Physician’s Guide
2004

Physician’s Guide for Blood and Blood Product Utilization
Since publication of this handbook, one case of variant Creutzfeldt-Jakob disease (vCJD) possibly transmitted by transfusion has arisen in the United Kingdom (vCJD is described on p. 46-47). Although not definitively proven, preliminary investigations indicate that there is a high likelihood that this case was transfusion-transmitted. This is the first time an incident of this nature has been reported anywhere in the world. For up-to-date information on the status of this investigation, please visit www.TraQprogram.ca.
I am pleased to introduce this third edition of the *Physician’s Guide*, which is a resource intended to help British Columbia physicians appreciate the risks associated with blood and blood products, to support the informed consent process with their patients, and to aid them in making appropriate therapeutic decisions.

When used appropriately, blood and blood products can save lives and provide clinical benefit to patients. However, transfusion entails risks, both infectious and non-infectious. Although we have seen advances in screening for some known blood-borne pathogens, we have also experienced the emergence of new pathogens. The concern this year about the potential for transmission of West Nile Virus through the blood supply has highlighted the ongoing need to be vigilant about the dangers associated with transfusion. This latest edition of the *Physician’s Guide* includes a new section on West Nile Virus, as well as updated risk estimates for other transfusion hazards, and an updated section on alternatives.

Due to the risks related to blood transfusion, whenever possible, patients or their surrogates must be involved in the decision-making process through informed consent. The first edition of the *Physician’s Guide*, which appeared in 1999, supported the province’s implementation of the Krever Commission’s recommendation that an informed consent process for blood and blood products be in place. This edition continues to support the informed consent process and expands on transfusion-related risk.

In addition, this edition of the *Physician’s Guide* includes guidelines for red blood cell (RBC) transfusion. Based on the best available evidence, the guidelines represent the consensus of the BC Transfusion Medicine Advisory Group (TMAG) and mark the start of a concerted program of RBC utilization management in British Columbia.

RBCs account for the largest single blood component used in the province. Media reports in the late 1980s and early 1990s of hepatitis C virus and HIV transmission through transfusions and the resulting Krever inquiry raised public awareness about the risks of transfusion and led to a reduction in allogeneic RBC use across North America. However, the introduction of more stringent blood testing methods, resulting in a greater assurance of safety, combined with the development of more aggressive approaches to treating some medical conditions, has resulted in the RBC transfusion rate climbing again in BC and across Canada.

The aim in launching the RBC provincial utilization management program is four-fold:
1) to provide guidance and support for practice changes that reduce inappropriate use and thus unnecessary risk and waste of RBCs;
2) to increase physician awareness for accountability for RBC use in their patients;
3) to monitor RBC use in BC to facilitate clinical and administrative decision making to ensure an adequate supply; and
4) to facilitate research on appropriate transfusion practice, including the consideration of alternative products and technologies.

The program involves:
- encouraging appropriate use of RBCs through assuring informed consent, the implementation of standardized transfusion guidelines and related tools, and consideration of alternatives to RBC use, where appropriate and feasible; and
• continued RBC waste reduction through blood redistribution and promotion of other operational efficiency measures, including inventory management.

More educational material will be provided during the coming months.

Thank you for your cooperation in this effort to encourage prudent clinical use of the precious blood resource and to ensure that BC patients are informed and are exposed to transfusion risks only when clinically necessary.

Penny Ballem, MD
Deputy Minister
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PREFACE

This is the third edition of the Physician’s Guide, which is intended to serve as a resource to physicians who use blood and blood products. The first and second editions, which focused on supporting the informed consent process, were well received throughout British Columbia and across Canada. This third edition marks a change in title and an expansion of focus to include guidelines for appropriate blood utilization, in view of the ongoing risks of transfusion, as exemplified by West Nile Virus. As a first step, the Physician’s Guide now includes guidelines for red blood cell transfusion, developed by the British Columbia Transfusion Medicine Advisory Group. Future editions will incorporate guidelines for platelets and plasma utilization. This edition also includes a new section on West Nile Virus and an updated section on alternatives to blood products. All of the risk estimates have been recalculated to reflect the current risk from transfusion in Canada.

Physicians should not be expected to explain the complete contents of the Physician’s Guide to their patients. Rather, the Physician’s Guide is intended to help physicians appreciate the risks associated with blood and blood products, to consider whether the benefits outweigh the risks, and to assist them in making appropriate therapeutic decisions in treating patients. A laminated quick-reference card has been developed to help physicians convey the essential information in informed consent discussions with their patients.

The medical information provided on the risks of administering blood and blood products is based on a comprehensive review of the most current literature. However, due to constantly emerging transfusion medicine information vis-à-vis new risks and safety measures, the authors acknowledge and regret the possibility of omissions.

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WAIVER OF LIABILITY

The information contained in this document is intended to serve as a guideline only. Any decision involving patient care must be based on the judgment of the attending physician according to the needs and condition of each individual patient. The responsibility for obtaining informed consent lies with the attending physician. Neither the contributing authors nor the British Columbia Provincial Blood Coordinating Office shall be liable for any actions, claims, damages, costs or obligations that may arise from the use or misuse of the material contained in this document.

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1. GUIDELINES FOR RED BLOOD CELL TRANSFUSION

Purpose
The purpose of these guidelines is to support physicians in their clinical decisions related to the appropriate use of red blood cells (RBCs). They are not intended to provide a rigid prescription for care and do not replace the need to consult with an expert in transfusion medicine. The decision to transfuse RBCs should be based on the judgment of the attending physician after careful review of the patient’s condition and clinical situation. The goal is to optimize patient outcomes and to ensure appropriate use of the allogeneic (donor) blood supply.

The guidelines apply to RBC transfusion in adults and children over 4 months of age.

General Considerations
1. Informed consent is required for the transfusion of RBCs.

2. A patient’s hemoglobin value, although important, should not be the sole deciding factor when considering whether to transfuse RBCs. The decision to transfuse should be supported by the need to prevent or alleviate clinical symptoms, signs or morbidity due to inadequate tissue oxygen delivery. RBC transfusion should not be used to expand vascular volume when oxygen-carrying capacity is adequate.

3. RBC transfusion should be given only after the risks associated with transfusion have been considered and only when the benefits outweigh the risks, taking into account the expected life span of the patient. It is particularly important to avoid the long-term complications of transfusion in a young patient.

4. Strategies should be undertaken to minimize the need to transfuse RBCs (see Alternatives to Blood and Blood Product Usage):
   - investigate, diagnose and treat previously recognized anemia;
   - implement available alternatives, when appropriate, to reduce the risk of allogeneic transfusion, i.e. iron supplement (oral or IV), erythropoietin, autologous blood donation, cell saver, etc.;
   - preoperatively assess for anemia (within 28-35 days) prior to surgical intervention with anticipated risk of transfusion (significant blood loss);
   - discontinue anti-coagulants and antiplatelet drugs before planned surgery;
   - minimize the frequency and volume of blood sampling for laboratory testing;
   - utilize a simple protocol to guide when hemoglobin should be assessed and when RBCs should be transfused;
   - utilize a surgical technique that minimizes blood loss;
   - utilize appropriate pharmacologic interventions to minimize blood loss (e.g., antifibrinolytics).

5. A patient with acute blood loss should receive effective resuscitation (appropriate volume replacement with crystalloid solutions or colloids, i.e. Pentastarch), while the need for transfusion is assessed.

6. In non-urgent settings, RBCs should be administered one unit at a time and the patient should be assessed prior to transfusing additional units (clinical exam and hemoglobin level).

7. In situations where RBCs are transfused, the reasons for the transfusion should be clearly and accurately recorded in the patient’s chart and in any documentation used in ordering or administering RBCs.
8. Hospital transfusion committees should function at the local level to promote, guide and direct prudent transfusion practice and assist in the dissemination of information pertaining to safe transfusion practice.

9. In all situations where RBCs are transfused, a process for clinical review should be in place and utilized to monitor the appropriateness of RBC use and to develop systems for the implementation of these guidelines.

Threshold and target hemoglobin levels for RBC transfusion
As a general guide, in normal healthy individuals, a transfusion threshold of 70 g/L is appropriate and leaves some margin of safety over the critical level of 40-50 g/L. In patients with indications of cardiac disease, the available evidence suggests that, as a general guide, it may be safer to maintain the hemoglobin above 90 g/L. Transfusion at hemoglobin above 100 g/L is unlikely to be appropriate unless there are specific indications.

For patients undergoing planned surgery
Where the patient is stable, is not bleeding and further major bleeding is not anticipated:
- For patients without cardiovascular disease, and especially younger patients, transfusion is likely to be appropriate to maintain hemoglobin levels in the range of 70-90 g/L. Lower thresholds may be acceptable in younger patients without signs or symptoms of impaired oxygen transport. Transfusion is unlikely to be appropriate at hemoglobin levels above 90 g/L.
- For patients known to have or likely to have cardiovascular disease, transfusion is likely to be appropriate to maintain hemoglobin in the range of 90-100 g/L.

Specific factors to consider include:
- Patient’s cardiopulmonary reserve – if pulmonary function is not normal, it may be necessary to consider transfusing at a higher hemoglobin threshold.
- Volume of blood loss – clinical assessment should attempt to quantify the volume of blood loss before, during and after surgery, to ensure maintenance of normal blood volume.
- Oxygen consumption – this may be affected by a number of factors, including fever, anesthesia and shivering; if increased, then the patient’s need for RBC transfusion could be higher.
- Atherosclerotic disease – critical arterial stenosis to major organs, particularly the heart, may modify indications for the use of RBCs.

This general guidance also applies to prescribing a postoperative transfusion. Postoperative blood loss must be accurately monitored and documented and there should be a clear protocol or individual management plan, including the criteria for the administration of a transfusion, and for surgical re-exploration if blood loss is excessive.

For patients with acute blood loss
Maintaining adequate intravascular volume (including crystalloid and colloid infusion) is critical to ensuring adequate tissue oxygenation. Transfusion is likely to be appropriate to maintain hemoglobin above 70 g/L during active bleeding. Consider the rate of bleeding, assess hemodynamic factors, observe for evidence of tissue ischemia, and take into account the institutional challenges of providing appropriate blood products and laboratory testing in the decision to transfuse.

Consider maintaining a higher hemoglobin level for patients with:
- Impaired pulmonary function
- Increased oxygen consumption (fever, chills)
- Coronary artery disease
- Unstable coronary syndromes
- Uncontrolled/unpredictable bleeding.
Patients with hemoglobin above 100 g/L are unlikely to benefit from transfusion.
**For critically ill patients with anemia**

Patients with critical illness frequently develop anemia. Transfusion may be appropriate to control anemia-related symptoms if the hemoglobin falls below 70 g/L, with the aim of maintaining the hemoglobin concentration in the range of 70-90 g/L. A possible exception to this guideline is patients with known ischemic heart disease, where it may be preferable to maintain the hemoglobin in the range of 90-100 g/L. The aim is not to achieve a predetermined oxygen delivery but to assess whether the oxygen delivery is adequate by examining urine output, skin temperature, and the severity of lactic acidosis.

**For patients with chronic anemia**

Determine the cause of anemia so that, where appropriate, treatment other than RBC transfusion may be used. Administer RBCs at intervals to relieve symptoms of anemia and to maintain the hemoglobin at a reasonable and safe level to compensate for unexpected blood loss. Maintaining the hemoglobin greater than 80 g/L may be appropriate in a patient on a chronic transfusion regimen or during bone marrow suppressive therapy. Assess patients that are expected to have long-term transfusion-dependent survival for iron overload and treat if appropriate.

**Source**

These guidelines have been developed through the consensus of the British Columbia Transfusion Medicine Advisory Group (TMAG), which consists of transfusion medicine physicians, technologists and nurses from hospitals across BC. The guidelines are based on existing guidelines for transfusion medicine practice, in particular the UK Blood Transfusion and Tissue Transplantation Guidelines (UK Handbook of Transfusion Medicine, Third Edition 2001) and the Australian National Health and Medical Research Council/Australasian Society of Blood Transfusion Clinical Practice Guidelines for the Appropriate Use of Red Blood Cells (2001), and the best available published research regarding the clinical indications for transfusion.

For more information, consult the following:


National Health and Medical Research Council. Clinical practice guidelines on the use of blood components.  

Alternatives to Blood and Blood Product Usage

Recycle, Replace, Reduce and Regenerate

Surgical Transfusion

1. Pre-operative:
   - Early assessment to allow time for feasible alternatives
   - Autologous predonation
   - Investigation and management of anemia
     i. Iron
     ii. Folic acid
     iii. Vitamin B-12
     iv. Erthropoietin
   - Investigation and management of coagulopathies

2. Intra-operatively
   - Regional Anaesthetic
   - Controlled Hypotension
   - Acute normovolemic Hemodilution
   - Normothermia
   - Cell Saver
   - Plateletpheresis
   - Surgical Technique – meticulous hemostasis
   - Volume replacement:
     i. Crystalloid solutions i.e. Ringer’s Lactate, Normal saline, Normosol™, Plasma-lyte™
     ii. Colloids i.e. Dextran; Pentastarch i.e. Pentaspan®
   - Pharmacological agents to reduce or control bleeding:
     i. Hemostatic Agents i.e. Aprotinin
     ii. Antidiuretic Hormone i.e. DDAVP
     iii. Antifibrinolytics i.e. e-Aminocaproic acid, Tranexamic acid
     iv. Vitamin K

3. Post-operatively
   - Autotransfusion
   - Optimum fluid and volume management
   - Normothermia
   - Assessment and management of post-op bleeding
   - Transfuse based on clinical assessment, O2 content and transport ability of red cells
   - Single unit transfusion and reevaluate
   - Pharmacological agents to manage anemia
     i. Iron
     ii. Folic acid
     iii. Vitamin B-12
     iv. Erthropoietin
   - Restrict to a minimum the frequency of phlebotomy and specimen (volume) requirements

Medical Transfusion

1. Assessment and management of anemia
   - Iron deficiency
   - Folic acid/ Vitamin B-12 deficiency
   - Erthropoietin (Eprex™)
2. Assessment and management of coagulopathies

3. Single unit transfusion and evaluate

*Detailed discussion of these alternatives is beyond the scope of this Guide. The use of alternatives must be in accordance with clinical needs and subject to program/product availability.*
2. INFORMED CONSENT

Informed consent is a process undertaken jointly by a patient and a physician to make a therapeutic decision that allows the patient to preserve the primary decision-making role in determining a course of treatment. As part of this process, the physician must conform to a standard of disclosure regarding benefits and risks of a particular therapy. This standard requires that a physician disclose information, which the physician knows or ought to know, that a reasonable person in the patient’s position would wish to be aware of prior to making a decision about undergoing treatment or a procedure.

In the report of the Commission of Inquiry on the Blood System in Canada, Justice Krever recommended:

- that the licensing bodies of the medical profession require in their standards of practice that the treating physician obtain the informed consent of the patient to the administration of blood and blood products, in such a way that patients in Canada, barring incompetency or an emergency surgical procedure, will be informed of the risks and benefits of, and alternatives to, allogeneic blood transfusions;
- that risks, benefits, and alternatives be presented in language the patient will understand and in a manner that permits questions, repetitions, and sufficient time for assimilation;
- that the discussion between the physician and the patient take place well in advance of the surgical procedure or blood therapy to enable the patient to employ some of the alternatives to an allogeneic blood transfusion, such as the advance deposit of autologous blood, and to allow the patient to participate in a meaningful way in the decisions relating to the administration of blood and blood products.

Physicians should not rely on the informed consent form as having fully satisfied the requirements of informed consent. A standardized document does not take into account factors unique to individual patients. Therefore, it cannot be a substitute for the participatory process of consent wherein the physician informs the patient. Ultimately, it is the attending physician who bears the legal responsibility for obtaining informed consent.²

Elements of Informed Consent³

The basic requirements to be communicated in informed consent discussions are identified as follows:

1. Information provided by physician
   - Risks of treatment;
   - Benefits of treatment;
   - Alternative treatments and their associated risks and benefits.

2. Opportunity for questions and clarification:
   - Patient competency;
   - Patient (or surrogate decision maker) understands;
   - Patient decides on basis of complete information.

3. Patient agrees or refuses

4. Documentation⁴

Hospitals may customize documentation to meet their policy requirements; however, the following essential elements should be included:
   - Statements that benefits, risks and alternatives were explained; and

* Throughout this guide, the term patient includes parent or guardian.
• Statements that the patient had the opportunity to ask questions and received satisfactory answers; and
• A section where the patient agrees to receive the transfusion or refuses the transfusion.

Specific hospital policies and procedures relative to Informed Consent for Blood and Blood Products must reflect current provincial health care consent legislation.
3. IMMUNOLOGICAL HAZARDS OF TRANSFUSION

Alloimmunization

Humans when exposed through blood transfusion to "foreign" antigens, which they themselves lack, may develop alloantibodies to these antigens. A similar process may occur with fetomaternal hemorrhages during pregnancy and solid organ and bone marrow/stem cell transplants. Antibodies directed against these antigens may develop days, weeks or months following exposure. Some antigens are more immunogenic than others and the incidence of alloimmunization is dependent on a complex interaction between antigen structure, number and volume of exposures and recipient genetic susceptibility.

Immunogenic antigens include those which are found on all nucleated cells (e.g. HLA antigens) or those which are for the most part restricted to specific cell types (e.g. red cell antigens) or to plasma proteins (e.g. immunoglobulin proteins).

Multiply transfused patients and multiparous women are the most common patients in whom clinically significant alloantibodies can be detected against red cell, granulocyte, platelet or plasma protein antigens. Alloantibodies directed against plasma proteins may also occur in patients with congenital deficiency of a plasma protein (viz. congenital IgA deficiency); in these patients alloantibodies can develop without a history of transfusion or pregnancy. In the latter group, it is postulated that an environmental agent with a shared or similar antigenic structure has led to alloimmunization.

Specific syndromes related to transfusion risks associated with alloimmunization in the setting of blood transfusion are discussed below.

1) Hemolytic Transfusion Reaction

The principal clinical features of hemolytic transfusion reactions are:
- Mild: anxiety, fever, chills, flushing, mild hypotension and tachycardia.
- Severe: All of the above with low back pain, dyspnea and precordial pain, heat and pain in the iv line area, hemoglobinuria, shock, capillary bleeding, disseminated intravascular coagulation and oliguria/anuria.

a) Acute

Incidence: 1: 7000^\text{\textsuperscript{5}}

Incidence with fatal outcomes: 1:600,000

Red Cells

Most immediate hemolytic transfusion reactions are initiated by the interaction of IgM antibodies with their corresponding antigens on erythrocytes. The majority of these reactions are due to ABO incompatibilities, usually as a consequence of human error resulting from the mislabelling of a patient crossmatch sample or giving a unit of correctly crossmatched blood to the wrong patient. Rarely, other blood group system antibodies are involved.

Plasma

Incompatibility between transfused plasma and recipient red blood cells has been documented; this condition usually results from transfusion of large amounts of group O plasma to group A, AB or B recipients. Most examples of this type of incompatibility are caused by plasma with potent anti-A activity, with actual hemolysis occurring in only 1% of patients receiving incompatible plasma.

Platelets

\textsuperscript{5} Based on 0-14.3/100,000 units
Hemolytic transfusion reaction (HTR) is a rare complication of platelet transfusion. A report of acute HTR following transfusion of O platelets to an A recipient has been published. However, this was the only hemolytic reaction identified among over 40,000 platelet transfusions at one institution, 21% of these platelet infusions were plasma incompatible. The same authors were unable to find an increase in hemolysis following platelet transfusion in a small cohort who received ABO identical or plasma incompatible apheresis platelets. It is predicted that annually in Canada there will be less than one case of acute hemolysis due to platelet infusion.

b) Delayed

_Incidence: 1: 5500_\(^B\)

Delayed hemolytic reactions are generally caused by very low titre alloantibodies not detectable at the time of pretransfusion antibody screening or compatibility testing. In most cases, there has been a primary immunizing event (previous transfusion and/or obstetric history). Prevention of delayed HTR is difficult. There is no way of predicting which patients have been sensitized to a given blood group antigen by previous transfusion or pregnancy if their antibody screen is negative. Where persons have received multiple transfusions and have previous detectable antibodies, extended phenotyping and consideration of provision of phenotype negative units matched for clinically important antigens is advisable.

2) Non-Hemolytic Transfusion Reaction

a) Febrile

_Incidence: 1:500 units with leukoreduced products_\(^5\)

The typical febrile reaction usually begins relatively early during the transfusion process, often within the first half hour and should be considered when the patient’s underlying clinical condition provides no explanation for the symptoms and signs. Occasionally, the reaction will occur shortly after the transfusion has been completed. The patient typically complains of being cold, and this is soon followed by the onset of chills or rigors that may be quite severe. These are soon followed by a rapid rise in temperature >1°C. The patient may also experience headache, nausea and vomiting. In exceptional cases, some degree of diastolic hypertension may also occur.

In general, reaction results either from the interaction between leukocyte antibodies in the recipient and leukocyte antigens in the donor product, or may be due to cytokines liberated by white blood cells, particularly when the reaction is a consequence of platelet transfusion. It has been shown that leukocytes release a variety of cytokines during storage, and many reactions have been linked to these bioactive substances in the plasma supernatant of platelets. White blood cell reduction at the time of preparation can reduce the severity of these reactions.

In Canada, since the risk of febrile reactions may now be diminished by universal prestorage leukoreduction, it is necessary to pay close attention to fever with transfusion as it may indicate another serious complication such as bacterial sepsis. As part of the routine investigation of a febrile reaction, it is advisable to undertake a bacterial culture on both a patient blood sample and the blood bag.

b) Transfusion Related Acute Lung Injury (TRALI)

_Estimated Incidence: 1: 71,500\(^C\) red cell units; 1:8300 platelet pools\(^5\)_

\(^B\) Based on 0-18.1/100,000 units

\(^C\) Based on 1.4/100,000 red cell units; 12.1/100,000 platelet pools
Transfusion related acute lung injury (TRALI) presents as severe dyspnea, with non-productive cough, cyanosis, pulmonary rales, tachycardia, fever and hypotension. All of these symptoms arise in the setting of recent transfusion of plasma-containing blood components, including red blood cells, (usually greater than 60 mL of plasma) within 1 to 6 hours and usually within 1 to 2 hours. One case report associates TRALI with a fractionated plasma product.\(^7\) This complication constitutes a major medical emergency but has a low probability for mortality if respiratory distress is properly managed. In almost all cases oxygen supplementation is necessary and, if the hypoxemia is severe, intubation and mechanical ventilation are important supportive measures. Pressor agents may be useful in cases of sustained hypotension. The pathophysiology of TRALI is postulated as an immune-mediated reaction triggered by antibodies to HLA or granulocyte antigens that originate in the donor. However, anti-leukocyte antibodies are not detected in all cases. Therefore, strategies aimed at reducing the incidence of reactions are presently inadequate.\(^8\) Recent articles\(^9,10\) postulate that TRALI results from two insults, the first of which relates to the clinical condition of the patient such as recent surgery, cytokine treatment, active infection or inflammation, or massive transfusion. The second insult is the transfusion of biologically active lipids associated with near-outdating blood components. However, the presence of leukoagglutinins in the donor or the recipient could also serve as one of these insults.

c) IgE-mediated Allergic Reactions

Minor

*Incidence: 1:250\(^5\)*

IgE-mediated "allergic" reactions are among the most commonly observed adverse manifestations of transfusion of blood products. Most frequently, these present as urticarial reactions of varying severity. In the most severe cases, bronchospasm, laryngeal edema, airway obstruction, epigastric pain, nausea, and all other manifestations of acute anaphylaxis may occur. In general, however, most of these reactions are mild, self-limited, and easily controlled by a brief (15 minute) interruption of the transfusion, administration of an antihistamine, and resumption of the transfusion at a reduced rate with careful monitoring. For repeat allergic reactions, prophylactic administration of antihistamine is advisable.

Latex Allergies

*Prevalence: Less than 1% in general population\(^11\)*

More than 40,000 household and medical products now contain latex, so it is difficult if not impossible to avoid latex exposure. Repeated exposure to latex leads to increased sensitization in susceptible people, resulting in significant, sometimes life-threatening problems. Health care workers need to be aware of latex allergy for their patients’ protection. Proper identification of a potential or known latex allergy, awareness and avoidance of products containing latex (i.e., latex stoppers on blood products such as albumin), and appropriate management can avert a potentially serious medical situation. Some physicians will consider antihistamine prophylaxis to avoid a latex allergy response, but this practice is not well established.\(^12\) Many hospital transfusion services have protocols in place regarding the provision of blood and blood products with respect to patients with known latex allergies. For a list of latex-free medical products, see Reference 11.

d) Anaphylactic Reactions

*Estimated incidence: 1:23,250 units of red cells; 1:1600 platelet pools\(^5\)*

Fortunately, severe anaphylactic reactions are rare. In some cases they are associated with the production of an IgG anti-IgA antibody in patients with hereditary IgA deficiency. Anaphylaxis has been reported in the literature in association with negatively charged white blood cell filters,\(^13,14\) non-HLA matched platelets\(^15\) and the administration of aprotinin.\(^16\) In Asian populations, antihaptoglobin antibodies
in anhaptoglobinemic patients have been reported to cause anaphylactic transfusion reactions. The incidence of anhaptoglobinemia is 1/4,000 Japanese, 1/1,500 Koreans and 1/1,000 Chinese.\textsuperscript{17} A severe allergic (anaphylactic) reaction may present with angioedema, signs of upper or lower airway obstruction (hoarseness, wheezing, dyspnea and cyanosis), gastrointestinal symptoms (nausea, cramps and diarrhea), intractable hypotension or shock, cardiac arrhythmias, and cardiac arrest. The patient should be managed as for any anaphylactic reaction. Resuscitation of the patient, including airway and cardiovascular management, is of primary concern. The prevention of anaphylactic reactions in the case of confirmed IgA deficiency or anhaptoglobinemia requires transfusions of washed red cells and washed platelet concentrates. In the case of patients with anti-IgA antibodies, plasma products for transfusion must be prepared from IgA deficient donors.\textsuperscript{18}

\textbf{e) Transfusion associated Graft-vs-Host Disease (TA-GVHD)}

\textit{Incidence: Rare}\textsuperscript{5}

Transfusion associated graft-vs-host disease (TA-GVHD) is a potentially lethal complication following the transfusion of any blood component containing viable donor T-lymphocytes to severely immunocompromised patients or to recipients who share an HLA haplotype with a specific donor. This is more likely to occur with blood donations from family members and in populations with a higher incidence of HLA homozygosity. The risk is highest in recipients with immunodeficiency or immunosuppression. Patients with HIV infection appear not to be at increased risk. There is no consensus on the use of irradiated blood for all patient categories. For example, the British Committee for Standardisation in Haematology (BCSH) Blood Transfusion Task Force\textsuperscript{19} recently recommended prophylactic blood component gamma irradiation where the risk of TA-GVHD is sufficiently high. The British Columbia Transfusion Medicine Advisory Group (TMAG) has recently issued a guideline regarding the use of irradiated blood products in British Columbia (see Appendix B).
4. NON-IMMUNOLOGICAL HAZARDS OF TRANSFUSION

1) Circulatory Overload

*Estimated incidence 1:2400 red cells units; 1:5950 platelet pools*\(^5\)

Circulatory overload is generally associated with rapid infusion of large volumes of blood products. This is more likely to occur in patients with either pre-existing cardiopulmonary disease or chronic anemia.

2) Microaggregate Infusion

*Incidence: Unknown*

During the course of blood storage, microaggregates (composed of platelets, leukocytes, and leukocyte fragments) and small amounts of fibrin gradually form. These aggregates range in size from 10 to 200 µm in diameter. The significance of microaggregates in massively transfused patients remains controversial, but there is a potential for microembolization to the pulmonary capillary bed resulting in an acute respiratory distress syndrome. A critical strategy in avoiding this hazard is to ensure that all blood products are infused through a filter appropriate for the specific product.

3) Air Embolism

*Incidence: Very rare*

Air embolism is characterized by the sudden onset of severe hypotension, breathlessness, cyanosis, and collapse. A loud precordial murmur is audible on auscultation. Estimates of the volume of air necessary to produce a fatal result range from 10 to 200 mL.\(^20\) The use of collapsible blood containers for the collection, storage, and administration of blood components has virtually eliminated venous air embolism as a transfusion risk. This hazard may occur when blood is being infused under pressure.

4) Transfusion of Exogenous Material

*Incidence: Very rare*

In the past, problems resulting from small particles of rubber, glass, or cellulose fibres (from filters) entering into the circulation have been reported. Improvements in transfusion equipment and manufacturing quality control have virtually eliminated these problems.

5) Hypothermia

*Incidence: Unlikely to occur when less than 1.5 blood volumes are replaced*

The administration of relatively large amounts of refrigerated blood may produce hypothermia, especially when the blood is transfused through a central line. Cardiac arrhythmias are not infrequent in surgical patients who are rapidly transfused with large volumes of unwarmed blood.\(^21\) Hypothermia induced coagulopathy may be an additional complication.\(^22\) The use of properly designed, approved and controlled blood warmers in massive transfusion situations minimizes the risk of hypothermia.

6) Metabolic, Biochemical, and Hemostatic Problems of Transfusion

a) Citrate Toxicity

*Incidence: Unlikely to occur when less than 1.5 blood volumes are replaced*
Rapid administration (rates exceeding 100 mL/minute) of large volumes of blood products containing citrate anticoagulant-preservative solutions can produce adverse effects, primarily by chelating ionized calcium. Patients with hepatocellular disease or significant biliary obstruction are more likely to develop this complication due to the reduced ability of the liver to metabolize citrate. Clinical manifestations correlate with the degree of hypocalcemia: in milder cases, circumoral and other paresthesias occur; in more severe cases, increased neuromuscular sensitivity with involuntary twitching and ultimately tetany with bipedal spasm may be seen; in severe cases, cardiac arrhythmia and abnormal ECG have also been described. These problems may be difficult to detect while the patient is anesthetized.

b) Hyperkalemia and Hypokalemia

**Incidence:** Unlikely to occur when less than 1.5 blood volumes are replaced

During storage of red blood cells, increasing levels of potassium are found in the supernatant fluid. Large volumes of older blood, with high supernatant potassium levels, are unlikely to produce significant adverse effects unless the patient is already hyperkalemic, or has significantly impaired renal function. Occasionally, cardiac arrhythmia or even cardiac arrest can occur when infusion of hyperkalemic plasma is combined with citrate toxicity, and hypothermia.

Occasionally, hypokalemia can occur when a very large volume of blood is transfused. The risk of hyperkalemia should be considered with red blood cell transfusions to unhealthy, premature neonates.

c) Reactions Associated with Vasoactive Substances

**Incidence:** Unknown

Freezing of freshly drawn plasma may facilitate the activation of prekallikrein activator (PKA), with subsequent generation of bradykinin either within the unit itself or within the recipient after transfusion. Severe hypotensive reactions have been observed in some patients undergoing cardiopulmonary bypass surgery. This is possibly due to the bypassing of the pulmonary circulation where most of the inactivation of bradykinin occurs. More recently there have been several reports of hypotension in patients receiving Angiotensin-Converting Enzyme (ACE) inhibitors who receive blood through a negatively charged bedside filter. This effect has not been seen in patients who are not on ACE inhibitor therapy, or in patients who receive blood through a positively charged bedside filter. In theory, these reactions should not be seen when blood is filtered (leukoreduced) prior to storage.

Significant levels of bradykinin are generated when platelets are filtered with a negatively charged leukoreduction filter (but not with positively charged or neutral LR filters). Normal ACE activity is required to catabolize bradykinin generated by the negatively charged filter. Generated bradykinin is rapidly degradable and not detectable at 60 minutes post-filtration. Universal prestorage leukoreduction should decrease the generation of bradykinin in collected blood units because the filters used for this process are positively charged. In addition, any generated bradykinin would be catabolized prior to infusion to the recipient and would thus be unlikely to cause problems for patients on ACE inhibitors.

Transfusions have rarely been associated with severe hypertensive reactions accompanied by a sharp rise in blood pressure, vasoconstriction, convulsions, and sometimes fatal cerebral hemorrhage in chronically transfused patients with thalassemia major. Pressor agent generation affecting peripheral vascular resistance has been suggested, but not proven, to be the etiology.

d) Iron Overload

**Incidence:** Typically begins after the 20th red cell unit transfused
Accumulation of iron is a well-recognized complication of long-term red blood cell transfusion therapy. It is usually found in transfusion dependent persons with inherited hemoglobinopathies and thalassemia major. The following complications have been described: cardiac dysfunction with arrhythmias and heart failure; hepatic dysfunction due to fibrosis; pancreatic fibrosis associated with diabetes mellitus; and endocrine dysfunction resulting in growth retardation and delayed sexual development in children.\textsuperscript{31} Iron chelators given either subcutaneously, intramuscularly, intravenously, or orally, are important strategies in the management of iron overload but are not completely effective.\textsuperscript{32}

**e) Adverse Effects due to Plasticizer in Blood Bags**
Currently Canadian Blood Services (CBS) supplies blood in packs which contain the plasticizer di (2-ethylhexyl) phthalate, this is usually abbreviated as DEHP. DEHP has been linked with liver tumours and reduced sperm production in laboratory rats. This has yet to be confirmed in humans but there is a theoretical possibility of similar consequences in humans if they are exposed to DEHP over long periods of time.

Health Canada and the US FDA have issued a guidance stating that: “those most susceptible (male newborns, infants, pregnant women carrying a male fetus and persons requiring prolonged medical treatment- hemodialysis, blood transfusion, cardiac bypass) be protected from prolonged exposure to DEHP” and that “products containing DEHP be labeled as such.”

To mitigate these potential effects for populations at risk, CBS in August 2003 announced a switch to a different plasticizer, tri-(2-ethylhexyl) trimellitate as an alternate to DEHP. This plasticizer results in a shortening of the allowable storage time to 21 days and as a consequence will only be used in satellite containers, not the primary collection pack.

These guidelines and changes should be considered when transfusing the at risk patient populations.\textsuperscript{23}
5. TRANSFUSION TRANSMITTED DISEASES

The following per unit risk estimates are supplied based on the estimated risk of transmission for a number of infectious agents. These estimates are based on the projected efficacy of current clinical and analytical testing of donors and on outcomes in transfusion recipients. Given inherent limitations in follow up and surveillance programs, the confidence intervals for these estimates are generally wide.

1) Viruses

a) Human Immunodeficiency Virus (HIV)

Per unit risk: 1:4.7 million to 1:10 million

HIV is a retrovirus which, after infection, integrates its nucleic acid into the genome of the host and establishes life-long infection. Prior to HIV antibody screening of donated blood in 1985, HIV was transmitted by all blood components and by coagulation factor concentrates. Since 1987, viral inactivation of coagulation factor concentrates has eradicated HIV transmission by this route. All donated units are screened for HIV antibody using a test that detects antibody to two genetically diverse isolates of HIV: HIV-1 and HIV-2. HIV-1 is the common strain of HIV that exists worldwide. It can be sub-classified into main (M) and outlier (O) groups. HIV-2 was discovered in 1985 in West Africa and subsequently was found in Western Europe, but is rare in North America. HIV-1 group O was discovered in Africa in the 1990s and is quite rare in North America. Because the sensitivity of HIV-1 antibody assays to HIV-2 is less than 100%, a combined assay using both HIV-1 and HIV-2 antigens was introduced into routine blood donor screening in North America in 1992. Further protection against HIV transmission is provided by the screening via questionnaire and interview of all potential donors for behaviours that place them at high risk for HIV infection.

Despite the fact that HIV-infected people develop antibodies that persist for the individual's lifetime (or at least until late-stage AIDS develops), HIV can be transmitted by transfusion if a newly infected person donates blood prior to the development of a positive laboratory test. This infectious window period for transfusion transmission was estimated to be 22 days with HIV antibody testing that was in place in the mid 1990s. In 1997, the risk of HIV transfusion transmission from such early window period infections in Canada was estimated as 1 in 913,000 per unit. Since the time of that report, additional testing to reduce the HIV window period has been implemented into routine donor screening. From 1996 through 2003, in addition to HIV 1/2 antibody testing, all donated units were tested for HIV-1 p24 antigen. In 2001, nucleic acid testing (NAT) of pools of 24 donor samples to detect HIV nucleic acids was implemented. This NAT testing has decreased the infectious window period to approximately 13 days. Because an extensive amount of data has proven that all new HIV infections detected by p24 antigen testing are also detected by HIV NAT, the p24 antigen test was discontinued upon licensure of HIV NAT in 2003.

Using the incidence-window period mathematical model with the input values of an HIV incidence of 0.53 per 100,000 person years in CBS donors in 1998-99 and a window period of 13 days, it is estimated that the current per unit risk for HIV infection is 1 per 4.7 million units. Given this estimate, a clinically significant case of HIV transmission from blood transfusion in Canada would be expected to occur once in seven to eight years. A second published estimate using a similar method placed the current per unit risk for HIV infection at 1 per 10 million units. Given the statistical variation in the mathematical models, these estimates are equivalent.

b) Human T-Cell Lymphotropic Virus (HTLV)

Per unit risk: Very rare
Human T-cell leukemia viruses (HTLV-I and HTLV-II) are RNA-containing retroviruses. HTLV-I is endemic in Japan, Africa, and the Caribbean. HTLV-II infection is endemic in some indigenous North and South American Indian populations. HTLV-II and, to a lesser extent, HTLV-I have been found in intravenous drug users and their sexual partners. Most HTLV-I infected persons are asymptomatic, but there is a 4% lifetime risk of developing adult T-cell leukemia/lymphoma (ATLL) in persons infected at an early age. There is also a smaller risk (0.25%) of developing a neurologic disease known as HTLV-1 associated myelopathy (HAM). HTLV-II infection has been associated with this same neurologic syndrome, but at a lower frequency and has not been associated with ATLL. Both HTLV-I and HTLV-II can be transmitted by blood transfusion. These viruses are highly leukocyte associated and have never been transmitted by transfusions of plasma, cryoprecipitate, or plasma derivatives. They can be transmitted by transfusions of red blood cells and platelets. In the case of red blood cells, transmission is related to the component age, with units stored greater than 14 days rarely, if ever, transmitting the infection. Several cases of symptomatic post-transfusion HAM occurring within several years of transfusion have been reported.

All blood donations are routinely tested for antibodies to HTLV-I and HTLV-II in a combined assay that detects antibodies to either agent. HTLV antibodies persist throughout an individual’s life. Ongoing transmission is due to donations made after the time of exposure but before the development of antibody at approximately 51 days post infection. In 1996, US investigators estimated that 1 in 641,000 units would be donated by a person in the window period. More recently, the risk of a unit being donated in the HTLV window period in Canada has been estimated to be 1 in 1.5 million. However, the risk of HTLV transmission to the transfusion recipient will be significantly lower for two reasons: 1) blood component storage lowers the HTLV transmission rate by approximately two-thirds (i.e. only one-third of potentially infectious units transmit), and 2) universal prestorage leukoreduction of platelets and red blood cells substantially reduces leukocyte levels. Since HTLV-I and HTLV-II are highly leukocyte associated, leukoreduced units from infected donors will, in most cases, no longer contain enough virus to cause infection. For these reasons, the risk of HTLV infection will be very rare or even virtually eliminated.

c) Hepatitis A (HAV)

*Per unit risk: Very rare*

Hepatitis A is a single stranded non-enveloped RNA virus. Since Hepatitis A does not induce a chronic carrier state, it can only be transmitted by transfusion if a person donates during the several week interval of viremia prior to development of acute clinical symptoms. This has resulted in rare cases of transfusion transmitted hepatitis A from blood components, with about 25 cases reported in the literature.

Transfusion-related infection has been suspected in recipients of coagulation factor concentrates and intravenous immune globulin (IVIG). Although, these products are subjected to viral inactivation processes, these procedures do not efficiently kill non-lipid enveloped viruses such as hepatitis A. Because of the extremely small risk of acquiring hepatitis A from transfusion, and the typically mild and self-limiting nature of the infection, HAV serologic testing is not routinely performed on donor blood. The donor screening questionnaire attempts to exclude prospective donors who have had recent contact with an individual who has clinical hepatitis. HAV immunization should be considered in those who will require lifelong infusion of blood products.

d) Hepatitis B (HBV)

*Per unit risk: 1:31,000 to 1:82,000; risk of clinical disease is 1:1.2 million units*

Hepatitis B is a DNA virus that is common in many parts of the world and is highly infectious by parenteral routes. All donated blood is tested for the presence of Hepatitis B surface antigen (HBsAg), a
marker of acute and chronic HBV infection. Prior to the implementation of HBsAg testing in the 1970s, transfusion transmitted HBV was more common. Subsequent to routine HBsAg testing, such infection can still occur in two circumstances: if the donation is made early in acute HBV infection prior to development of HBsAg or, rarely, from a chronic carrier who tests negative for HBsAg yet is infectious. Based on incidence data in CBS blood donors in 1998-99, it is estimated that the risk from a window period donation is 1 per 82,000 units. Risks from chronic carriers have been estimated to be as high as 1 per 50,000 units based on the detection of low levels of HBV DNA in such donors; however, it is uncertain whether these units contain enough virus to infect transfusion recipients. Thus the estimated per unit risk of HBV infection in Canada may be as high as 1 in 31,000 (if all chronic carriers transmit) to 1 in 82,000 (if none transmit). Plasma derivative products, such as albumin, coagulation factor concentrates, and intravenous immunoglobulin, will not transmit hepatitis B due to viral inactivation procedures.

Only 5% of adults acquiring HBV will fail to resolve the infection and progress to a chronic carrier state. Chronic sequelae include chronic hepatitis, cirrhosis and liver cancer. Combining this estimate for development of the chronic carrier state with recipient survival data, it can be estimated that the risk of clinically significant disease developing from a transfusion transmitted HBV infection in Canada is 1 per 1.24 million units.

Donor selection is used to reduce the risk of transfusion transmitted HBV infection. Individuals with a history of hepatitis are excluded, as are those known to be HBsAg positive. Since HBV and HIV infections have similar risk factors, the exclusion of those with high-risk behaviours for HIV likely reduces the transmission of HBV as well. Potential HBV exposures such as tattooing and body piercing result in deferral of the blood donor for one year, as does a history of blood or body fluid exposure and accidental needle-stick injury. Physical examination of potential donors is used to eliminate those with evidence of needle tracts or sclerotic veins, which may be indicative of intravenous drug abuse.

e) Hepatitis C (HCV)

Per unit risk: 1:3.1 million

Hepatitis C virus, a single stranded RNA virus, is the main etiologic agent of the disease formerly known as non A, non B hepatitis, accounting for approximately 90% of such cases. Hepatitis C can be transmitted by parenteral routes and is very common in intravenous drug users. It is rarely transmitted sexually. HCV has been transmitted by transfusions of red blood cells, platelets, plasma, and cryoprecipitate. Prior to the use of viral inactivation techniques, factor concentrates and immune globulin preparations also transmitted HCV. HCV is usually asymptomatic in the acute phase, but chronic infection occurs in 60 to 85% of cases. This chronic infection may be asymptomatic but may cause liver enzyme elevations. Chronic sequelae occur in a minority of patients and may take two to three decades to develop; these include chronic active hepatitis, cirrhosis and hepatocellular carcinoma.

All donated blood has been tested for the presence of antibody to HCV since 1990. HCV antibody develops approximately 70 days after acute infection and, according to current knowledge, remains present throughout a chronically infected individual’s life. In 1999, HCV NAT performed on minipools of 24 samples was implemented in Canada. NAT testing has decreased the HCV infectious window period to approximately 12 days. Using the incidence-window period mathematical model, a reported incidence of 0.89 per 100,000 person years in CBS donors in 1998-99, and a window period of 12 days, it is estimated that the current per unit risk for HCV infection is 1 per 3.1 million units. Given this estimate, a clinically significant case of HCV transmission from blood transfusion in Canada would be expected to occur once in six to seven years.

f) Hepatitis D (HDV)
Per unit risk: Unknown, but very rare

Hepatitis D virus, originally known as the delta agent, is a defective RNA virus that can replicate only in the presence of HBV. It is estimated that approximately 5% of HBV carriers are infected with HDV. HDV can be transmitted by blood and plasma derivatives. One third of HBV-infected hemophiliac patients, transfused prior to viral inactivation of coagulation factor concentrates, were infected with HDV. Since HDV requires simultaneous infection with HBV to replicate, and because HDV uses surface membrane from HBV to form its virion, screening for HBV concomitantly reduces the risk of transfusion transmission and serious consequences of HDV.\textsuperscript{53}

g) Hepatitis E

Per unit risk: Very rare

Hepatitis E is a non-enveloped RNA virus. It is enterically transmitted and causes sporadic and epidemic hepatitis in developing countries. It is somewhat distinct in that it causes a particularly virulent form of hepatitis in pregnant women.\textsuperscript{54} A recent preliminary report suggests that a case of transfusion-transmission has been documented in an HEV endemic region in Japan; currently, the risk for such transmission in North America should be regarded as very rare.

h) Non A-E Hepatitis

Per unit risk: Rare

Clinical and laboratory evidence has suggested for two decades that a viral agent other than Hepatitis C causes some cases of transfusion-transmitted non-A non-B hepatitis. Prior to the discovery of HCV, such cases constituted a very small fraction (approximately 5-10%) of non-A non-B cases.\textsuperscript{55} Currently the risk of this non A-E agent is not quantifiable but is likely to be rare; the risk may be lower than it was prior to 1990, assuming that this agent affects many of the same persons that are identified and excluded from blood donation by HCV antibody testing. Epidemiologic evidence suggests that non A-E hepatitis is milder and less likely to become chronic than HCV.

When initially discovered, both HGV/GBV-C and TTV were thought to represent this agent, but subsequent intensive study has shown that neither of these agents is the non A-E virus. Recently, a new viral agent isolated in Italy, termed SENV, has been postulated to be this causative agent; however, subsequent studies have not provided additional support for this hypothesis.

i) Hepatitis F

Per unit risk: None known

Initial isolates of a virus termed hepatitis F have not been confirmed and it seems probable that this agent, if it exists, is not a cause of any known transfusion transmitted disease.\textsuperscript{56}

j) Hepatitis G (HGV)/GBV-C

Per unit risk: 1:100, but no known associated disease

Hepatitis G, also more appropriately called GBV-C after the name of the initial isolate, is a lipid enveloped single stranded RNA virus. A preponderance of data has established that this virus is as frequent in patients without biochemical or clinical hepatitis as in patients with these conditions and that there is no causal relationship between GBV-C infection and hepatitis.\textsuperscript{57,58,59} GBV-C does not infect hepatocytes or replicate in the liver. GBV-C is readily transmitted by transfusion as demonstrated by linked donor-recipient studies. Multiple international studies have demonstrated that 1-4% of blood
donors are viremic for GBV-C and 3 to 6 times this number are positive for antibodies to GBV-C. The immune response excludes the viral genome from serum; persons that tested positive for RNA were negative for the antibody and vice versa. Plasma derivatives subject to viral inactivation will not transmit GBV-C.

Currently there is no practical test for GBV-C that can be applied in the blood donor setting. Furthermore, blood donor screening does not appear to be indicated given the high prevalence of the virus in donors and its lack of association with disease.

**k) TT Virus (TTV)**

*Per unit risk: 1:10 to 1:50, but no known associated disease*

DNA sequences attributed to a new virus were discovered in Japan in 1997 in the stored serum of a patient who had previously developed non A-G post-transfusion hepatitis. The virus was named after the index patient whose initials were TT. Subsequent to the discovery of this isolate, it has been shown that TTV consists of a large family of circular single-stranded DNA viruses with a high degree of genetic diversity. TTV viremia rates in donors were initially reported to range between 1 and 10% in developed countries; however, with the development of more sensitive PCR assays using conserved regions of the genome common to many TTV isolates, viremia has been documented to be as high as 90% in a recent study of Norwegian blood donors. TTV can establish a chronic asymptomatic carrier state and can be transmitted by non-parenteral as well as parenteral routes including transfusion. The virus was transmitted to hemophiliacs by factor concentrates prior to routine use of viral inactivation techniques and appears to be inactivated by some, but not all, viral inactivation procedures. TT virus does not appear to be a causative agent of hepatitis, as it is found just as frequently in patients with and without hepatitis, it is not associated with non A-E hepatitis, and it has no effect on the severity or duration of coexistent hepatitis C. The virus has not been demonstrated to infect liver cells.

Currently there is no practical test for the TTV family that can be applied in the blood donor setting. Furthermore, blood donor screening does not appear to be indicated given the high prevalence of the virus in donors and its lack of association with disease.

**l) SEN Virus (SENV)**

*Per unit risk: 1:50, but no known associated disease*

Recently, two variants of a new class of viral agents termed SENV (SENV-D and SENV-H), which are genetically related to the expanding class of TT viruses, have been hypothesized to be the causative agent(s) of non A-E hepatitis. Initial studies have shown an association between infection with these two SENV subtypes and transfusion-transmitted hepatitis cases from the 1970s. However, no causal relationship has been demonstrated and other studies in patient groups with liver disease suggest that SENV does not cause such disease. It has been demonstrated that SENV is transmitted by transfusion and can establish chronic asymptomatic infection. The prevalence of SENV viremia in blood donors has been reported to be approximately 2% for SENV D and H variants in US blood donors and 10% in Japanese blood donors.

**m) Cytomegalovirus (CMV)**

*Per unit risk: Low but not quantifiable; significant clinical disease rare*

CMV is a ubiquitous DNA virus in the herpes virus family. Primary CMV infection in older children and adults usually results in an asymptomatic or mildly symptomatic mononucleosis-like syndrome. However, in the immunocompromised host, severe disease including interstitial pneumonitis, retinitis, and gastroenteritis may result, with potentially fatal outcome. Serious morbidity and mortality from transfusion
transmitted CMV infection is largely restricted to susceptible groups of patients. These groups include bone-marrow transplant patients, other immunocompromised hosts, very low birth weight infants (<1,200g), and seronegative women in the early stages of pregnancy where there is a risk of congenital infection of the fetus. Features of congenital CMV disease include petechiae, hepatosplenomegaly, jaundice, and microcephaly.

CMV is transmitted by leukocyte containing cellular products but not by fresh frozen plasma and cryoprecipitate. CMV risk from cellular blood products (e.g. platelets, red cells) can be greatly reduced by leukodepletion. Techniques that reduce the number of leukocytes in the transfused product to fewer than $5 \times 10^6$ have been demonstrated to provide substantial protection against CMV infection. This level of leukodepletion is achieved with leukocyte reduction filters routinely used to produce platelet concentrates and red blood cells in Canada. Further protection for high-risk recipients is achieved by supplying blood components collected from donors who test negative for CMV antibody (CMV seronegative products). Fifty to 65% of Canadian blood donors are CMV seronegative. Prior to the implementation of universal leukoreduction for cellular blood components in Canada, provision of CMV seronegative cellular components for high risk recipients was the method used to reduce the risk of post-transfusion CMV disease.

Despite use of measures to decrease CMV transmission to susceptible recipients, primary CMV infections have been demonstrated in 1-4% of CMV seronegative allogeneic bone marrow transplant patients receiving either CMV seronegative or leukoreduced components. However, it is unknown whether these highly immunosuppressed post-transplant patients acquired their CMV infection from transfusion or from other nosocomial routes known to transmit CMV.

There are no data available to assess whether the combination of leukoreduction and CMV antibody screening provides an additional level of safety in preventing CMV transmission as compared to using only one of these methods. This lack of data, combined with the possibility of breakthrough transfusion infections (as described above), led to a recent Canadian consensus conference recommending transfusion of CMV seronegative, leukoreduced cellular blood components to specific patient groups at the greatest risk of severe morbidity from transfusion-transmitted CMV infection. These high risk patients groups were CMV seronegative pregnant women, CMV seronegative women receiving intrauterine transfusions, and CMV seronegative patients who undergo allogeneic bone marrow transplantation. For three other patient groups, use of CMV seronegative leukoreduced blood components was felt to be probably indicated: CMV seronegative patients undergoing solid organ transplantation from a CMV seronegative organ donor, CMV seronegative patients with conditions that were likely to require an allogeneic bone marrow transplantation, and CMV seronegative patients with HIV. Provision of CMV seronegative cellular blood components was not recommended for transfusion of patients undergoing autologous bone marrow transplantation or for neonates, due to the lower risk of severe CMV clinical disease in these groups.

Although reinfection with a second strain of CMV in CMV seropositive patients has been demonstrated in recipients of solid organ transplants, it has not been demonstrated in recipients of blood components. Furthermore, reactivation of CMV infection in immunosuppressed patients does not appear to be linked to transfusion of CMV positive blood components. Currently there is no evidence that patients previously infected with CMV need to receive or will benefit from CMV reduced-risk (either CMV seronegative or leukoreduced) blood components.

Due to several factors (e.g. the potential marked influence of the recipient’s immune system on whether CMV is reactivated from a transfused unit, the use of CMV seronegative components for some patient populations, and the uncertainty in the data concerning breakthrough infections), it is not possible to assign a CMV risk per unit as can be done with other infectious agents. However, it is possible to
conclude that the risk of significant CMV clinical disease from transfusion of cellular blood components in Canada, even in high risk patient groups, should be rare.

**n) Epstein-Barr Virus (EBV)**

*Per unit risk: Rare for clinically significant disease*

EBV is a herpes family virus that establishes latent infection in lymphocytes. EBV is ubiquitous, with over 90% of the adult population testing seropositive. Primary infection in childhood is often asymptomatic, but when delayed until adolescence or early adulthood can manifest as infectious mononucleosis. In immunosuppressed individuals, EBV may cause malignancy including several different types of lymphoma and nasopharyngeal carcinoma. A case of transfusion transmitted EBV infection in a liver transplant recipient resulting in B cell lymphoproliferative disease has been reported in Canada.\(^{77}\) Previously, transfusion transmitted EBV infection had been reported to rarely cause a mononucleosis-like syndrome.\(^{78}\) There are no studies to assess the magnitude of EBV risk in susceptible patient populations. Based on the extremely high prevalence of EBV antibody in blood donors and the lack of adverse effects in other than severely immunosuppressed persons, serological screening of blood donors for EBV is neither feasible nor warranted. Prestorage leukoreduction of blood products is expected to further reduce or eliminate the risk of EBV transmission.

**o) Human Herpes Virus 6 (HHV-6)**

*Per unit risk: None known*

HHV-6 infection is common, with 85% of adults having antibodies to the virus. Infection usually occurs early in childhood, most probably via the oral route through infected saliva. The virus may be present in a latent or low replicative state in peripheral blood mononuclear cells but is reactivated in immunosuppressive states, such as AIDS. HHV-6 has been recognized as the cause of exanthem subitum and other febrile illnesses in infants and young children. Other disease associations have not been proven. There are no known cases of transfusion transmission.\(^{79}\)

**p) Human Herpes Virus 7 (HHV-7)**

*Per unit risk: None known*

HHV-7 is a recently discovered herpes virus that has some genetic similarities to HHV-6. Eighty-five percent of adults have antibodies to HHV-7, with infection usually occurring early in childhood, most probably through saliva. There are no proven disease associations and no cases of transmission by transfusion.

**q) Human Herpes Virus 8 (HHV-8)**

*Per unit risk: None known*

HHV-8, also known as Kaposi’s sarcoma associated virus, is a recently discovered leukocyte associated herpes virus that has been implicated as the causative agent of Kaposi’s sarcoma and possibly of multicentric lymphoma (Castleman’s disease).\(^{63}\) It is known to be sexually transmitted and a study in injection drug users has suggested parenteral transmission by this route.\(^{85}\) There is a single case report of HHV-8 being cultured from an asymptomatic blood donor and infecting allogeneic lymphocytes in the in-vitro culture system.\(^{81}\) This has sparked concern over the potential for transfusion transmission. Preliminary studies have failed to detect HHV-8 transmission in small numbers of recipients of blood from HHV-8 antibody positive blood donors and have documented low rates of HHV-8 seropositivity in hemophiliacs transfused with coagulation factor concentrates prior to viral inactivation.\(^{82,83}\) Furthermore, in a study that demonstrated an HHV-8 seropositivity rate of 3.3% in US donors, HHV-8 viremia could not
be demonstrated in 37 seropositive donors.\textsuperscript{84} Thus, seropositivity does not appear to correlate with viremia, making the possibility of transfusion-transmission from seropositive donors unlikely. Due to the leukocyte-associated nature of the virus, universal leukoreduction of red cells and platelets in Canada should virtually eliminate any risk of HHV-8 transfusion-transmission.

\textbf{r) Human Parvovirus B19 (HPV-B19)}

*Per unit risk: Very rare for clinically significant disease in special groups of recipients*

Human Parvovirus B19, a non-enveloped DNA virus, is usually transmitted by respiratory droplets. Most normal individuals who become infected with B19 are asymptomatic. Children may develop a contagious exanthemous rash known as Fifth disease. If infected in early pregnancy, non-immune women can transmit the virus to the fetus sometimes resulting in suppression of erythropoiesis in the fetus and anemia, which may result in spontaneous abortion or in utero fetal death. Serious clinical consequences of infection can occur in children with anemias secondary to decreased red cell survival (e.g., hereditary spherocytosis, sickle cell disease, thalassemia) who may develop a transient erythroid aplastic crisis. Persons with immunodeficiencies, including HIV seropositive patients, may develop severe chronic anemia secondary to chronic pure red cell aplasia following infection with B19.\textsuperscript{85}

Parvovirus B19 nucleic acid in donated blood has been detected in 1 in 3,300 blood donors and may even be higher during seasonal epidemics.\textsuperscript{86} Nevertheless, transfusion transmission from blood components has been reported only rarely and clinical disease (anemia) associated with Parvovirus B19 transmission is well documented in only three cases in North America and Europe.\textsuperscript{87} This low number may be due to recipient immunity due to previous B19 exposure, a low rate of transmission due to low B19 viral concentration in donor blood, or the lack of clinical symptoms in most persons who acquire the infection. B19 is poorly inactivated by the solvent/detergent and heat treatment methods of viral inactivation; a high prevalence of B19 antibody in hemophiliacs as well as documented cases of seroconversion indicate that this virus is transmissible by coagulation factor concentrates.\textsuperscript{87,88} Despite relatively high transmission rates to recipients of pooled plasma products, very few adverse clinical outcomes have been reported in patients with hemophilia; a 1999 review article cites only three cases of erythema infectiosum and one case of hypoplastic anemia.\textsuperscript{87} Recently, most manufacturers of plasma derivatives have adopted minipool NAT screening to eliminate plasma from donors with high titres of Parvovirus B19 viremia from the manufacturing pool.

\textbf{s) West Nile Virus}

*Per unit risk: Rare*

West Nile virus (WNV) is a single stranded lipid enveloped RNA virus in the flavivirus family. It was first reported in the United States in Queens, New York in 1999.\textsuperscript{89} Birds are the primary hosts with secondary spread to humans and other mammals by bites of infected mosquitoes (principally Culex spp) in late summer and early fall. By late 2002, WNV had spread to the midwestern and southern United States as well as to central Canada with a dramatic increase in human infections and deaths.\textsuperscript{90,91} The majority (70-80\%) of infections are asymptomatic. Symptoms, if present, will usually develop within 2-15 days after the bite of an infected mosquito and may include flu-like symptoms (generalized weakness, muscle weakness, fever, headache, body aches, joint pain, bone pain, chills), a rash, swollen glands, and gastrointestinal problems (vomiting, diarrhea, abdominal pain). Severe illness such as meningitis, encephalitis, or meningoencephalitis is rare affecting less than 1\% of infected persons, with >50 year-old individuals and immunocompromised patients at higher risk.\textsuperscript{90}

Although no cases of transfusion-transmitted WNV had been reported worldwide prior to the current US epidemic, such transmission had been considered plausible given the large number of people that can be simultaneously infected in an epidemic and the estimated 5-10 day period of viremia that occurs during the asymptomatic incubation phase of infection.\textsuperscript{89} In August 2002, transmission of WNV by organ
transplantation was proven through detection of a cluster of four WNV infected organ recipients all of whom received organs from a donor who was later found to be viremic for WNV. An extensive evaluation conducted by the Centers for Disease Control and Prevention proved that 23 cases of WNV infection were transmitted by transfusion in the US during the summer and fall of 2002. In Canada, three cases of WNV infection (all in Ontario) have been accepted as having been transfusion-transmitted in 2002.

Canadian Blood Operators (Canadian Blood Services (CBS) and Hema Quebec) implemented universal donor screening for WNV on 2 July 2003, using an investigational nucleic acid test (WNV-NAT). This test will detect WNV and other genetically related flaviviruses within the Japanese encephalitis serocomplex (e.g. St Louis encephalitis virus). The WNV-NAT has very good analytic sensitivity (<100 viral copies/mL). The clinical sensitivity and specificity of the test in detecting WNV in a blood donor population have not been determined.

WNV is a reportable disease in most Canadian provinces/territories and CBS reports positive screening test results to the donor and public health within 48-72 hours of donation so that appropriate medical follow-up can occur. Further testing, arranged through the donor's family doctor and/or local Medical Health Officer is necessary to identify and confirm the specific virus from a blood donor with a positive WNV screening test. Positive donors are deferred 56 days from donating blood. A WNV-like illness (e.g. fever with headache) shortly before or after a donation is also an indication for temporary donor deferral and/or product retrieval. Another measure taken to enhance blood safety from WNV is stockpiling of frozen plasma collected outside of mosquito season, for use in regions that experience high levels of WNV activity in later summer or autumn. CBS, provincial and Health Canada public health officials also work closely to monitor WNV surveillance and ensure appropriate action is taken to protect the blood supply when new cases of WNV are reported.

Since WNV is a lipid enveloped flavivirus, existing data strongly suggest that it should be easily inactivated by viral inactivation procedures used to prepare plasma derivatives. Preliminary experimental data have shown this to be the case.

2) Prions, Bacterial Agents and Parasites

a) Creutzfeldt-Jakob Disease (CJD)

*Per unit risk: Risk is theoretical only*

CJD is one of the transmissible spongiform encephalopathies that lead to dementia and death. A prion, which is an abnormal version of a normally occurring protein, is thought to be the causative agent. CJD has a worldwide incidence of 1 per million, which is identical to its rate in Canada. Most CJD is sporadic, but iatrogenic disease has been identified. CJD has been transmitted from human to human by corneal transplant, dura mater transplant, intracerebral placement of contaminated electrodes, and injection of growth hormone derived from infected cadaveric pituitary glands. The source of all of these transmissions was from infected brain tissue and, with the exception of growth hormone recipients, resulted from direct exposure of the recipients’ central nervous system to infected material. The latency period from exposure to CJD development in growth hormone recipients is one to two decades.

These human-to-human transmissions have caused concern that CJD could be transmitted by transfusion of blood components or plasma derivatives. However, there have been no known cases of transfusion transmitted CJD and epidemiologic data argue against such transmission occurring.

Although experimental evidence suggests that if prions are present in source plasma, they are more likely to partition to the coagulation factor fraction, an increased incidence of CJD has not been detected in hemophiliacs. Recent epidemiologic evidence in patients with hemophilia, laboratory evidence in experimental animal models, and measurement of prion inactivation in the plasma fractionation process.
has provided evidence against classical CJD transmission by plasma fractionation products. With regard to blood components, an increased incidence of CJD has not been detected in recipients of blood components from donors who later were diagnosed with CJD. CJD incidence has not changed with the increased use of blood components over the last several decades and patients dying of CJD do not show an increased incidence of transfusion. Although still regarded as a theoretical risk, there is an emerging consensus that CJD is not transmitted by transfusion.

The theoretical risk of transfusion transmission of CJD has led to questioning and exclusion of potential blood donors with a family history of CJD or an exposure to CJD containing material such as human derived growth hormone. Currently there is no screening test for CJD.

**b) variant Creutzfeldt-Jakob Disease (vCJD)**

*Per unit risk: Risk is theoretical only*

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal, degenerative neurological disease newly discovered in the United Kingdom (UK) in 1996. As of May 2003, 135 definite or probable cases had been reported in the UK with an additional six cases originating in France and one in Italy. Four additional reported cases have occurred elsewhere (one each in Canada, the US, Hong Kong, and Ireland) but are assumed to have been acquired in the UK. The only significant change in vCJD epidemiology is the observation that, in the last several years, there is no increase in the rate of vCJD in the UK, resulting in substantially reduced projections for the total number of likely vCJD cases and carriers.

It has been proven that the etiologic agent of vCJD (probably a prion) is the same agent that causes bovine spongiform encephalopathy (BSE). The spread of the agent from cattle to man and the detection of the vCJD prion protein in lymphoid tissue has raised concern that there is a biological basis for the possibility that vCJD is transmissible by peripheral routes, including blood transfusion. To date, no cases of transfusion-transmitted vCJD have been reported anywhere in the world. However, since vCJD is a new disease and other transmissible spongiform encephalopathies are known to have long incubation periods, the seven-year observation period since the discovery of the disease is too short to draw firm conclusions. The biological differences between vCJD and classical CJD are significant enough to make it unreasonable to confidently extrapolate epidemiological data about the lack of transfusion-transmission of classical CJD to vCJD.

Although the risk of transfusion-transmitted vCJD is currently theoretical, donor deferral policies to lower this theoretical risk have been implemented in Canada. These policies are based on length of stay in European countries in which vCJD or BSE have been documented. The 2003 criteria are for donors to be deferred if they had spent more than 3 months in the UK, 3 months in France, or 5 years in Europe since 1980. With this policy in place, it is reasonable to conclude that the risk of transfusion-transmitted vCJD in Canada, if it exists at all, is extremely low. Currently there is no blood screening test for vCJD.

**c) Bacterial Sepsis**

*Per unit risk: General estimate of morbidity from transfusion of platelet pools is 1:2500 to 1:12,000; risk is less than 1:1 million for fatal reactions from red blood cell transfusion*

From 1976 through 1998 in the US, there were 51 cases reported to the FDA of fatal septicemia resulting from transfusion of platelets. The implicated bacteria were most often (58%) gram-negative, but could also be gram-positive skin flora. The risk of contaminated platelet units increases when platelets are stored for four to five days. The incidence of non-fatal transfusion transmitted bacterial disease is unknown and controversial, since such reactions are not routinely reported and may go unrecognized. Several studies have estimated that the risk of symptomatic bacterial sepsis may be as high as 1:2,500 to 1:12,000 platelet pools (assuming a pool consists of 5 or 6 platelet concentrates). Recent data from the hemovigilance system in Quebec are similar. Clinical symptoms are often less severe and more
variable than in patients with sepsis due to red blood cell transfusions. It is hypothesized that many patients may have only mild symptoms due to pre-existing treatment with antibiotics.  

From 1976 through 1998 in the US, there were 26 cases reported to the FDA of fatal septicemia resulting from transfusion of red cells. The most common causative agents were Yersinia enterocolitica (54%) and pseudomonas and serratia species, all of which are capable of growing in 4°C stored red cell units. Red cell contamination by such cold growing gram negative bacteria can result in the accumulation of large amounts of endotoxins in vitro, which can yield clinically significant levels by 21 to 25 days of storage.

The infusion of red blood cell units contaminated with bacteria causes a characteristic clinical syndrome. The patient may have violent chills as the unit is infused or shortly thereafter, accompanied by fever, tachycardia, hypotension, nausea, vomiting, and circulatory collapse. This reaction can be distinguished from a hemolytic transfusion reaction by the lack of hemoglobinemia or hemoglobinuria. Survival depends on the recognition of septic shock, discontinuation of the infusion, and the rapid institution of appropriate treatment. More recently, it appears that transfusion of bacterially contaminated red cell units may result in only mild febrile symptoms.

The potential sources of bacterial contamination of blood units include inadequate skin preparation or poor venipuncture technique, “coring” of the skin with the venipuncture needle, defects in collection equipment, and donor bacteremia. Methods of preventing transfusion transmission of bacterial infection include: deferral of potential donors with an elevated temperature or with recent dental work; aseptic blood collection techniques with careful skin sterilization; and aseptic handling of blood components for pooling and transfusion. Red blood cell units are stored refrigerated under temperature control and blood components are visually inspected prior to release for transfusion. A strategy currently being adopted in Canada to reduce the inocula of bacteria entering the collected unit of blood consists of diversion of the initial 43 mL of donor blood away from the final collection container into a separate collection pouch that is an integral part of the blood collection set. The blood in this diversion pouch is then used for required donor infectious disease testing. This strategy has been shown to reduce (but not eliminate) the number of units contaminated with gram positive skin flora (e.g. Staphylococcus spp.).

Currently, strong consideration is being given to introducing a laboratory based bacterial detection system for testing at least a portion of the platelet inventory in the near future.

d) Syphilis

Per unit risk: Very rare

All donated blood is screened with a serologic test for syphilis. Transmission of syphilis by transfusion in Canada has been virtually eliminated by a combination of careful donor screening, serological testing and storage and refrigeration of blood at 4°C for 48 to 96 hours, which eliminates infectivity. Although platelets stored at room temperature could theoretically transmit syphilis, there have been only two cases of transfusion transmitted syphilis reported in the literature in the past 40 years.

e) Lyme Disease

Per unit risk: None known

The organism of Lyme disease is a spirochete, Borrelia burgdorferi. It is transmitted by several species of ticks, with the most prominent being the deer tick, Ixodes scapularis, the same vector that carries Babesia microti. Lyme disease is endemic in parts of the US but is not common in Canada.

Spirochetemia has been documented in patients with early Lyme disease and it has been shown that B. burgdorferi can survive in both stored platelets and red cells. These conditions establish the theoretical
possibility of transfusion-transmission, but there have been no reported transfusion-transmission cases and there have been two studies in endemic areas providing evidence against such transmission.\textsuperscript{112, 113}

Lyme disease may evolve through stages, beginning with characteristic fever and skin lesions that later may progress to neurological, joint, or cardiac abnormalities. Donors with treated and resolved Lyme disease are eligible to donate.

\section*{f) Malaria}

\textit{Per unit risk: 1:4 million}

The four species of malarial parasites (Plasmodium spp) are transmitted by the bite of an infected mosquito in endemic areas. Transfusion-transmitted malaria is common in some parts of the world but is rare in North America. Patients with transfusion-transmitted disease manifest typical malarial symptoms (e.g. fever and chills) within days to several weeks following transfusion. Hemolysis may occur and the disease can be lethal, especially in asplenic patients.

The malarial parasite exists in blood in the intraerythrocytic state; therefore, it can be transmitted by transfusion of red blood cells and occasionally by platelets that contain contaminating red blood cells. Malarial parasites survive for at least 1 week in whole blood, red cell, and platelet concentrates and can also survive in red cell units that are frozen. Malarial parasites should not survive in acellular frozen thawed plasma and cryoprecipitate.

In the US, malarial surveillance over the past several decades has detected an average of three transfusion transmitted malaria cases annually, for a risk of 1 per 4 million units.\textsuperscript{114, 115} Infection has most often been with \textit{P. Falciparum}. In Canada, three cases (all caused by \textit{P. Falciparum}) were diagnosed in the six-year period from 1994 through 2000, yielding a similar risk to that in the US. Two of these cases occurred prior to the revision of blood donor questioning in 1995, while only one case has occurred in the five years (1996-2000) since the revised criteria were adopted.\textsuperscript{116}

Transmission occurs from donors who acquired infection from foreign travel, residency, or birth and who either have become chronic long-term carriers (which is rare) or who have not responded correctly to questions that are part of the blood donor screening process. The primary defence against transfusion transmitted malaria is careful questioning of prospective donors to identify those whose travel or emigration histories will result in their temporary or permanent deferral.\textsuperscript{114,115} Blood screening assays have not been developed for use in North America.

\section*{g) Babesiosis}

\textit{Per unit risk: Rare; risk of severe clinical disease is very rare in non-immunosuppressed recipient}

\textit{Babesia microti} is a small protozoan parasite that infects red blood cells and is transmitted by the bite of the deer tick, \textit{Ixodes scapularis}. Babesiosis is endemic in islands and coastal lands of the Northeast US (Nantucket Island, Martha’s Vineyard, Cape Cod, Mass. and Long Island NY). It has also been found in the upper midwest and a variant has been identified on the west coast. Although Babesia is not endemic in Canada, the possibility for an increased number of cases exists given the common border with endemic US states.

\textit{B. microti} is the second most commonly reported cause of transfusion transmitted parasitic infection in the US, with over 40 cases reported in the literature in the last two decades.\textsuperscript{111,117} Only one transfusion transmitted case has thus far been documented in Canada from a donor who had visited an endemic area in the US.\textsuperscript{118}
Babesiosis has been transmitted via red blood cells, deglycerolized red blood cells and occasionally by platelets. Most transfusion cases have occurred in asplenic or immunocompromised patients; these patients may develop life-threatening disease characterized by fulminant hemolytic anemia and renal failure. Disseminated intravascular coagulation may also occur. In contrast, symptoms in immunocompetent individuals are much milder and may not result in the diagnosis of babesiosis; symptoms may include headache, hemolysis, and hemoglobinuria and fever with or without chills. A babesia-like organism with increased virulence, termed WA-1, has also been found in the Pacific Northwest and has been documented to be transmitted by transfusion. There are no serologic tests available for blood donor screening. Prospective donors with a history of babesiosis are permanently deferred from donating.

h) Chagas’ Disease

Per unit risk: Rare; risk of severe clinical disease is very rare in non-immunosuppressed recipient

Chagas’ disease is caused by a protozoan parasite, Trypanosome cruzi (T. Cruzi). This parasite is endemic to Mexico and Central and South America, where significant numbers of transfusion transmitted cases have been documented. The parasite can persist for decades in an infected person with the person remaining asymptomatic; past exposure is detected by antibody tests. Concern for transfusion transmission of T. Cruzi has arisen in North America due to participation in blood donation by Latin American immigrants. Several studies in the US have documented low rates of T. Cruzi seropositivity in blood donors, with the highest rates found in geographic regions with increased numbers of Hispanic donors. In the last 15 years, only six cases of acute fulminant transfusion-transmitted Chagas’ disease have been reported in North America (two in Canada), all in immunocompromised patients. Platelets have been the implicated blood component in cases in which data were available. Recently, an additional case of asymptomatic transfusion-transmitted T. cruzi infection has been documented in the US in a recipient transfused with a T. cruzi seropositive platelet unit. This latter case indicates that cases of asymptomatic transfusion-transmitted T. cruzi infection may occur and not be recognized. Blood donor testing for antibody to T. Cruzi is not currently performed in Canada or the US due to the low risk of transfusion transmitted Chagas’ disease. Prospective donors with a history of Chagas’ disease are permanently deferred from donating.

i) Ehrlichiosis

Per unit risk: Very rare

Ehrlichia organisms, which have recently been renamed anaplasma, are aerobic gram-negative bacteria that infect leukocytes. Several different species affect humans and are responsible for two acute febrile illnesses, Human Monocytic Ehrlichiosis (HME) and Human Granulocytic Ehrlichiosis (HGE). Ehrlichia are transmitted by ticks; Ixodes scapularis, the same tick that carries Lyme disease and Babesiosis, is the vector of HGE. Ehrlichia species can survive in stored red cells for up to one to two weeks. The prevalence of antibodies to the HGE agent is highest in the northeastern and upper mid-western US in states that are in close proximity to Canada. A single case of probable transfusion-transmission of Ehrlichia with resultant HGE in a recipient occurred in the US in 1998. Because of its leukocyte tropism, leukoreduction would be expected to decrease, if not eliminate, the risk of transfusion-transmission.

j) Leishmaniasis

Per unit risk: Rare, none documented in Canada; risk of severe clinical disease is very rare in non-immunosuppressed recipient
Visceral leishmaniasis infection’s traditionally recognized causative organism was *Leishmania donovani*, which is transmitted by the bite of a sand fly. Clinical symptoms include fever, anemia, lymphadenopathy, and hepatosplenomegaly, which may be chronic. Although there are five transfusion associated cases reported in the literature in newborns and immunosuppressed patients, no cases have been reported in North America. At the time of the Persian Gulf War in 1991, some US servicemen were infected with another Leishmania parasite, *L. tropica*, and developed visceral leishmaniasis; concern was raised that this leishmania parasite might be capable of being transmitted by transfusion. No such transmissions were detected. Blood donor screening will permanently exclude a prospective donor with a history of leishmaniasis.

**k) Toxoplasmosis**

*Per unit risk: Very rare*

Toxoplasmosis, caused by *Toxoplasma gondii*, is usually an asymptomatic infection but can occasionally cause lymphadenopathy, malaise, fever, headaches, and sore throat. Splenomegaly, hepatomegaly and rash may also be present and the acute illness may mimic infectious mononucleosis. Prior infection is common in North America and the trophozoite form of the organism can circulate in infected individuals and survive in refrigerated blood. Transfusion transmitted toxoplasmosis was reported in the 1970s when transfusions of white cell concentrates from individuals with chronic myelogenous leukemia were used to treat granulocyte deficient patients. Since the use of cells obtained from ill patients was discontinued shortly after its introduction, only one case of transfusion transmitted toxoplasmosis has been reported. Blood donations are not screened for toxoplasmosis and blood donors are not questioned as to a previous diagnosis.

**l) Microfiliariasis**

*Per unit risk: Rare, none documented in Canada*

Transfusion transmitted microfiliariasis has never been reported in North America. The different organisms that cause microfiliariasis are found in Southeast Asia, Africa, Latin America and the West Indies. Transfusion acquired microfilaremia is mild and self-limited because transfused microfilariae do not develop into adult filarial worms. Transfused microfilariae may elicit an allergic reaction or an inflammatory reaction in the infected host tissues, and fever, headache, and rash have occurred in individuals intentionally transfused with microfilariae. Due to the rarity of microfiliariasis in North America, no specific procedures are needed to prevent its transmission.
6. EFFECTS OF BLOOD TRANSFUSION ON IMMUNE FUNCTION

Experimental data in animals and clinical studies in humans suggest that recipients of a blood transfusion demonstrate changes in their immune response. This immunomodulatory reaction may be responsible for such positive outcomes as improved organ allograft survival,\textsuperscript{130} enhanced fertility in recurrent aborters,\textsuperscript{131} and suppression of immune inflammatory disease. However, the literature also contains many descriptions of the potential negative effects of immune modulation associated with blood transfusions, such as increased post-operative wound infections,\textsuperscript{132} early recurrence and increased metastatic rates in cancer,\textsuperscript{133} and reactivation of latent viruses.\textsuperscript{134} The data, however, are conflicting and inconclusive.\textsuperscript{135,136}

Available human and animal data suggest that any of these effects are most likely mediated by transfused allogeneic WBCs.\textsuperscript{137} Arguably, leukoreduction of the blood supply should result in blood components which are immunologically neutral, although this has not yet been borne out in the literature.\textsuperscript{135}

1) Postoperative Infection and Mortality

Several studies examining postoperative wound infections have noted an increase in the frequency and severity of infections in patients receiving allogeneic blood.\textsuperscript{138,139,140} Other studies\textsuperscript{141,142} suggest significant decreased risk with leukoreduced blood, however, there are conflicting data in the literature and meta-analyses have been inconclusive.\textsuperscript{135} Recently a Canadian, retrospective before and after cohort study examined clinical outcomes following the adoption of prestorage leukoreduction.\textsuperscript{143} The incidence of serious nosocomial infection did not decrease following the implementation of PSLR (adjusted OR 0.97, 95% CI 0.87-1.09).

However, this study did find a statistically significant reduction in in-hospital mortality following the implementation of PSLR from 7.03% to 6.19% (p < 0.5). Compared with the control period where non-leukoreduced blood was transfused, the adjusted odds of death following leukoreduction was reduced (OR 0.87, 95% CI 0.75 –0.99).

2) Cancer Recurrence

Controversy exists as to whether allogeneic blood transfusion promotes tumor spread by immunological suppression of the recipient. Many of the studies have been re-examined using meta-analysis and multivariate stratification with conflicting outcomes.\textsuperscript{144} However, recent prospective observational and experimental studies have refuted the impression that the perioperative transfusion of unfiltered allogeneic blood is associated with a higher risk of cancer recurrence than the receipt of autologous or filtered blood.\textsuperscript{145,146} While the current evidence does demonstrate an association between transfusion and poor outcome, especially in cancer of the colon, causality remains to be proven.\textsuperscript{134,147}
7. BLOOD COMPONENTS AND FRACTIONATED PRODUCTS

1) Red Blood Cells
The standard unit of whole blood (WB) consists of approximately 450 mL of blood taken into 63 mL of citrate, phosphate, double dextrose (CP2D) anticoagulant. Red blood cells (RBCs) are prepared by centrifugation with removal of the supernatant plasma and platelets. 100 mL of AS-3 (Nutricel) is then added as a preservative. This red blood cell unit has an average hematocrit of about 55% with a shelf life of 42 days. All red blood cells prepared by Canadian Blood Services undergo prestorage leukoreduction. In the average adult, each unit of blood should raise the hemoglobin by about 10 g/L. The specific risks of RBC use are described in earlier chapters.

2) Platelets

a) Platelet Concentrate Preparation
Platelet concentrates are derived from whole blood donations or by apheresis. Whole blood derived random donor concentrates are harvested from donations of whole blood and contain at least 55 x 10^9 platelets suspended in about 50 mL of plasma. A standard adult dose treatment is 5 units of random donor platelets. Packs of single donor platelets prepared by apheresis are equivalent to 4 to 8 units of whole blood platelets and contain at least 300 x 10^9 platelets. Both products have a maximum shelf life of 5 days at 20°C. Whole blood derived platelets are prepared by prestorage leukoreduction but may contain small numbers of red blood cells, potentially leading to alloimmunization. Platelets obtained by apheresis are also leukoreduced at source. In the average adult, 5 units of random donor platelets, or 1 unit of apheresis platelets should raise the platelet count by 25 to 50 x 10^9/L in the absence of ongoing platelet consumption, sequestration, or destruction.

b) Specific Risks of Platelet Therapy

Bacterial Contamination
Bacterial contamination of platelet products is much more common than RBC or plasma products because storage at 20-24°C allows for proliferation of organisms which may occasionally contaminate blood at the time of collection. Contamination may be due to bacteria on the donor's skin, which are not killed by normal skin antisepsis techniques, or by donors who are bacteremic at the time of donation. Both gram negative and gram positive organisms have been cultured from platelet products.

Alloimmunization
The presence of trace amounts of red blood cells in platelet concentrates may immunize an Rh-negative patient. Whenever possible, Rh compatible platelets should be transfused. In the event that Rh-positive platelets are transfused to an Rh-negative recipient, Rh immune globulin should be administered. Antibodies to HLA antigens generally cause refractoriness to platelet transfusion. HLA antibodies can be seen in previously transfused patients and multiparous women. Approximately 50% of patients who receive multiple platelet transfusions eventually become refractory to platelet transfusions. Alloimmune destruction of platelets is mediated by expression of foreign class I HLA antigens on these cells, however, the presence of contaminating leukocytes enhances the immunogenicity of platelet products. While leukoreduction has been shown to reduce HLA alloimmunization, it has not eliminated it. Patients with HLA-antibodies who are refractory to platelet transfusion may benefit from HLA-matched platelets.

* This section addresses major blood and blood components only. For a complete description of other blood components (including cryoprecipitate and cryo-supernatant plasma), refer to publications available through Canadian Blood Services.
Febrile Transfusion Reactions

Prior to the implementation of PSLR, as many as 20% of patients receiving platelet transfusions had febrile reactions. In general, platelets are associated with a higher incidence of febrile reactions than RBC transfusion. In Canada, all platelets are prepared by prestorage leukoreduction, thus reducing the white cell numbers to less than $5 \times 10^6$ per unit and reducing the incidence of febrile transfusion reactions. Thus, the current risk is estimated at approximately 1:15 platelet pools.

Plasma Reactions

Platelets contain a larger amount of residual plasma compared to red blood cells. Bioactive substances released into the plasma of platelet concentrates during storage have been shown to cause most of the febrile reactions associated with platelet transfusions. Some patients may have allergic reactions, such as urticaria, angioedema, wheezing, or dyspnea. The supernatant plasma containing the proteins responsible for these reactions may be removed by washing although this is rarely done in practice. Antihistamine pre-medication should be considered for affected patients.

3) Plasma

a) Plasma Preparation

Plasma for transfusion is prepared by centrifuging anticoagulated whole blood from a single donor followed by storage at or below -30°C. Larger volumes of plasma may be collected using automated apheresis units and similarly stored. A typical unit of plasma has a volume of 200-250 mL when obtained from whole blood donation or 400-600 mL when obtained by apheresis (FFPA). Plasma frozen within 8 hours of donation is referred to as fresh frozen plasma (FFP). Once frozen and stored at < -30°C, plasma has a shelf life of 1 year.

b) Specific Risks of Plasma Therapy

Antibodies, present in either the plasma donor or the plasma recipient, can mediate a number of immunological reactions, often serious in nature. The most severe of these reactions, anaphylaxis, is characterized by wheezing, flushing, hypotension, and substernal chest pain. This reaction can be traced to a class specific anti-immunoglobulin A (IgA) formed in an IgA-deficient recipient (see Anaphylactic Reactions).

Excluding viruses such as human cytomegalovirus (CMV) and human T-cell lymphotropic virus type II (HTLV-II), which are transmitted only by infected leukocytes in cellular blood products, plasma carries the same risk of viral transmission per donor exposure as that of red blood cells.

Transfusion related acute lung injury (TRALI) is an uncommon but well-recognized complication of plasma or plasma-containing product transfusion that is related to antileukocyte antibodies present in the donor (see TRALI).

c) Solvent/Detergent Treated Plasma (SD Plasma)

Current risk is virtually zero for HIV/HCV/HBV and not quantifiable but probably negligible for non-lipid enveloped viruses (HAV, Parvovirus B19)

SD plasma is not yet generally available, but some manufacturers have introduced this viral inactivation step into their manufacturing process. SD plasma is a pooled plasma product manufactured by pooling approximately 2000 to 2500 units of ABO identical FFP prior to solvent/detergent treatment. Extensive experience in Europe has established that SD plasma has an efficacy similar to FFP and does not transmit HIV, HBV or HCV. In contrast, lots of SD plasma have transmitted Parvovirus B19 infection in the US and theoretically may transmit hepatitis A or other non-lipid enveloped viruses. Subsequent to
the Parvovirus B19 transmissions, the manufacturer of this product has initiated minipool high titre Parvovirus B19 nucleic acid testing of input plasma.

4) Fractionated Products

a) General

Fractionated plasma products (plasma derivatives) are preparations of purified plasma proteins prepared by a process known as Cohn alcohol fractionation. Plasma derivatives include AHF (Factor VIII concentrate), Factor IX concentrate, albumin, plasma protein fraction (PPF), intravenous immunoglobulin (IVIG), and intramuscular immunoglobulin (IMIG). Since the preparation of plasma derivatives by commercial manufacturers involves the pooling of plasma from tens of thousands of donors, there is a significant likelihood that the pool includes plasma from at least one infectious donor, even if the prevalence of the infectious agent in the donor population is low. Furthermore, plasma for fractionation is often collected from donor populations with higher rates of infectious disease and from very frequent donors (up to twice per week), thereby increasing the likelihood of donation during a pre-symptomatic, high titre viremic phase of infection. However, additional safety measures such as solvent detergent treatment and heat pasteurization mitigate this risk for lipid-enveloped viruses.

b) Coagulation Factor (Factor VIII and IX) Preparations

Current risk is virtually zero for HIV/HCV/HBV and negligible for non-lipid enveloped viruses (HAV, Parvovirus B19)

Prior to the application of viral inactivation procedures in the early to mid-1980s, Factor VIII and IX preparations prepared from human plasma transmitted HIV and Hepatitis C at high rates. Since 1987, coagulation factor products prepared by solvent/detergent treatment or by wet heating (pasteurization) methods have not transmitted any cases of HIV, HBV or HCV to recipients. Despite this absolute record of safety, in an effort to reduce the possibility of risk due to manufacturing errors, plasma derivative manufacturers have recently introduced minipool NAT for HCV, HIV, and HBV prior to creating plasma pools for further manufacture.

Solvent/detergent treatment is only partially effective against non-lipid enveloped viruses such as Hepatitis A and Parvovirus B19. Although Hepatitis A transmission by coagulation factor concentrates is rare, six documented outbreaks occurred worldwide from 1987 to 1997. These involved approximately 100 recipients of particular batches of Factor VIII concentrate treated only by the solvent/detergent procedure; one of these outbreaks was also associated with Factor IX concentrate.

Parvovirus B19 is more readily transmitted by coagulation factor concentrates than is Hepatitis A. Recipients of human plasma derived coagulation factor concentrates treated by multiple viral inactivation methods have high rates of infection (estimated at 40%) with Parvovirus B19. Despite this high transmission rate, very few clinical sequelae have been observed; as of 1999, only one case of hypoplastic anemia and three cases of erythema infectiosum had been reported in hemophilia patients.

In the last few years, recombinant Factor VIII and, more recently, Factor IX preparations have replaced human derived products. Initially, these factor concentrates were stabilized with human albumin, thereby raising the concern that the factors might pose an infectious risk due to the presence of the albumin. Fortunately, this concern has thus far been theoretical since albumin has never been known to transmit any infectious agents (see below). Nevertheless, these concerns have led to the recent introduction of recombinant Factor VIII and IX concentrates, which do not use albumin as a stabilizer; these factor concentrates should be considered to be risk free with respect to transfusion transmitted agents.

c) Immunoglobulin Preparations
Side Effects: Mild reactions common with IVIG (see below); severe reactions uncommon; current risk virtually zero for all known viral agents

There are two theoretical reasons why immunoglobulin preparations have historically been of very low risk for infectious disease transmission: 1) the plasma derivative manufacturing process has been shown to result in partitioning of viruses into plasma products other than the immune globulin fraction; and 2) the immune globulin fraction contains antibodies from thousands of donors that may serve to neutralize any viruses that partition into this fraction.

Intramuscular Immune Globulin (IMIG)

HIV has never been transmitted by IMIG and the only outbreak of HBV transmission occurred prior to HBsAg screening of blood donors in the 1970s. HCV has never been known to be transmitted by IMIG in North America. Currently, IMIG products manufactured in North America are either subjected to virus inactivation and removal procedures or undergo final product testing for HCV RNA.

Rh Immune Globulin (RhIg)

Rh Immune Globulin manufactured by different methods than those used in North America has transmitted HCV in separate outbreaks in Ireland and Eastern Europe. Current products are now subjected to virus inactivation and removal procedures and undergo viral nucleic acid testing.

Additional risks are associated with the administration of RhIg to Rh-positive individuals for treatment of hematologic disorders such as immune thrombocytopenia (ITP). There is a small risk of hemolysis which varies across studies but is in the order of a mean decrease in hemoglobin of 8 g/L. Although not necessarily generalizable to the adult population, Blanchette et al documented a maximum drop in hemoglobin of 12 g/L in a study of 38 children randomized to receive RhIg and a decrease of over 40 g/L was seen in 3.7%. Caution must be used when administering this medication to adults with coronary disease who may not tolerate an abrupt decrease in hemoglobin.

Intravenous Immune Globulin (IVIG)

Adverse events associated with the administration of IVIG are reported by the manufacturers to be in the range of 1 to 15%, although usually less than 5%. Most of these reactions are mild and self-limited. Often, these reactions are related to the rate of infusion. Reducing the rate of infusion is often effective in preventing reactions for subsequent transfusions of IVIG.

Severe reactions occur infrequently and usually do not contraindicate further IVIG therapy. Types of adverse reactions include: fever and systemic symptoms such as headache, myalgia, chills, light-headedness, nausea and/or vomiting. Aseptic meningitis has been infrequently reported in patients with severe systemic reactions. Rare cases of hypersensitivity and anaphylactic reactions with major vasomotor and/or cardiovascular manifestations, marked blood pressure changes and tachycardia have been reported. A change to an alternative brand is often successful in alleviating the problem.

Since IVIG became generally available in 1981, the US Food and Drug Administration (FDA) has received over 114 worldwide (approximately 83 US) adverse event reports of renal dysfunction and/or acute renal failure associated with the administration of IVIG. Although acute renal failure (ARF) was successfully managed in the majority of cases, deaths were reported in 17 patients worldwide. Many of the patients who died had serious pre-existing medical conditions. Preliminary evidence suggests that IVIG products containing sucrose may present a greater risk for this complication. Hyperosmolality of certain reconstituted products, as well as differences in the choice and content of stabilizer sugar between IVIG, may be among the factors that have contributed to different reporting rates for renal dysfunction among the various IVIG products. A disproportionate share of the cases (approximately 88% of US reports) have been associated with the sucrose-containing products.
A total of 78 adverse drug reaction reports concerning IVIG products were received in Canada between 1965 and 1998. None of these reports implicate renal complications as an adverse effect of the IVIG products used in Canada. In the last 10 years, Health Canada has not released any lots of IVIG products containing sucrose, which were associated with the majority of the ARF-associated adverse events reported in the US FDA drug-warning announcement.\textsuperscript{164}

In the past, several preparations of IVIG used in Europe and a single manufacturer's product in the US have been documented to transmit non-A, non-B hepatitis or hepatitis C.\textsuperscript{165,166} Subsequent to the US episode in 1994, IVIG products have been subjected to viral inactivation procedures and, more recently, input plasma is screened by minipool NAT for HCV, HIV, and HBV.\textsuperscript{49}

\textbf{d) Albumin and Plasma Protein Fraction (PPF)}

\textit{Current risk is virtually zero for all known viral agents}

There have been no known documented transmissions of HBV, HIV, or HCV by albumin in its 50 years of clinical use and only one instance of HBV transmission by PPF, which occurred prior to 1977 when current pasteurization procedures were adopted.\textsuperscript{49} There are two theoretical reasons why albumin and PPF (since 1977) have been free of the risk of infectious disease transmission: 1) the plasma derivative manufacturing process has been shown to result in partitioning of viruses into different plasma products (other than albumin and PPF); and 2) albumin and PPF have long been subjected to pasteurization procedures.
### Appendix A

#### Risks Associated with Blood and Blood Products

<table>
<thead>
<tr>
<th>Risk</th>
<th>Blood Product</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hemolytic reaction</td>
<td></td>
<td>1:7000</td>
</tr>
<tr>
<td>Fatal acute hemolytic reaction</td>
<td></td>
<td>1:600,000</td>
</tr>
<tr>
<td>Delayed hemolytic reaction</td>
<td></td>
<td>1:5500</td>
</tr>
<tr>
<td>Febrile, non-hemolytic</td>
<td>Red Blood Cells</td>
<td>1:500</td>
</tr>
<tr>
<td></td>
<td>Platelets Pools</td>
<td>1:15</td>
</tr>
<tr>
<td>Transfusion Related Acute Lung Injury (TRALI)</td>
<td>Red Blood Cells</td>
<td>1:71,500</td>
</tr>
<tr>
<td></td>
<td>Platelet Pools</td>
<td>1:8300</td>
</tr>
<tr>
<td>Allergic</td>
<td></td>
<td>1:250</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Red Blood Cells</td>
<td>1:23,250</td>
</tr>
<tr>
<td></td>
<td>Platelet Pools</td>
<td>1:1600</td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>Circulatory Overload</td>
<td>Red Blood Cells</td>
<td>1:2400</td>
</tr>
<tr>
<td></td>
<td>Platelet Pools</td>
<td>1:5950</td>
</tr>
<tr>
<td>Air embolism</td>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td>Exogenous material</td>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td>Hypothermia</td>
<td></td>
<td>Unlikely to occur when &lt;1.5 blood volumes replaced</td>
</tr>
<tr>
<td>Citrate toxicity</td>
<td></td>
<td>Unlikely to occur when &lt;1.5 blood volumes replaced</td>
</tr>
<tr>
<td>Hyperkalemia/Hypokalemia</td>
<td></td>
<td>Unlikely to occur when &lt;1.5 blood volumes replaced</td>
</tr>
<tr>
<td>Iron overload</td>
<td></td>
<td>Begins after the 20th RBC unit transfused</td>
</tr>
<tr>
<td>Immunoglobulin-related reactions</td>
<td>IVIG</td>
<td>Mild: common; Severe: uncommon</td>
</tr>
<tr>
<td>Viral infections</td>
<td>HIV</td>
<td>1:4.7 million to 1:10 million</td>
</tr>
<tr>
<td></td>
<td>HTLV-I&amp;II</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>1:31,000 to 1:82,000; risk of clinical disease is 1:1.2 million units</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>1: 3.1 million</td>
</tr>
<tr>
<td></td>
<td>HGV</td>
<td>1:100 but no known associated disease</td>
</tr>
<tr>
<td></td>
<td>TTV</td>
<td>1:10 to 1:50 but no known associated disease</td>
</tr>
<tr>
<td></td>
<td>SENV</td>
<td>1:50 but no known associated disease</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td>Low but not quantifiable; significant clinical disease rare</td>
</tr>
<tr>
<td></td>
<td>EBV</td>
<td>Rare for clinically significant disease</td>
</tr>
<tr>
<td></td>
<td>HPV-B19</td>
<td>Very rare for clinically significant disease in special groups of recipients</td>
</tr>
<tr>
<td></td>
<td>WNV</td>
<td>Rare</td>
</tr>
<tr>
<td>Prions</td>
<td>CJD; vCJD*</td>
<td>Theoretical risk only</td>
</tr>
<tr>
<td>Bacterial Agents</td>
<td>Sepsis</td>
<td>1:2500 to 1:12,000 morbidity from platelet pools; &lt;1:1 million for fatal reactions from red blood cells</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Parasites</td>
<td>Malaria</td>
<td>1:4 million</td>
</tr>
<tr>
<td></td>
<td>Babesiosis</td>
<td>Rare; risk of severe clinical disease is very rare in healthy recipients</td>
</tr>
</tbody>
</table>

* One case of vCJD possibly transmitted by transfusion has arisen in the United Kingdom; for up-to-date information on the status of this investigation, please visit www.TraQprogram.ca
<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chagas' disease</td>
<td>Rare; risk of severe clinical disease is very rare in healthy recipients</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Rare; risk of severe clinical disease is very rare in healthy recipients</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Microfilariasis</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Appendix B: British Columbia Transfusion Medicine Advisory Group (TMAG) Indications for Blood Component Irradiation

General Comments:
1. For patients with Non-Hodgkins lymphoma, every attempt to determine purine drug analogue treatment status should be made.
2. When a patient’s status is in doubt, irradiated blood components should be transfused.
3. If irradiated blood components are not readily available and a delay in transfusion could compromise patient care, transfusion may proceed with regular blood components at the discretion of the patient’s primary physician.

All Patients:
- Any blood components collected from 1st and 2nd degree relatives
- All HLA matched components
- All granulocyte transfusions
- All patients with chronic graft-vs-host disease
- Hodgkin’s Lymphoma
- Non-Hodgkin’s Lymphoma, CLL, Myeloma patients who have received purine analogue drugs (Fludarabine, Cladribine, 2-CDA, Pentastatin)
- Allogeneic BMT from start of conditioning to end of GVHD prophylaxis
- Within 7 days prior to “harvesting” of autologous stem cell transplant to 3 mo. post-transplant (or 6 mo. if TBI used)
- Aplastic Anemia/undiagnosed pancytopenia
- ALL/AML in any patient for stem cell transplant

Pediatric Patients:
- All intrauterine transfusions of RBC’s or Platelet concentrates (IUT)
- Any “top-up” transfusion if previous IUT
- All Exchange Transfusion (ET) or Platelet transfusions following IUT
- Any ET if delay for preparation does not compromise care
- Small blue cell tumors in childhood
- All acute Lymphoblastic Leukemia
- All acute Myeloblastic Leukemia
- Burkitt’s Lymphoma/Leukemia
- Solid Tumors (e.g.: Ewing’s Sarcoma, Hepatoblastoma, Neuroblastoma, Osteogenetic Sarcoma, Retinoblastoma, Rhabdomyosarcoma)
- Langerhan’s Cell Histiocytosis

Congenital Immune Deficiency:
- Di George’s Syndrome
- Any congenital heart disease or open heart surgery patient < 6 mo. old
- Congenital “cell mediated immune deficiency”
- Severe Combined Immune Deficiency
- Wiskott-Aldrich Syndrome
- Purine Nucleoside Phosphorylase Deficiency
- Reticular Dysgenesis
- Adenosine Deaminase Deficiency
- MCH I, II Deficiency
- Leukocyte Adhesion Molecular Deficiency
- Cell-mediated deficiency not otherwise specified

1 The Provincial Blood Coordinating Office gratefully acknowledges the BCSH Blood Transfusion Task Force for developing the Guidelines on Gamma Irradiation of Blood Components for the Prevention of Transfusion Associated Graft-vs-Host Disease.
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