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, bloodletting 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."[1] 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. Also at that time Landsteiner discovered the Rh factor, which made a significant impact by enhancing the compatibility between recipient and donor.1

The International Society of Blood Transfusion (ISBT) recognizes 29 blood group systems with 302 specificities. 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.[2] 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.[3,4] 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.[2]

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.[5] (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).[5] 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

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

From: 15th edition of AABB Technical Manual (2005), pp. 634-635.

Table 2. Timeline of Blood Donor Testing

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

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 mosquitos 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.[10,11] 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.[13] 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.[13] Other travel-based risks include malaria exposure and new-variant Creutzfeldt-Jakob disease (mad cow disease). Several cases of transmission of nvCJD by blood products have occurred in the United Kingdom.[13]

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.[12,13] Babesia microti is tick borne as is Borrelia burgdorferi which causes Lyme disease.[14] 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.[13] 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 3. Infectious Disease Complications of Blood Transfusion

Infectious Agent	Estimated Risk per Unit Tranfused
HIV1 and 2	1:1,400,000 to 1:2,400,000
HTLV I and II	1:256,000 to 1:2,000,000
Hepatitis A	1:1,000,000
Hepatitis B	1:137,000
Hepatitis C	1:872,000 to 1:1,700,000
B19 parvovirus	1:3,300 to 1:40,000
Bacteria	RBCs-1:1,000 Platelets screened by pH and glucose- 1:2000 to 1:4000 Platelets screened by aerobic culture-<1:10,000
Babesia and malaria	<1:1,000,000
Trypanosoma cruzi	unknown

From: 15th edition AABB Technical Manual (2005) p. 700.

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.[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 fourfold 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.[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 prestorage 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.[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.

Fig. 1

Lancaster General Hospital
Lancaster General Health

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)*

     Product Requirements

     ☐ No Specific Requirements / Leukoreduced if available ☐ CMV Negative
     ☐ Washed ☐ Leukoreduced (Required Open Heart Surgery)
     ☐ Irradiated (Required if possible Ventricular Assist Device) ☐ Sickle Negative (Indicated for Sickle Cell Anemia)

_____ _____ / _____
PHYSICIAN STAMP / PRINTED NAME PHYSICIAN SIGNATURE DATE/TIME

2. **Transfusion/Administration** ☐ STAT ☐ Today Date to be Administered: _____

   Product Requirements

   ☐ No Specific Requirements / Leukoreduced if available ☐ CMV Negative
   ☐ Washed ☐ Leukoreduced (Required Open Heart Surgery)
   ☐ Irradiated (Required if possible Ventricular Assist Device) ☐ Sickle Negative (Indicated for Sickle Cell Anemia)

   ☐ **RED BLOOD CELLS (TRANSFUSE):**
   - ☐ Type and Crossmatch _____ units Comments: ☐ Autologous ☐ Directed

     Transfuse _____units

     Checkmark indication for transfusion below.
     - ☐ Hemoglobin *less than* 7gm/dL or Hematocrit *less than* 21%
     - ☐ Hemoglobin *less than* 8gm/dL or Hematocrit *less than* 24% in a patient with unstable angina/myocardial infarction/cardiogenic shock
     - ☐ The patient has been determined to be normovolemic and there is evidence to support the need for increased oxygen carrying capacity as witnessed by (indicate):
       - ☐ 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-*specify*_____
       - ☐ Sepsis/Septic Shock not responding to first line treatment
       - ☐ Other-*specify*
     - ☐ 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 ☐ Random or Single Donor Platelets acceptable ☐ 6 units ☐ 12 units
   ☐ Random Donor Platelets ☐ 6 units ☐ 12 units
   ☐ Single Donor Platelets ☐ 6 equivalent units ☐ 12 equivalent units
   ☐ Random Donor Platelets ☐ 4 units

   Checkmark indication for transfusion below.
   - ☐ Platelet count *less than* 10,000/cc3 prophylactically in a patient with failure of platelet production
   - ☐ Platelet count *less than* 20,000/cc3 and signs of hemorrhagic diasthesis (petechiae, mucosal bleeding)
   - ☐ Platelet count *less than* 50,000/cc3 in a patient with (indicate):
     - ☐ Active hemorrhage ☐ Invasive procedure (recent, in-progress, planned)
   - ☐ Platelet count dysfunction with acute hemostatic need.
   - ☐ Platelet count less than 100,000 in neurosurgical patient.

   ☐ **CRYOPRECIPITATE - *Checkmark indication for transfusion below.***

   Transfuse _____ units
   - ☐ Fibrinogen *less than* 100mg/dL ☐ Fibrinogen *less than* 150 mg/dL with active hemorrhage

3. **Follow-up Labs:**

   ☐ Hgb and Hct ____hrs post infusion ☐ Next AM ☐ PT/INR ___hrs post infusion ☐ Next AM
   ☐ Platelet count ____ hrs post infusion ☐ Next AM ☐ Other: _____

_____ _____ / _____
PHYSICIAN STAMP / PRINTED NAME PHYSICIAN SIGNATURE DATE/TIME

Rev. 8/11

* L G H A 6 9 6 2 *

Fig. 2

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/cc^3 prophylactically in a patient with failure of platelet production
2. Platelet count *less than* 20,000/cc^3 and signs of hemorrhagic diasthesis (petechiae, mucosal bleeding)
3. Platelet count *less than* 50,000/cc^3 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

1. Mollison, P. L., C. P. Enbelfriet, M. Contreras. Blood Transfusion in Clinical Medicine, 8th edition. Blackwell Scientific Publications, Boston, 1987: xix, 41.
2. J.D. Roback, M.R. Combs, B. Grossman, C.D. Hillyer, Eds. AABB Technical Manual, 16th edition. American Association of Blood Banks, Bethesda, 2008: 200, 466.
3. Blood History Timeline. 1920-1949: www.pbs.org/wnet/redgold/history/timeline4.html 11/29/2010.
4. The History of Blood Transfusion Medicine BloodBook, Blood Information for Life: www.bloodbook.com/trans-history.html 11/29/10.
5. Brecher, M.E., Ed. Look It Up! (A Quick Reference in Transfusion Medicine). AABB Press, Bethesda, 2006: 116-122, 142-143.
6. Paxton, A. Closing the Gap in Transfusion-related Iron Overload, CAP Today. 2010; 24, number 5: 1, 30-36.
7. Chapman, C.E. et al. Serious Hazards of Transfusion Steering Group. Ten Years of Hemovigilance Reports of Transfusion-related Acute Lung Injury in the United Kingdom and the Impact of Preferential Use of Male Donor Plasma, Transfusion 2009, 49: 440-452.
8. Nakayawa, H et al. Impact of FFP from Male-only Donors Versus Mixed-sex Donors on Postoperative Respiratory Function in Surgical Patients: A prospective Case-controlled Study, Transfusion 2009;49: 2434-2441.
9. Aubuchon, J. and W. Dzik. Reports on Clinical Transfusion Medicine in the Early Days of Transfusion, Transfusion 2010; 50: 963-967.
10. Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion, US Department of Health and Human Services, FDA Center for Biologics Evaluation and Research November 2009.
11. O'Brien, S. et al. West Nile Virus in 2006 and 2007: The Canadian Blood Services Experience, Transfusion 2010; 50: 1118-1125.
12. Transfusion-Transmitted Babesia. AABB Association Bulletin 09-06 (August 5, 2009).
13. Perkins, H.A. and M.P. Busch. Transfusion-associated Infections: 50 Years of Relentless Challenges and Remarkable Progress, Transfusion 2010; 50: 2080-2099.
14. Kontra, J. Tick-Borne Illnesses, Part I: Lyme Disease, Anaplasmosis, and Babesiosis. J Lanc Gen Hosp. 2010. 2:42-49. www.jlgh.org/Past-Issues/Volume-5---Issue-2/Tick-Borne-Illnesses-Part-I--Lyme-Disease-Anapla.aspx
15. Hannon, T. Strategic Blood Management Presentation, 2009.
16. Nelzer, G. et al. Transfusion Practice in the Intensive Care Unit: a 10 Year Analysis, Transfusion 2010; 50: 2125-2134.
17. Hebert et al. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care, NEJM 1999; 340: 409-417.

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