INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

GUIDE TO INFECTION CONTROL IN THE HEALTHCARE SETTING

Transfusions

Author
Kimberly Williams Sanford, M.D.

Chapter Editor
Ziad Memish, M.D.

Topic Outline

Chapter last updated: June, 2019

KEY ISSUE

In the United States, approximately 21 million units of blood components are transfused annually and although steps are taken to ensure the blood supply is safe, there are infectious and non-infectious transfusion-related adverse events. In 2015, the Food and Drug Administration reported 42 documented transfusion-related mortalities. Due to the risks and the high costs associated with transfusion and treatment of adverse events, hemovigilance programs and blood utilization/management programs have been the subject for national and international organizations of transfusion services to improve patient safety.

KNOWN FACTS

- Prevention of transfusion transmitted infectious agents (TTIs) remains a key element of blood-transfusion safety, including an asymptomatic infectious phase in the donor and the ability to persist despite processing and storage.
- Measures taken by national and international transfusion services including donor deferral, testing, and pathogen-reduction technologies (PRTs) have advanced remarkably in terms of speed of assessment and implementation and efficacy of interventions.
- Since the 1970s, introduction of serological assays targeting virus-specific antibodies and antigens has been effective in identifying blood donations infected with the classic TTIs: HBV, HIV, human T-cell lymphotropic virus types I and II, HCV.
- Nucleic acid testing (NAT) to screen for bloodborne pathogens (HIV,HBV, HCV) and excluding donors with high-risk backgrounds or behaviors have decreased the risk of transfusion-related disease transmission considerably by detecting acute window period and occult infections.

- NAT screening has also been implemented for other acute infections transmitted by blood components (eg, WNV and ZIKV in the United States, and hepatitis E virus in Japan and some European countries).
- To reduce the cost of donor testing, all DNA testing of donors is performed in mini-pools where 8 to 16 donor sera are pooled together, and the NAT is performed on the pool. If the mini-pool nucleic acid test (MP-NAT) is positive, then each donor in the pool is individually tested.
- The high level of transfusion safety in high-income countries has not been matched in most low- to middle-income countries. According to WHO 2013 Global Database survey, more than 95% of countries reported having a policy of screening all donations for HIV, HBV, and HCV by serology. However, only two of 46 countries in Africa reported using NAT. Thus, it is estimated that as many as 5-10% of transfusions lead to a transfusion transmitted infection.
- Most patients are concerned about the transmission of emerging bloodborne pathogens from transfusion; however, the greatest risk to patients is the non-infectious complications of transfusion.
- In 2015, three of the most common causes for transfusion-related mortality were transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload, and transfusion-associated sepsis.
- Bacterial screening is still a major concern primarily in platelets because they are stored at room temperature and without a preservative. It is estimated that between 1:1000 and 1:4000 units are bacterially contaminated, but the incidence of septic transfusion reaction is much lower: 1/75,000 platelet transfusions and 1/500,000 RBC transfusions. The AABB standards require blood collection facilities to employ methods to limit and detect platelet contamination by bacteria. Platelet additive solutions and pathogen reduction systems are now available in the United States but the shelf life is still limited to 5 days and are not readily available in all locations in the country at the time of this writing.
- Approximately 41,000 blood donations are needed daily in the United States to support patients requiring transfusion.

- Currently, the risk of transfusion-transmitted infections in the United States is low but with emerging pathogens and persistent bacterial contamination of platelets, PRT has become more attractive. PRT can also inactive donor lymphocytes negating irradiation requirements as an additional benefit. At this time there is no requirement for PRT but its use in platelets is growing in the United States.
- Leukocyte reduction of blood products reduces the transmission of cytomegalovirus (CMV) and reduces the risk of HLA alloimmunization to prevent platelet transfusion refractoriness.

Controversial Issues

- Directed donations increase the risk of post-transfusion hepatitis since most donors feel obligated to donate and may not answer questions regarding high-risk behavior honestly.
- Autologous donations are not recommended because it induces a pre-surgical anemia in the patients, patients still experience transfusion reactions from storage lesions, and the risk of mistransfusion with the wrong unit of blood still exists.
- Leukocyte reduction theoretically decreases the incidence of febrile non-hemolytic transfusion reactions (FNHTR) caused by cytokines released from leukocytes in stored cellular blood components; however, universal leukocyte reduction has not decreased the incidence of FNHTR. This suggests there are other causative agents for FNHTR.
- Transfusion-related immunomodulation (TRIM) related to non-leukocyte reduced blood components is associated with suppression of the recipient's immune defenses and related with increased infections and risk of malignancy. Therefore, universal leukocyte reduction was believed to reduce the clinical sequelae caused by TRIM but these results have been contradictory.

SUGGESTED PRACTICE

General Principles

- Consider alternatives before transfusion and optimize the patient's pre-surgical hemoglobin.
- Hemoglobin levels alone should not be an indication for transfusion. Patients should be assessed for signs and symptoms of anemia.
- Blood collections facilities must follow a standardized protocol for screening and interviewing potential donors (see *Table 38.2*).
- The U.S. FDA requires routine screening for syphilis (non-treponemal test), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV1-2), human T-leukemia virus (HTLV-I/II), *Trypanosoma cruzi*, West Nile virus (WNV), and Zika virus (ZV).
- Blood transfusion and the use of derivatives should follow a careful protocol with registration of donor, serological studies, recipient, reasons to be transfused, and amount transfused.
- Platelets should be subject to strict protocols to make sure bacterial contamination has not occurred, including 24-48 hours cultures.
- Discontinue all transfusions immediately when a patient is experiencing adverse symptoms, check that the unit is labeled with the correct patient and medical record number and report it to the blood bank.
- Patients experiencing dramatic elevations in temperature (>2 C) during transfusion or fevers associated with chills and hypotension should have cultures of the blood component bag and the recipient's blood performed to exclude transfusion associated microbial infections.

Table 1: Infectious Disease Agents Associated with Transfusion-Associated Infections

Infectious Disease Agents	Risk of Transfusion Transmission

Hepatitis B virus	1 in 1/220,000-357,000 units when HBsAg and anti-HBc is performed, 1:843,000 to 1:1.2 million when MP-NAT used
Hepatitis C virus	Very low (1 in 1.1 million units when MP-NAT used)
Human immunodeficiency 1-2	Very low (1 in 1.5 million when MP-NAT used)
Hepatitis A, D, E viruses	Low to very low
Hepatitis G virus	Absent
Cytomegalovirus (CMV)	Risk of transmission in susceptible patients transfused with seronegative cellular components is 1-2%, risk of transmission with leukoreduced cellular components is 2-3%
Variant Creutzfeldt-Jakob disease (vCJD)	Since 1995 there have been 4 documented cases worldwide of transfusion-transmitted vCJD
Babesia spp.	*Babesia* spp. incidence is 1/100,000 in unscreened RBC units, as high as 1/18,000 in endemic areas

Zika virus	As of 2016, Zika virus is active in 61 countries with 4 cases of transfusion transmission in Brazil
Dengue virus, Chikungunya virus, St Louis encephalitis virus, *Leishmania* spp., *Plasmodium* spp., *Trypanosoma cruzi* *WNV & HTLV1/2*	Agents with scientific evidence of risk to blood safety
Chronic wasting disease, hepatitis A, human herpesvirus 8 (HHV-8), HIV variants, human parvovirus B19, influenza A (H5N1), spumavirus, *Borrelia burgodorferi*	Agents with absent to low scientific evidence of risk to blood safety
Viruses: Colorado tick fever virus, Crimean-Congo hemorrhagic fever virus, Eastern equine encephalitis, Epstein-Barr virus, hepatitis G virus, hepatitis B virus variants, hepatitis E virus, herpes viruses (excluding CMV & HHV-8), HTLV variants, influenza A & B, Japanese encephalitis virus, La Crosse virus, Lassa virus,	Agents evaluated but no prioritization for risk to blood safety

lymphocytic choriomeningitis, Marburg virus, monkeypox virus, mumps, papillomaviruses, polyomavirus, porcine endogenous retrovirus, porcine parvovius, rhabdovirus, SARS coronavirus, tickborne encephalitis, Torque teno virus, vaccinia virus, variola virus, Western equine encephalitis virus Rickettsial agents: *Anaplasma phagocytophilum, Ehrlichia chaffeensis, Orientia tsutsugamushi, Rickettsia prowazekii, R. rickettsii* Bacterial agents: *Coxiella burnetii, Borrelia* spp., *Brucella* spp., *Yersinia enterocolitica*, *Y. pestis* Protozoan & Nematode agents: Filariae, *Toxoplasma gondii*, *Trypanosoma brucei*	

Table 2: Physical Examination Requirements of Donors

General appearance	**Must appear in good health**

Skin	Venipuncture site must be free of lesions and free of stigmata of IV drug abuse
Temperature	≤ 37.5 C (99.5 F), measured orally
Pulse	Regular and between 50-100 beats per minute (bpm), <50 bpm may be accepted if an athlete
Blood pressure	Not > 180 systolic and 100 diastolic
Hemoglobin and hematocrit	≥ 12.5 g/dL or 38%, respectively

Table 3: Criteria for Protection of Recipients of Donor Blood

Reason for deferral	Length of Deferral Period
• Viral hepatitis after 11th birthday • Family history of CJD (Creutzfeldt-Jakob disease) • Travelers who have spent more than 3 months in the United Kingdom or 5 years total in Europe due to risk of vCJD areas • Received a blood transfusion in the United Kingdom or France • Received bovine insulin manufactured in UK • Receipt of dura mater or pituitary growth hormone of human origin • Confirmed positive test for HbsAg *or* repeatedly reactive test for anti-HBc • Present or past clinical or lab evidence of infection with HIV, HCV, HTLV, or *T. Cruzi* as excluded by current FDA regulations and recommendations for	Indefinite

the prevention of HIV transmission by blood and components • Use of bovine insulin manufactured in UK • Use of etretinate (Tegison) • History of babesiosis • Obvious stigmata of parenteral drug use or use of a needle to administer non-prescription drugs • Receiving money or drugs for sex	
Acitretin (Soriatane)	3 years after last dose
Malarial infection (after becoming asymptomatic)	3 years after resolution of symptoms
Lived for more than 5 years in malaria-endemic areas (after departure, if symptom free)	3 years after departure if asymptomatic
History of syphilis or gonorrhea, treatment for syphilis or gonorrhea, or positive syphilis screening test	12 months after completing treatment
Receipt of blood products, human tissue, or plasma-derived clotting factors	12 months
Hepatitis B immune globulin administration	12 months
Any other unlisted vaccine	12 months
Tattoo	12 months
Mucous membrane exposure to blood	12 months
Non-sterile skin penetration, including tattoos or permanent makeup, unless applied by a state-regulated entity with sterile needles and ink that has not been re-used	12 months
Residing with or having sexual contact with an individual with viral hepatitis	12 months

Sexual contact with an individual with HIV or high risk for HIV	12 months
Incarceration >72 consecutive hours	12 months
Travelers to malaria-endemic areas	12 months after departure regardless if asymptomatic or prophylaxis
Dutasteride (Avodart)	6 months after last dose
Recent blood donation	8 weeks for whole blood donation, 16 weeks for 2 unit RBC apheresis; 48 hours for plasma-, platelet-. or leukapheresis
Pregnancy	Defer until 6 weeks postpartum/post-termination. Exceptions are for transfusion to the infant with physician approval
Live attenuated vaccines: German measles (rubella) and chickenpox (varicella zoster) vaccines	4 weeks
Finasteride (Proscar, Propecia)	1 month after last dose
Isotretinoin (Accutane)	1 month after last dose
Clopidogrel (Plavix) and ticlopidine (Ticlid)	14 days (donor excluded from platelet donation)
Live attenuated vaccines: Measles (rubeola), polio (Sabin oral), mumps, typhoid (oral), and yellow fever vaccines	2 weeks
Smallpox vaccine	21 days or until scab falls off in a donor without complications from vaccine. In donor with severe

	complications from the vaccine, 14 days after resolution of symptoms. Asymptomatic contacts of vaccine recipient do not require deferral
West Nile virus (WNV)	14 days after resolved or 28 days after onset, whichever is longer. Positive WNV ab test without symptoms, no deferral.
Warfarin (Coumadin)	7 days (excluded from platelet donation)
Aspirin and piroxicam (Feldene)	48 hours (excluded from platelet donation)
Toxoids, synthetic or killed vaccines: anthrax, cholera, diphtheria, hepatitis A, hepatitis B, influenza, Lyme, paratyphoid, pertussis, plague, pneumococcal polysaccharide, poliomyelitis (Salk injection), rabies, Rocky Mountain spotted fever, tetanus, typhoid (injection), recombinant human papillomavirus (HPV) vaccine	None (if donor is afebrile and symptom-free)
Stigmata of alcohol intoxication or habituation	Exclude donor, no specific period of time stated
Other travel	Refer to http://www.cdc.gov/travel
Antibiotics	As defined by medical director

Transfusion-transmitted bloodborne infections have decreased considerably after implementation of more rigorous donor screening and routine testing for the most common transfusion-associated pathogens. The U.S. FDA requires donor testing for HBsAg and anti-HBc which reduces the risk of transfusion transmission to 1/220,000-357,000 units. The window period from time of infection to time of detection of HBV virus with MP-NAT is 18.5-26.5 days and decreases the transfusion-transmission risk to 1/843,000-1/1.2 million. Hepatitis C was one of the most common causes of post-transfusion hepatitis, but with the use of serologic assays to detect HCV antibodies combined with HCV MP-NAT the risk of transfusion transmitted HCV is now 1 in 1.1 million units. The window period from time of infection to time of detection of HCV virus with MP-NAT is only 7.4 days. Due to the high incidence of HIV transfusion transmitted infections in the mid to late 1980's, more rigorous donor screening to defer donors who engaged in high-risk behavior, such as intravenous drug use, high-risk heterosexual behavior and males who have sex with other males. These donors engaging in high-risk behaviors are now deferred for 12 months. This rigorous screening combined with serologic testing to detect antibodies to HIV-1, HIV-2, and MP-NAT reduced the window period to 9 days and dramatically reduced the risk of transmission to 1 in 1.5 million.

Babesia microti is the most commonly tickborne transmitted by blood products in the United States according to the FDA and has been reported to occur with both platelets and red blood cells (RBCs), even though the incidence is higher in RBCs. The reason for the high incidence is related to the fact that asymptomatic patients can donate and there is no FDA approved screening test for Babesia for blood donors. Donors are asked if they have a history of babesiosis and are permanently deferred from donation for affirmative responses. Since blood donations are distributed nationally, there are units contaminated going to non-endemic areas for transfusion and therefore when transfused patients present with symptoms of *Babesia*, it may not be considered in the differential diagnosis.

Therefore, physicians should consider transfusion transmitted *Babesia* in a patient with a fever of unknown origin with a recent transfusion history.

Bacterial contamination of blood products has become a growing concern and is one of the top 3 causes for transfusion-related fatalities. The source of the contamination is the donor's skin during the phlebotomy or the donor has asymptomatic bacteremia at the time of collection. The amount of bacteria initially contaminating the unit is small, but the bacteria proliferate during storage. This is a higher risk for platelets because they are incubated at room temperature whereas red blood cells are refrigerated during storage. The different storage temperatures also select for different bacteria. Gram-positive skin contaminants proliferate best in platelets and psychrophilic enteric organisms are the most common contaminating bacteria in refrigerated red blood cells. To reduce the risk of bacterial contamination, in 2008 the AABB required all donor centers to use collection bags that divert the first 10-40 ml of blood to minimize the risk of skin bacteria contaminating the collected product. Also in 2004, the AABB required all blood collection centers to implement a process to limit the bacterial contamination of all platelets. Most blood centers store the platelets for 24 hours before sampling the units for culture and then incubate the cultures 12-24 hours before releasing the units to transfusion services. As of March 2016, the U.S. FDA released a draft guidance to further reduce the risk of bacterial contamination in platelets by requiring point of issue assays to re-screen platelets for bacterial contamination before transfusion or transfusion services can use PRT platelets as an alternative. The advantage of the rapid PGD Test (Verax Biomedical) is that it can be used as a safety measure to extend the shelf life of platelets from 5 to 7 days, which can offset some of the cost. As of this writing, point of issue re-screening of platelets by a rapid detection test or use of PRT platelets to reduce bacterial contamination has not been mandated or widely implemented in the United States.

SUGGESTED PRACTICE IN UNDER-RESOURCED SETTINGS

- Rural and under-resourced countries struggle with a constant shortage of blood products coupled with a high incidence of transfusion transmitted infections (TTI) such as malaria, Zika virus, typhoid fever, HIV and Hepatitides, etc.
- A majority of blood donors are family replacement donors (FRD). These are donors who are family or friends must donate to replace the units transfused to the patient. This results in a high percentage of first time donors who have a higher incidence of HIV, HBV and HCV infection.
- Under-resourced countries lack qualified personnel and laboratory equipment, therefore, testing for HIV, HCV and HBV is performed using rapid diagnostic testing (RDTs). RDTs are used to screen donors quickly in lieu of more expensive and technically more complex 4th generation Enzyme-Linked Immunosorbent Assay (ELISA) and Nucleic Acid Testing (NAT). RDTs have lower sensitivity and specificity than ELISA/NAT testing and therefore is capable of missing donors with infectious diseases.

SUMMARY

Blood transfusion can be a life-saving therapy for patients suffering with severe anemia. However, there are global problems associated with transfusion such as chronic shortages, risk of transfusion transmitted diseases and non-infectious transfusion related complications that can cause severe adverse events. Volunteer non-remunerated donor are the standard in the USA for supplying blood products to medical institutions but in under-resourced countries this is not the case. The blood supply in rural or under-resourced countries relies on family replacement donors (FRD) from transfused patients and these donors typically have a higher rate of infectious diseases. Additionally, FDA standard in the US require a strict

donor history with clearly defined deferral periods and ELISA/NAT testing for blood donors to minimize the risk of TTI. Under-resourced countries may rely on RDTs instead which may have a higher false negative rate and therefore a higher rate of TTI.

REFERENCES

1. AABB Association Bulletin #04-07. Actions Following an Initial Positive Test for Possible Bacterial Contamination of a Platelet Unit. 14 Oct 2004.
2. AABB Association Bulletin #12-04. Recommendations to Address Residual Risk of Bacterial Contamination of Platelets. 14 Oct 2012.
3. American Red Cross Blood Facts and Statistics. Available at http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics. Accessed 22 Jan 2014.
4. Busch MP, Glynn SA, Stramer SL, et al. A New Strategy for Estimating Risks of Transfusion-Transmitted Viral Infections Based on Rates of Detection of Recently Infected Donors. Transfusion 2005; 45(2): 254–64.
5. Crowder LA, Schonberger LB, Dodd RY, Steele WR. [2017] Creutzfeldt-Jakob Disease Lookback Study: 21 Years of Surveillance for Transfusion Transmission Risk. Transfusion 57(8):1875–8. doi: 10.1111/trf.14145.
6. U.S. Food and Drug Administration. Fatalities Reported to FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2015. Silver Spring, Maryland: CBER Office of Communication, Outreach, and Development, 2015.
7. U.S. Food and Drug Administration. Draft Guidance for industry: Bacterial risk control strategies for blood collection establishments and transfusion services to enhance the safety and availability of

platelets for transfusion. (March 2016) Silver Spring, Maryland: CBER Office of Communication, Outreach, and Development, 2016.
8. Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion; https://www.fda.gov/downloads/Guidances/Blood/UCM425952.pdf. Accessed 15 Nov 2017.
9. Hébert PC, Fergusson D, Blajchman MA, et al. Clinical Outcomes Following Institution of the Canadian Universal Leukoreduction Program for Red Blood Cell Transfusions. JAMA 2003; 289(15):1941-9.
10. Klein HG, Anderson D, Bernardi MJ, et al. Pathogen Inactivation: Making Decisions about New Technologies. Report of a Consensus Conference. Transfusion 2007; 47(12):2338–47.
11. LeBel DP, Moritz ED, O'Brien JJ, et al. Cases of Transfusion-Transmitted Babesiosis Occurring in Nonendemic Areas: A Diagnostic Dilemma. Transfusion 2017; 57(10):2348–54.
12. Standards for Blood Banks and Transfusion Services. (28th Edition), Bethesda, Maryland. AABB. ISBN 10: 1563958384.
13. Stramer SL, Hollinger FB, Katz LM, et al. Emerging Infectious Disease Agents and Their Potential Threat to Transfusion Safety. Transfusion 2009; 49 Suppl 2:1S–29S. doi: 10.1111/j.1537-2995.2009.02279.x.
14. Zou S, Stramer SL, Notari EP, et al. Current Incidence and Residual Risk of Hepatitis B Infection among Blood Donors in the United States. Transfusion 2009; 49(8):1609–20.
15. Standards for Blood Banks and Transfusion Services (30th Edition). McKenna DH (Ed.) 2016. Bethesda, Maryland. AABB. ISBN9781563959271.
16. Technical Manual (19th Edition). Fung MK, Eder AF, Spitalnik SL, Westhoff CM (Eds.) 2017. AABB. ISBN9781563959479.

17. Bisseye C, Mombo LE, Bie SMM, et al. Trends of blood-borne infectious diseases in a rural blood donation center of southeast Gabon (Koula-Moutou). Pan Afr Med J. 2018; 31:81.