What every physician should know about transfusion reactions

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Blood transfusions can be life-saving in the appropriate setting. The vast majority of transfusions are completed without incident, but every transfusion recipient is at risk of a variety of adverse events (termed transfusion reactions) that can occur during, shortly after or long after the transfusion. Most transfusion reactions are diagnosed by exclusion; thus, any significant change in a patient's condition during transfusion should prompt an investigation. Successful investigation of a transfusion reaction depends on detailed observation, documentation and reporting of the patient's vital signs, before and after the transfusion, and the signs and symptoms that prompted the investigation. In this article, we review some of the most common transfusion reactions using a case-based approach.

Case 1

A 56-year-old woman with leukemia, neutropenia and thrombocytopenia required a platelet transfusion after chemotherapy. Midway through the transfusion, the patient developed chills and rigors, her temperature rose from 37.2°C to 38.4°C and her heart rate increased slightly. Her other vital signs remained stable. The transfusion was stopped and samples were sent to the blood bank for investigation. The results of a direct anti-globulin test were negative, and no free hemoglobin was observed on visual inspection of the plasma. The initial clinical management and investigation at the blood bank of a transfusion reaction are shown in Figure 1.

The findings in this case are characteristic of a febrile nonhemolytic transfusion reaction. This diagnosis is usually defined by an otherwise unexplained rise in temperature of at least 1°C during or shortly after transfusion. It can be difficult to diagnose with certainty if the patient is already at risk for developing a fever; however, an increase of 1°C that is temporally related to transfusion should always prompt an investigation (other causes of transfusion-related fever are shown in Table 1). Antipyretic premedications may obscure a fever, but they do not usually prevent chills and rigors, which are manifestations of a cytokine-mediated systemic inflammatory response.

Platelets, more often than red blood cells, are the cause of febrile nonhemolytic transfusion reaction because they are stored at room temperature, which is conducive to leukocyte activation and cytokine accumulation. When caused by red blood cells, febrile nonhemolytic transfusion reactions are usually mediated by recipient antibodies against donor leukocytes; therefore, removing leukocytes from blood products before transfusion can reduce this type of reaction. This is one of the reasons that the Canadian Blood Services adopted universal leukoreduction of blood products in 1999.

Treatment of febrile nonhemolytic transfusion reactions is symptomatic (Figure 1). Medication with antipyretics before any subsequent transfusions and the use of leukoreduced components can help to reduce the frequency and severity of these reactions.

Case 2

A 46-year-old man required urgent reversal of warfarin anticoagulation before a surgical procedure. Twenty minutes after starting transfusion of a unit of fresh-frozen plasma, the patient developed an itchy rash on his face, chest and arms, and he remarked that his throat felt a little "tight." His blood pressure and temperature remained unchanged. The transfusion was immediately stopped and an antihistamine was administered. The patient's symptoms resolved 45 minutes later. The blood-bank investigation for hemolysis was negative.

An allergic reaction is a common reaction to a transfusion and is mediated by recognition of antigens in the donor plasma by preformed recipient IgE antibodies. In the case of a simple allergic reaction (a mild rash that resolves with antihistamine administration, accompanied by stable blood pressure and no dyspnea), some institutions allow the same unit to be restarted after the symptoms resolve. Other institutions require a new unit of blood product be provided if the transfusion remains necessary.

More severe allergic reactions are associated with hypotension and airway edema, and sometimes require administration of epinephrine and emergent intubation. People who are IgA deficient and have anti-IgA antibodies may experience severe allergic reactions to blood products and require plasma products from IgA-deficient donors for future transfusions. These patients may receive red blood cells and platelets from donors who are not IgA deficient if the plasma component is removed by repeated washing. Consultation with the blood bank is advised if a severe allergic reaction is suspected.

Any medications or other substances administered around the time of transfusion should be considered before attributing an allergic reaction to the blood product. Prophylactic measures for future transfusions depend on the severity of the reaction. Premedication with antihistamines before transfusion is usually sufficient for patients who have had a previous simple allergic reaction. Additional prophylaxis with corticosteroids may be beneficial to those with a history of moderate to severe allergic reactions.

Case 3

A 78-year-old woman with anemia and congestive heart failure received 200 mL of red blood cells over a 30-minute period before tachypnea developed and she began complaining of dyspnea and mild chest pain. The transfusion was

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immediately stopped. The patient did not have fever or chills. Rales and crackles were heard in both lung fields, jugular venous distention was apparent and hypertension was noted. A chest radiograph showed cardiogenic pulmonary edema. The results of a blood-bank investigation for hemolysis were negative. Her symptoms were relieved when a diuretic was administered and 1 L fluid was voided.

This clinical scenario is typical of transfusion-associated circulatory overload, which is underreported and should be suspected when a patient at risk of volume overload (e.g., heart, lung or kidney failure) complains of dyspnea or demonstrates signs of respiratory distress. The treatment of transfusion-associated circulatory overload includes supplemental oxygen and diuretics.

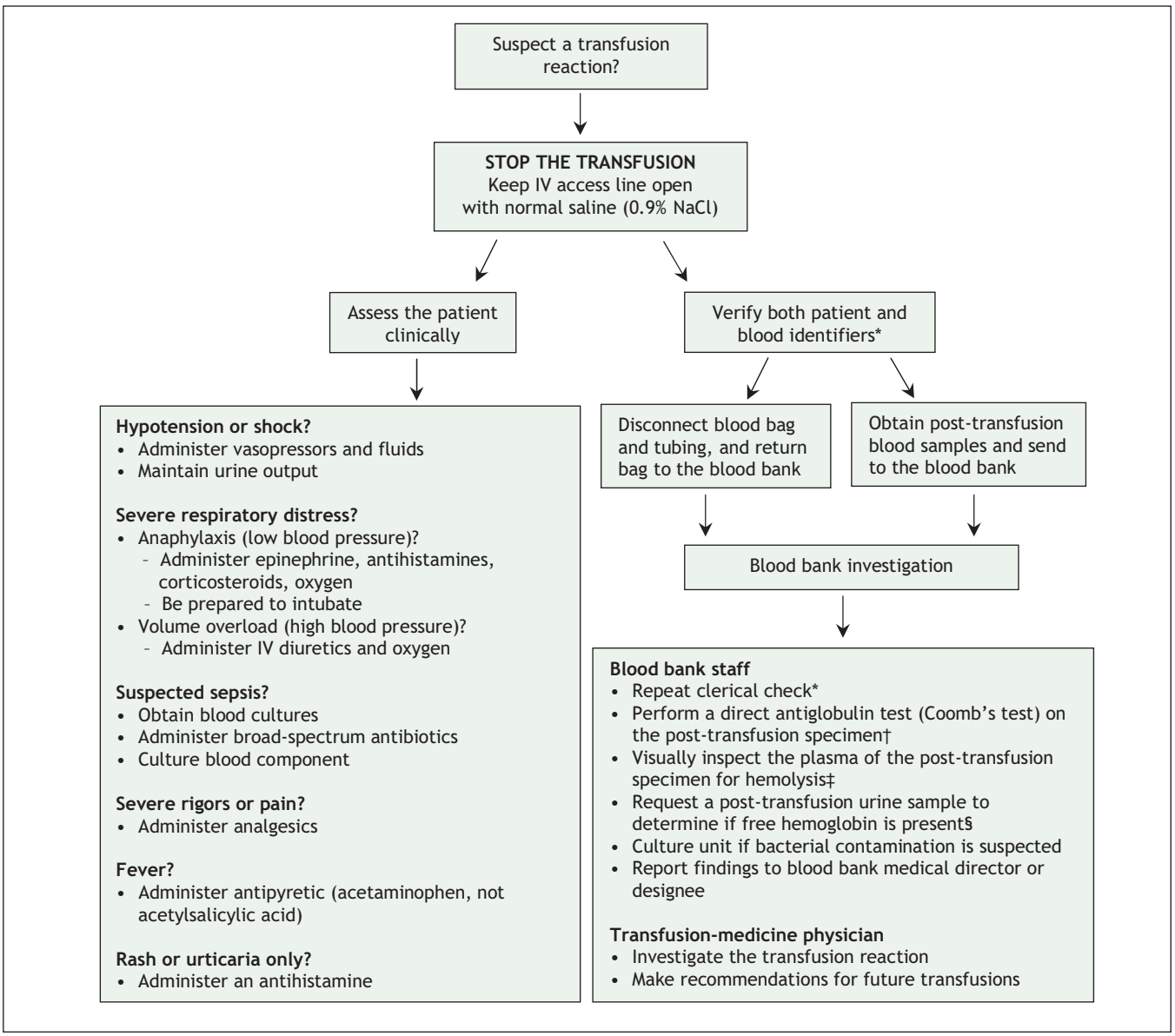

Figure 1: Management and blood bank investigation of a suspected transfusion reaction. Specific therapeutic interventions should be based on the recipient's signs, symptoms and underlying medical condition. *Transfusion can only be started after the recipient's identity is verified and matches the information on the blood unit. If a transfusion reaction is suspected, the clinical staff should repeat this verification. The blood bank will also compare the identifiers on the returned unit with that on the accompanying documentation to verify that the correct patient received the unit. †Identifies whether hemolysis, mediated by IgG or complement, has occurred. In most blood banks, this test is performed on the post-reaction specimen and, if positive, is also performed on a pre-transfusion sample for comparison. ‡Visual inspection for colour change is a sensitive test that can detect small amounts of free hemoglobin in the plasma. This test complements the direct antiglobulin test and may be the only indicator of hemolysis if the antibody or complement-coated red blood cells were rapidly cleared from the patient's circulation (resulting in a negative result of a direct antigen test despite the presence of immune-mediated hemolysis). §Although post-transfusion urine samples may be difficult to obtain, the presence of free hemoglobin in the urine indicates the presence of a large amount of free hemoglobin in the plasma, which exceeds the binding capacity of circulating haptoglobin.

Although much less common than transfusion-associated circulatory overload, transfusion-related acute lung injury (TRALI) may present in a similar manner. Transfusion-related acute lung injury can be differentiated by the typical chest radiograph findings of noncardiogenic pulmonary edema and by the absence of jugular venous distension and normal right-atrial pressure. Brain (b-type) natriuretic peptide is normally used to help diagnose the presence and severity of heart failure. However, in a transfusion setting, elevated post transfusion levels are suggestive of transfusion-associated circulatory overload and maintenance of pre-transfusion levels is suggestive of transfusion-related acute lung injury. This test may be used as a marker to help to distinguish between these 2 types of reactions, although this test is not yet available at all hospitals.

Case 4

A 67-year-old man presented with an upper gastrointestinal bleed secondary to a perforated ulcer. The patient received a total of 6 units of red blood cells over a 2-day period. The pre-transfusion results of a direct anti-globulin test and an antibody screen were negative. Two weeks later, the patient presented to his primary care physician with complaints of fatigue. On examination, the patient appeared mildly jaundiced, and the results of laboratory tests showed a 28 g/L decrease in his hemoglobin level, as well as decreased haptoglobin and increased lactate dehydrogenase and bilirubin levels. The results of a new direct anti-globulin test and an antibody screen were positive, and red-cell alloantibodies were identified.

This case highlights some of the findings of delayed extravascular immune-mediated hemolysis. The antibody titre in patients who form alloantibodies against red blood cells following a pregnancy or transfusion can sometimes drop over time until it falls below the limit of detection of an antibody screening test. If the transfusion service does not have a record of this antibody, no special measures would be taken to avoid transfusing the patient with red blood cells that carry the corresponding antigen. Transfusion of such a product may trigger an anamnestic immune response leading to increased antibody production and immune-mediated hemolysis of the donor red blood cells (i.e., a delayed hemolytic transfusion reaction), and the "new" antibodies would be detected upon subsequent screening. Less frequently, delayed hemolytic transfusion reactions may be caused by the formation of new alloantibodies against recently transfused red blood cells. This type of transfusion reaction can occur any time from 3 days to 2 weeks post transfusion, and it may be observed before or after the patient is discharged from hospital. Delayed hemolytic transfusion reactions may be asymptomatic and might only be detected by abnormal results of follow-up testing. If a delayed hemolytic transfusion reaction is suspected, tests for laboratory markers of hemolysis should be ordered (e.g., haptoglobin, lactate dehydrogenase, bilirubin), and a direct anti-globulin test and an antibody screen should be performed. Management of delayed hemolytic transfusion reactions is supportive and may include additional transfusions with antigen-negative units.

In contrast, acute hemolytic transfusion reactions are associated with immune-mediated intravascular hemolysis, and the mortality rate is 1 in 30. The presentation can vary (Table 1); therefore, every time a transfusion

Table 1: Common signs and symptoms of suspected transfusion reactions

Signs and symptoms	Most common causes	Less common causes
Fever, with or without chills and rigors	• Patient's underlying condition • Febrile nonhemolytic transfusion reaction	• Acute hemolytic transfusion reaction (intravascular hemolysis) • Septic transfusion reaction • Transfusion-related acute lung injury*
Rash	• Mild allergic reaction (to transfused blood product or to a recently administered medication)	• Severe allergic reaction or anaphylaxis
Marked hypotension or shock	• Patient's underlying condition • Severe allergic reaction or anaphylaxis	• Acute hemolytic transfusion reaction • Septic transfusion reaction • Transfusion-related acute lung injury *
Dyspnea	• Patient's underlying condition • Volume overload	• Acute hemolytic transfusion reaction • Severe allergic reaction or anaphylaxis • Transfusion-related acute lung injury * • Severe rigors • Patient anxiety
Pain with localization	• Patient's underlying condition	• Acute hemolytic transfusion reaction (pain at site of infusion, chest pain, flank pain) • Severe allergic reaction/anaphylaxis (abdominal pain and cramping) • Volume overload (chest pain)

*Characterized by marked dyspnea with decreased oxygen saturation (usually requires supplemental oxygen) and a chest radiograph showing new noncardiogenic pulmonary edema and normal heart size, and may be accompanied by fever and changes in blood pressure.

reaction is suspected, acute hemolysis must be ruled out by a clerical check, direct anti-globulin testing and visual inspection of the recipient's post-transfusion plasma for the presence of free hemoglobin. Post-transfusion urine can also be analyzed for presence of free hemoglobin. ABO incompatibility because of clerical error or patient misidentification remains the most frequent cause of acute hemolytic transfusion reactions. ABO in-

Table 2: Time from transfusion to onset or diagnosis of clinically important transfusion-associated adverse events and their estimated incidence.

Adverse event	Typical time to occurrence or diagnosis	Incidence* and mortality
Acute		
Acute hemolytic transfusion reaction	• During transfusion (within minutes) or up to 4 h post transfusion	Incidence¶ • 1:38 000–1:70 000 Mortality • About 1:30
Febrile nonhemolytic transfusion reaction	• During transfusion or up to 4–6 h post transfusion	Incidence† • Red blood cells, about 1:526 • Platelets, about 1:900
Simple allergic transfusion reaction	• During transfusion or up to a few hours post transfusion	Incidence • 1:3–1:300
Severe allergic or anaphylactic transfusion reaction	• Usually during transfusion (within minutes) but can occur up to 4 h post transfusion	Incidence • 1:20 000–1:50 000
Transfusion-associated circulatory overload	• During transfusion or up to a few hours post transfusion	Incidence • < 1:100 (higher in susceptible patients [e.g., heart failure])
Transfusion-related acute lung injury	• During transfusion or up to 6 h post transfusion	Incidence • 1:5 000–1:190 000
Sepsis	• Usually during or within an hour of transfusion, but can be seen up to 4–8 h post transfusion	Incidence • Detectable bacterial contamination of platelets‡, 1:1000–1:10 000 • Red blood cell contamination (symptomatic septic reactions), 1:65 000–1:500 000 Mortality • Sepsis due to platelet transfusion, 1:7500–1:100 000 • Sepsis due to red blood cell transfusion, 60% with gram-negative organisms
Delayed		
Delayed hemolytic transfusion reaction (immune-mediated)	• From 3 d to 2 or more weeks post transfusion	Incidence • 1:4000–1:11 000
Alloimmunization to red blood cell antigens	• IgM response: 10 d to 2 wk post transfusion IgG response: 3 or more wk post transfusion	Incidence§ • 1:10–1:100
Transfusion-associated graft-versus-host disease	• 2–30 d post transfusion (most commonly within 4–10 d of transfusion)	Incidence¶ • 1:400 000 Mortality • Virtually 100%
Transfusion-transmitted diseases	• Days to years post transfusion (varies by causative agent)	Incidence • Varies by infectious agent and disease (Table 3)

*Estimated incidence varies widely in the published literature; the reported numbers are representative estimates.[1-10]
†Based on observed rates using pre-storage leukoreduced products, such as those available from Canadian Blood Services.[6]
‡Reported range of detectable bacterial contamination in platelet products is broad because tests with different sensitivities are used at different centres. See Yazer and Triulzi[7] for details.
§Incidence of alloimmunization to red blood cell antigens increases with the number of transfusions and is therefore more common in chronically transfused patients (e.g., those with sickle cell anemia).
¶Only a select population of highly immunosuppressed patients or those receiving products from donors with shared HLA haplotypes are at risk for transfusion-associated graft-versus-host disease.

Table 3: Estimated incidence of clinically important transfusion-transmitted infectious diseases and the precautions and screening methods used to minimize their risk[1-5, 7-10]

Infectious agent or disease	Incidence*	Precautions and screening methods
Viral		
Hepatitis B	• 1:250 000–1:580 000	• Donors screened by questionnaire • Donated units tested
Hepatitis C	• 1:2 900 000–1:1 390 000 (with NAT)	• Donors screened by questionnaire • Donated units tested
HIV-1 and HIV-2	• 1:1 400 000–1:7 800 000 (with NAT)	• Donors screened by questionnaire • Donated units tested
Human T-cell lymphoma virus types 1 and 2	• 1:1 200 000–1:5 000 000	• Donors screened by questionnaire • Donated units tested
Cytomegalovirus	• Seroconversion, 1.5%–3% • Risk of cytomegalovirus disease much lower	• Transmission poses a serious risk to a very select population of patients who are highly immunosuppressed and are seronegative for cytomegalovirus
Other (e.g., hepatitis A, West Nile virus)	• Varies by donor population (geographic location and season also important for West Nile virus)	• Donors screened by questionnaire • Donated units tested for West Nile virus in high-risk seasons and regions
Bacterial		
Bacterial contamination	Incidence • Detectable bacterial contamination of platelets†, 1:1000–1:10 000 • Red blood cell contamination (symptomatic septic reactions), 1:65 000–1:500 000 Mortality • Sepsis due to platelet transfusion, 1:7500–1:100 000 • Sepsis due to red blood cell transfusion, 60% with gram-negative organisms	• Donors screened by questionnaire • Sterile preparation of donation site • Special collection techniques used to minimize contamination • Platelet units screened by bacterial detection methods
Syphilis	• No reported cases of transfusion-transmitted syphilis in the United States since the 1960s	• Donors screened by questionnaire • Donated units tested
Parasitic		
Malaria	• Low incidence • Varies by geographic origin and travel history of donor population	• Donors screened by questionnaire • No test currently available
Babesia	• Not infrequent in endemic areas • Varies by geographic region of donor population	• Donor questionnaire is ineffective for screening • No test currently available • Usually easily treatable
Chagas' disease	• Low incidence • Varies by geographic origin and travel history of donor population	• Donors screened by questionnaire • A recently licensed test may be used for screening of high-risk donors
Other		
Transmissible spongiform encephalopathy (CJD, vCJD)	• Unknown incidence, but probably very low • Varies by geographic origin and travel history of donor population	• Donors screened by questionnaire • No test currently available

Note: NAT = nucleic acid testing, CJD = Creutzfeldt-Jakob disease, vCJD = variant CJD or the human form of bovine spongiform encephalopathy.
*Estimated incidence with current testing methods. Estimates vary widely in the published literature; the reported numbers are representative estimates.[8-10]
†Reported range of detectable bacterial contamination in platelet products is broad because tests with different sensitivities are used at different centres. See Yazer and Triulzi[7] for details.

compatibility, transfusion-related acute lung injury and transfusion-associated sepsis are 3 of the most common causes of transfusion-associated fatalities. Transfusion-associated graft-versus-host disease, although rare, is another complication associated with a high mortality rate.

Comments

Approaches to the differential diagnosis and management of some of the more common manifestations of transfusion reactions are outlined in Table 1 and Figure 1, and the timeline of occurrence and the estimated risk are shown in Table 2. Other less common, but clinically important, transfusion sequelae include the transmission of viral infections. Table 3 describes a number of infectious agents and their current estimated risk of transmittance via transfusion of blood products. A recent paper provides a graph of the risk of acquiring several transfusion-transmitted viruses over time,[4] as well as a discussion of interventions that might further enhance the safety of the blood supply and of the emerging pathogen, human herpesvirus.

Appendix 1 presents a brief patient-oriented discussion of some of the more common questions and concerns that a patient may have about transfusions. Another source of information about transfusion reactions is the *Bloody Easy* handbook.[5]

In summary, a blood transfusion can be a vital medical intervention. Physicians and nurses who provide care to transfusion recipients need to remain alert for the signs and symptoms of transfusion reactions, particularly during and shortly after the transfusion; however, some adverse consequences of the transfusion may not become apparent until days, weeks or even years later. Complete documentation, reporting of suspected reactions and consultation with a transfusion-medicine physician provide the basis for successful investigation of transfusion reactions and the ability to implement interventions that may help protect the patient during subsequent transfusions.

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Appendix 1: A patient-oriented discussion of some of the more common questions and concerns about blood transfusions

This information sheet should NOT be a substitute for the informed consent process, nor should it replace a discussion between the physician and patient about the risks and benefits of a transfusion in the individual patient's case.

Why do I need a blood transfusion?

Only your doctor can tell you why you need a blood transfusion. Red blood cells help carry oxygen to different tissues in the body. In general, patients receive a transfusion of red blood cells if they have anemia (low hemoglobin) and have symptoms such as tiredness or shortness of breath. Patients may become anemic if they are bleeding, have cancer or other illnesses, or if they are receiving certain medications like chemotherapy. Plasma (the liquid part of the blood) and platelets (cells that help build clots) are usually given to help stop bleeding or reduce the risk of bleeding. Patients may need plasma or platelets if their body is not making enough or if they are being used up, or if the patient is taking anticlotting medicines and starts bleeding or requires surgery.

What might happen to me while I'm getting blood?

Most blood transfusions are completed without any problems at all. Sometimes, a patient may get an itchy rash or a fever with chills and may need some simple medicines to resolve these minor problems. In rare cases, a patient may have severe shaking, trouble breathing or become faint. In extremely rare cases, a patient can die because of a transfusion; this is more likely to happen if the patient receives the wrong blood.

How can I help make my blood transfusion safer?

Hospital staff are very careful and must follow a lot of rules to make blood transfusion as safe as possible for the patient. It never hurts to ask the nurse to check your wristband and to compare it to the blood label one more time before the transfusion starts. It is also very important to tell your doctors and nurses about any problems that you have had with previous blood transfusions and about any allergies or any medicines that you may be taking.

I'm afraid of getting blood from other people; can I donate blood for myself?

Sometimes, healthy patients who are going to have certain types of surgery can donate 1 or 2 units of blood that can only be used for them if required during or after their surgery. However, donating blood for yourself may also have some risks, so it is a decision that needs to be made after a thorough discussion about the risks and benefits with your doctor. Remember, blood from volunteer donors is always available and is quite safe.

What are my chances of getting a disease from the blood transfusion?

The screening and testing methods used today make the chances of getting a disease from a blood transfusion very low — about 1 in 1.5–3 million for hepatitis C and 1 in 1.5–8 million for HIV (the virus that causes AIDS). If your doctor thinks that you need a transfusion, your risk of becoming very sick or even dying without it would probably be much higher than the risk of acquiring a disease.

Where can I get more information about blood donation and transfusion?

You can talk to your doctor or to the transfusion-medicine doctor at your hospital. You can also contact the Canadian Blood Services or visit their Web site for more information (www.bloodservices.ca).