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About Risks of Blood Transfusion

Although blood transfusion saves lives and reduces morbidities in many clinical diseases and conditions, it is associated with certain risks. A transfusion-related adverse event, also called transfusion reaction, is any unfavourable event occurring in a patient during or after blood transfusion[1]. About 0.5% to 3% of all transfusions result in some adverse events, but the majority of them are minor reactions with no significant consequences. In general, transfusion-related adverse events are categorized as infectious and noninfectious. However, there are other classifications in the literature based on time of occurrence (i.e. acute versus delayed) or physiological mechanism (i.e. immune mediated versus nonimmune mediated) (Table 1)[2,3]. A significant proportion of adverse events may occur as a result of errors in preparation, ordering or administration of blood and blood products.

Infectious Risks of Transfusion

Currently, the risk of transmission of infectious diseases through transfusion in Canada is minimal, because effective preventive strategies, including new laboratory tests, have been implemented. Nevertheless, many infectious agents, including viruses, bacteria, and parasites, can be transmitted through blood transfusion. Well-recognized viruses include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis G virus/GB-C virus (HGV/GBV-C), human immunodeficiency virus types 1 and 2 (HIV-1/2), human T-cell lymphotropic virus types I and II (HTLV-I/II), cytomegalovirus (CMV), Epstein-Barr virus (EBV), TT virus (TTV), human herpesvirus type 6 (HHV-6), SEN virus (SEN-V), and human parvovirus (HPV-B19). Bacteria such as *Treponema pallidum* (the agent of syphilis), *Yersinia enterocolitica*, and *Staphylococcus* and *Streptococcus* species (common agents of bacterial contamination), and parasites such as *Plasmodium* species (the agent of malaria), *Trypanosoma cruzi* (agent of Chagas' disease), and *Babesia microti* (agent of babesiosis) have also been reported to be transmitted through blood transfusion. In addition, emerging blood-borne pathogens such as hepatitis E virus (HEV), human herpesvirus type 8 (HHV-8), *Borrelia burgdorferi* (agent of Lyme disease), and the unknown agent of Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) may pose a threat to the safety of blood.

Infectious agents may be classified into five categories based on transmissibility through transfusion, pathogenicity of the agent, availability of donor serologic test, and effectiveness of pathogen inactivation (Table 2)[4-8]. The risk of transmission for the first group of agents is minimal because of donor screening and testing, and is normally associated with donations collected during the window period. For example, the risk of transmission of HIV and HCV in Canada through blood transfusion was estimated to be 1 in 752,000 and 1 in 225,000 donations respectively[9]. Infections caused by agents in the second and third group usually present clinical diseases in high-risk recipients, such as immunocompromised individuals; however, the transfusion transmission risk is also very small because of preventive strategies such as universal leukodepletion and solvent-detergent treatment. Transfusion Transmitted bacterial reaction resulting from bacterial contamination of blood components is the most common infectious adverse event. Approximately 1 in 2,000-3,300 units of platelets and 1 in 38,500 units of red cells are contaminated with bacteria; however, not every contaminated component causes reactions. The incidence of Transfusion Transmitted bacterial reaction is estimated to range from 1 in 500,000 units of red cells to 1 in 50,000 units of platelets[10].

Infectious agents in the fourth and fifth group may pose a potential risk following transfusion. Although agents in the fourth group have been proved to be transfusion transmissible, the pathogenicity of these agents is currently not established. Similarly, even though agents in the last group usually cause disease, their transfusion transmissibility has not been established.

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Noninfectious Risks of Transfusion

Although Transfusion Transmitted infections have received the greatest attention, noninfectious adverse events remain the most common complications associated with transfusion. The majority of these noninfectious adverse events are immune mediated. Acute immune mediated reactions include acute hemolytic transfusion reaction (AHTR), transfusion-related acute lung injury (TRALI), febrile nonhemolytic transfusion reaction (FNHTR), urticarial reaction and anaphylaxis. Delayed immune mediated reactions consist of delayed hemolytic transfusion reaction (DHTR), transfusion associated graft-versus-host disease (TA-GVHD), and posttransfusion purpura (PTP)[3,11].

FNHTR and urticarial reaction are the most frequent non life-threatening acute transfusion reactions; however, AHTR is the most frequent severe reaction and the leading cause of death associated with transfusion[12]. On the other hand, TRALI and TA-GVHD are rare and the most fatal transfusion reactions. The case fatality rate is 5% to 14% for TRALI and over 90% for TA-GVHD[13,14]. TRALI has been recognized as the third leading cause of death associated with transfusion[12].

ABO incompatibility accounts for about 80% of AHTR-related deaths and occurs as a result of error. Well recognized errors include patient misidentification, sample error, wrong blood issued, transcription error, administration error, technical error and storage error. Identification and prevention of these errors have become an increasingly important issue in transfusion safety[3].

In general, nonimmune mediated transfusion reactions result in minor clinical manifestations. These include hemoglobinuria, hyperkalemia, hypocalcemia, hypothermia, and iron overload. However, air embolus and circulatory overload may also be life threatening. Again, these reactions are mostly error related and can usually be prevented by proper preparation and storage of components, and better transfusion practices[11].

Despite the risks associated with transfusion, the Canadian blood supply is one of the safest blood systems in the world. Effective strategies and laboratory test procedures are being implemented to further prevent and/or reduce transfusion-related adverse events.

Table 1. Classification of transfusion-related adverse events

Time of Occurrence	Mechanism	Infectious Reaction	Noninfectious Reaction
Acute[a]	Immune mediated	--	Acute hemolytic transfusion reaction Transfusion-related acute lung injury Febrile nonhemolytic transfusion reaction Urticarial reaction Anaphylactic
	Nonimmune mediated	Bacterial contamination	Nonimmune hemolysis (e.g. hemoglobinuria) Circulatory overload Metabolic (e.g. hyperkalemia) Embolic
Delayed[b]	Immune mediated	--	Delayed hemolytic transfusion reaction Transfusion associated graft-versus-host disease Posttransfusion purpura
	Nonimmune mediated	Transfusion Transmitted infections (viral, bacterial and parasitic)	Hemochromatosis (iron overload)

[a]Acute adverse event is defined as any unfavourable event occurring in a patient during or within 24 hours after transfusion, but the definition has minor variations in the literature.
[b]Delayed adverse event is defined as any unfavourable event occurring in a patient more than 24 hours and up to 3 months after transfusion, but the definition has minor variations in the literature.

Table 2. Categories of infectious agents according to transfusion transmissibility, pathogenicity, donor test and pathogen inactivation

	First Group	Second Group	Third Group	Fourth Group	Fifth Group
Agents	HBV, HCV, HIV-1/-2, HTLV-I/-II, *Treponema pallidum*	CMV, EBV, *Yersinia enterocolitica, Staphylococcus* and *Streptococcus* species, *Trypanosoma cruzi*	HAV, HPV-B19, HHV-6, *Plasmodium* species, *Babesia microti, Rickettsia rickettsii, Leishmania donovani, Toxoplasma gondii*	HGV/GBV-C, TTV, SEN-V	HEV, HHV-8, Borrelia burgdorferi, Ehrlichia phagocytophila, prions
Transfusion transmissibility	Established	Established	Established	Established	Not established
Pathogenicity	Cause diseases	Cause diseases largely in high risk individuals	Cause diseases largely in high risk individuals	Not established	Cause diseases
Donor serologic test	Available	Not available	Not available	Not available	Not available
Effectiveness of pathogen inactivation	Largely inactivated	Largely inactivated	Largely not inactivated	Unknown	Unknown

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[Blood Safety Surveillance and Health Care Acquired Infections Division]

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