark indication for transfusion below.**
    - [ ] Fibrinogen less than 100mg/dl
    - [ ] Fibrinogen less than 150 mg/dl with active hemorrhage

**Follow-up Labs:**
- [ ] Hgb and Hct _______ hrs post infusion
- [ ] Platelet count _______ hrs post infusion

**Comments:**
- [ ] PT/INR _______ hrs post infusion

**Autologous**
- [ ] Directed

**Sickle Negative**
- [ ] Directed

**CMV Negative**
- [ ] Directed

**Directed**
- [ ] Directed

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**Rev. 8/11**
## BLOOD PRODUCT USAGE SCREENING CRITERIA

**Packed red blood cells or whole blood, homologous and autologous**—One of:

1. Hgb < 7 gm/dl or Hematocrit < 21%
2. Hemoglobin less than 8gm/dL or Hematocrit less than 24% in a patient with coronary artery disease and unstable angina/myocardial infarction/cardiogenic shock
3. Patient age greater than 65 years with Hgb less than 8 gm/dL OR less than 10gm/dL for autologous transfusion
4. The patient has been determined to be normovolemic and there is evidence to support the need for increased oxygen carrying capacity as witnessed by tachycardia, hypotension not corrected by adequate volume replacement alone, PVO2 less than 25 torr, extraction ratio greater than 50%, VO2 less than 50% of baseline
5. Rapid blood loss with greater than 30-40% of estimated blood volume (greater than 1500-2000mL) not responding to appropriate volume resuscitation, or with ongoing blood loss

**Platelets** (normal range = 150,000-450,000)—One of:

1. Platelet count less than 10,000/cc³ prophylactically in a patient with failure of platelet production
2. Platelet count less than 20,000/cc³ and signs of hemorrhagic diathesis (petechiae, mucosal bleeding)
3. Platelet count less than 50,000/cc³ in a patient with active hemorrhage or invasive procedure (recent, in-progress, planned)
4. Qualitative platelet disorder, e.g. post cardiopulmonary bypass
5. MA <45 minutes (TEG)

**Fresh Frozen Plasma (FFP)**—One of:

1. Abnormal coagulation studies and significant hemorrhage
2. Prophylactic use for PT/APTT greater than 1.5 times the mean of the reference range
3. Emergent reversal of Coumadin/warfarin
4. PT > 16, or INR >1.8, with bleeding or anticipated invasive procedure PTT > 35 (normal = 21.1-29.7), with bleeding or anticipated invasive procedure
5. Documented coagulation factor deficiency with bleeding
6. Hemolytic uremic syndrome or thrombotic thrombocytopenic purpura (TTP)
7. Massive transfusions > 10 units of packed cells and/or whole blood
8. > 1500 cc cell saver blood reinfused
9. R >10 minutes (TEG)

**Cryoprecipitate (Cryo)**—One of:

1. Isolated Factor VIII deficiency (Hemophilia A or Van Willebrand’s disease)
2. Isolated Factor IX deficiency
3. Isolated Factor XIII deficiency
4. Fibrinogen less than 100mg/dL. Fibrinogen less than 150 mg/dL with active hemorrhage
5. Patient with surgical coagulopathy
6. Use as local factor coagulant during surgery
7. Alpha <45 degrees (TEG)
REFERENCES


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