Review Articles

Perioperative haemotherapy: II. Risks and complications of blood transfusion

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Major life-threatening complications following blood transfusion are rare and human error remains an important aetiological factor in many. The infectious risk from blood transfusion is predominantly hepatitis, and non-A, non-B and hepatitis C (HCV) are the most common subtypes noted. The risk of post-transfusion hepatitis (PTH) appears to be decreasing and this is attributed to both deferral of high-risk donors and more aggressive screening of donated blood. Screening for HCV is expected to decrease this risk further. The risk of HIV transmission following blood transfusion is negligibly small. There are data to suggest that perioperative blood transfusion results in suppression of the recipient's immune system. Earlier recurrence of cancer and an increased incidence of postoperative infection have been associated with perioperative blood transfusion although the evidence is not persuasive. Microaggregate blood filters are not recommended for routine blood transfusion but do have a role in the prophylaxis of non-haemolytic febrile reactions caused by platelet and granulocyte debris in the donor blood. Patients should be advised when there is likely to be a requirement for perioperative blood transfusion and informed consent for transfusion should be obtained.

Les transfusions sanguines sont rarement associées à des complications majeures et menaçantes pour la vie. L'erreur humaine demeure une cause importante de telles complications. Les infections les plus couramment causées par les transfusions sont les hépatites non-A, non-B et l'hépatite C. Le risque d'hépatite post-transfusionnelle semble diminuer et cela est dû à une meilleure sélection des donneurs et un dépistage plus agressif des porteurs d'antigènes viraux. Le dépistage de l'hépatite C permettra peut-être de diminuer davantage ce risque d'infection. Le risque de transmission du virus de l'immunodéficience humaine (HIV) par la tranfusion sanguine est minime. Certaines études suggèrent que les transfusions sanguines périopératoires peuvent déprimer le système immunitaire des receveurs et elles seraient associées à des récidives précoces de cancer de même qu'à une incidence plus élevée d'infections postopératoires. Les preuves en faveur de cette immunodépression sont cependant peu convaincantes. Les filtres à microaggrégats ne sont pas recommandés pour les tranfusions sanguines de routine, mais ils peuvent prévenir les réactions fébriles non-hémolytiques causées par les plaquettes et les débris de granulocytes. Avant toute intervention à risque de saignements importants, les patients devraient être informés de la possibilité de transfusions sanguines périopératoires et un consentement éclairé devrait être obtenus à ce sujet.

Key words
BLOOD: loss, replacement;
TRANSFUSION: complications, stored blood.

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Epidemiological linkage between blood transfusion and the acquired immunodeficiency syndrome (AIDS) was postulated in 1983 and established in 1984.[1,2] Although the risks and complications of blood transfusion had been well documented before the association between AIDS and blood transfusion was confirmed, many physicians had been slow to incorporate this data into their clinical practice. The advent of AIDS and the patient/consumer activism that has resulted has forced a re-evaluation of the risk factors relating to the adverse effects of blood transfusion. Not only has is it become necessary to establish a need for blood before each transfusion, but it is mandatory that the physician be aware of the risks of transfusion and be able to communicate these to the recipient. The purpose of the following discussion is to review the most recent data available in order to allow an accurate assessment of the risk of blood transfusion. Table I provides a list of complications related to homologous blood transfusion and will provide the basis for the following discussion.

TABLE I Complications of homologous blood transfusion

Immunological complications
1 Red cell antigens
- haemolytic reactions
  - immediate (ABO)
  - delayed (non-ABO)
- alloimmunization

2 White cell antigens
- febrile reactions
- transfusion-related acute lung injury (TRALI)
- alloimmunization (HLA)

3 Platelet antigens
- post-transfusion purpura
- alloimmunization

4 Plasma proteins
- hypersensitivity reactions

Transmitted infections
1 Hepatitis A, B, NANB/C
2 HIV 1 (formerly HTLV 3), HIV 2 (formerly HTLV 4), HTLV 1, HTLV 2
3 Cytomegalovirus, Epstein-Barr virus
4 Syphilis, malaria, babeosis, trypanosomiasis
5 Bacterial contamination

Complications related to large volume transfusions
1 Fluid overload
2 Dilutional thrombocytopaenia
3 Hyperkalaemia
4 Hypothermia
5 Hypocalcaemia

Immunological reactions

Immunological reactions may be divided into those mediated by cellular elements, either erythrocytes, leukocytes or platelets, and those mediated by the noncellular elements, specifically the protein and globulin elements. Immediate haemolytic reactions, although rare, continue to be a concern as they are the major cause of transfusion-associated mortality. Walker estimated that acute haemolytic transfusion reactions occurred at a rate of one per 25,000 units transfused and 51% of the transfusion-associated deaths reported to the US Food and Drug Administration (1976–85) were as a result of acute haemolysis.[3,4] The acute or immediate haemolytic reaction is almost invariably due to ABO incompatibility resulting from a type-mismatch between the donor and recipient. In the past this reaction was largely attributed to clerical error with the donor blood being mislabelled at some stage of processing. However, Honig has reported an increase in errors classified as "blood given to wrong patient."[5] Although physician error alone was implicated in only about 20% of the deaths resulting from such errors, the most common site of physician error was the operating room and the anaesthetist was the physician implicated most frequently. Protocols should be in place within operating theatres that allow for the proper identification of blood and recipient in order to eliminate such errors.

The quantity of antibody in the acute haemolytic reaction appears to determine the resultant morbidity and mortality. Group O recipients have both anti-A and anti-B antibodies distributed throughout their plasma volume and to a lesser extent, their extravascular space. If group O recipients receive type A, B or AB blood, the biological consequences of this incompatibility to the patient are greater than after a small volume of donor plasma containing antibodies directed against the recipient's cells is transfused (i.e., group O to a recipient of group A). Consequently, 81% of the transfusion-associated deaths due to acute haemolysis reported from 1976 through 1985 occurred in type O recipients receiving type A, B or AB blood.[4] The antigen-antibody interaction activates the complement cascade and this results in lysis of the donor cells.[6] Haemoglobin released from the lysed cells is bound to haptoglobin and albumin but these binding proteins are quickly saturated. The remaining free haemoglobin is cleared by the kidneys. Complement activation results in release of complement fragments which are potent vasodilating compounds as well as thrombin generation and platelet activation. These processes lead to hypotension and disseminated intravascular coagulation. Renal damage is a consequence of multiple factors including glomerular deposition of fibrin, reduced renal blood flow and deposition of Ab-Ag completes. Free haemoglobin does not directly damage the kidney but can contribute to renal failure if it is precipitated in the renal tubules. The most commonly cited signs and symptoms of an acute haemolytic reaction, each occurring in at least 20% of the cases reported to the FDA were: (1) haemoglobinuria, (2)

disseminated intravascular coagulation, (3) haemolysis, (4) oliguria with subsequent renal failure, and (5) hypotension.[4] In the anaesthetized patient, symptoms may be less variable and hypotension, urticaria and abnormal bleeding are common.[7]

If a haemolytic reaction is suspected, the transfusion should be stopped. The blood should be rechecked to ensure that the patient is receiving the correct blood and then returned to the blood bank for re-typing and microbiological assessment. Blood should be drawn from the patient to verify the ABO group, to look for free haemoglobin, to assess the coagulation status and for microbiological assessment. Patient management emphasizes support of the circulation with aggressive fluid therapy.[6] Renal function should be maintained by adequate fluid therapy and the use of osmotic diuretics. Renal morbidity may be lessened if urine volumes in excess of 60 ml · hour^{-1} can be maintained. Administration of platelet concentrates and plasma may be necessary to treat the intravascular coagulation. Plasma exchange has been recommended to remove the free haemoglobin in the event of large volume administration of incompatible blood.[7]

Delayed haemolytic reactions occur within one to two weeks of the transfusion of previously "compatible" blood. Most such reactions are characterized by the reappearance of an antibody directed against donor erythrocyte antigens that was initially and remotely produced in response to a pregnancy or previous transfusion. The antibody-coated donor erythrocytes are eliminated in the spleen and have a shortened survival time. The laboratory findings of the delayed haemolytic reaction include a positive direct or indirect antiglobulin test. Although delayed haemolytic reactions are not widely believed to be of serious consequence, 10% of the transfusion-associated deaths reported to the FDA were attributed to delayed haemolysis by the reporting physician.[4]

Alloimmunization occurs after red cell transfusion. The recipient may produce antibodies directed against antigens on the red cell membrane. Fluit reviewed 186 patients who received at least six units of blood.[8] Twenty-two patients produced antibodies and although the risk of alloimmunization increased with the number of units transfused, most patients were immunized after two or three transfusions. This phenomenon has implications for both difficulty in future crossmatching and perhaps an increased incidence of delayed haemolysis with future transfusion.

The most common immunological reactions to leukocyte antigens can be characterized as troublesome rather than clinically serious. The interaction of recipient leukocyte antibodies with donor leukocytes and phagocytosis of donor leukocyte fragments stimulate host macrophage production of endogenous pyrogens and result in a febrile, nonhaemolytic reaction. A more serious reaction is that of transfusion-associated acute lung injury, manifest as noncardiogenic pulmonary oedema, occurring during or within six hours of a transfusion. This reaction is estimated to occur in one in 10,000 transfusions.[3] The mechanism is considered to be a reaction between passively transferred antileukocyte antibodies and recipient leukocytes which are degraded particularly in the pulmonary circulation.[7,9] Fifteen percent of transfusion-associated mortality is attributed to acute pulmonary injury.[4]

Alloimmunization to platelet antigens following transfusion of platelet concentrates appears in about half the patients subjected to repeated platelet transfusions (i.e., for replacement in bone marrow depression after chemotherapy). The result is an antibody-dependent elimination of the platelets in the liver or spleen and a lack of therapeutic response to subsequently transfused platelets. Post-transfusion purpura is a rare syndrome occurring about one week after platelet transfusion. It is speculated that donor platelet glycoproteins complex with recipient platelet glycoproteins and that recipient antibodies are bound to native platelets. The platelet aggregates are then destroyed in the liver and spleen.

Mild hypersensitivity reactions to donor serum proteins occur in 0.2–2% of transfusions.[3,7,9] The full expression of anaphylactic shock manifest by skin rash, hypotension, bronchospasm and substernal pain, is rare with a frequency of about 1:20,000.[7] About one patient in 600 lacks IgA and forms anti-IgA. Serious anaphylactic reactions may occur when these patients are administered serum containing IgA. The reaction can be avoided by the use of IgA-free plasma, purified albumin solutions and washed red cells.

Disease transmission

HEPATITIS

In 1943 Beeson described "several cases of jaundice one to four months after transfusion of whole blood or plasma."[10] Since then post-transfusion hepatitis (PTH) has become well recognized as an important complication of blood transfusion. Although we do not know the true risk of acquiring hepatitis as a result of a blood transfusion, the available data do allow some conclusions to be drawn. Most cases of transfusion associated hepatitis are both anicteric and asymptomatic and the incidence of PTH derived from series of patients in whom serum transaminase levels are repeatedly sampled after transfusion may be 100-fold greater than when the incidence is derived from cases of reported clinical PTH.[11] The incidence of PTH appears to have declined over the last decade. This is a result not only of the implementation of screening tests (Table II) to eliminate donated units

TABLE II Canadian Red Cross Society Blood Transfusion Service (CRCSBTS). Screening policies for donated blood

1 Increased public awareness of the indications for donor self-excusion
2 Augmented donor screening by the nursing staff of the CRCSBTS
3 Testing donor specimens for:
(a) HBsAg (HBV)
(b) HCV
(c) HIV
(d) HTLV-1
(e) syphilis
4 After donation availability of confidential ballot to defer use of donated blood if donor has doubts about meeting criteria for blood donation

contaminated by hepatitis B (HBsAg) but also of the more recent exclusion of donors from the donor pool who were at increased risk for carriage of blood-transmissible disease. Nine percent of potential volunteer donors in Canada are deferred after completion of a screening questionnaire (personal communication, National Office, Canadian Red Cross Society). The incidence of PTH was estimated at between 6–38% before the implementation of HbsAg screening in 1972 and between 30–55% of PTH cases were attributed to hepatitis B virus.[12] Over the next decade, although hepatitis B-attributed PTH cases decreased to 10% of the total cases of PTH, there was little change in the overall incidence of PTH. This is presumed to be a result of the implementation of more intensive surveillance of patients after blood transfusion resulting in the more frequent diagnosis of asymptomatic and anicteric cases of PTH. Also, hepatitis B was probably overemphasized in earlier reported series of PTH because of the failure to diagnose a large number of the anicteric cases of PTH. Nevertheless, there appears to be a decrease in the incidence of PTH over the last decade in studies that emphasized careful and prospective surveillance of patients following blood transfusion.[13,14] Although most of the data collected on transfusion-associated infectious disease was collected on patients receiving red cell transfusion, it is generally assumed that the risk associated with other components is similar. Derivatives prepared from large donor pools (i.e., factor concentrates) or components from multiple donors concurrently administered (i.e., platelet concentrates) are associated with a higher risk of disease transmission. Although there is not a linear relationship between disease transmission and transfused volume, a relationship between the number of units transfused and the incidence of PTH has been reported.[15] Early studies failed to distinguish between volunteer and commercial blood donors but, given that the risk of disease transmission was as much as six-fold greater with commercial donations, this may have influenced their observed incidence of PTH.[15] A more recent report by Koziol documented an increased incidence of FTH with higher volumes of blood transfused.[16] However, the increased incidence of PTH was attributed to the increased likelihood of receiving an hepatitis C antibody (anti-HBC) positive unit with the higher transfused volumes rather than the increased volume *per se*.[16] The incidence of PTH must be related to the prevalence in the donor population and therefore the incidence of PTH in one geographic region does not reliably predict the incidence in another. Finally, there is a background incidence of hepatitis in hospitalized, non-transfused patients of 0.14–2.2% and though it is not likely that this background occurrence accounts for a large proportion of transfusion-associated hepatitis, it cannot be discounted.[17,18]

Hepatitis non-A, non-B (NANB) is the most frequent type of PTH, hepatitis B (HBV) is next and hepatitis as a result of hepatitis A virus (HAV), CMV or Epstein-Barr virus (EBV) occurs rarely. Dienstag[19] concluded that there was little evidence that HAV played an important role in PTH and Lindholm[13] reported only two cases of PTH as a result of HAV over an eight-year period with 360,000 transfusions assessed. Blood banks do not screen for HAV because it is rarely a factor in PTH, there is no HAV carrier state, and the infectious period for HAV is usually limited to a one-to-two-week viremic period.[20] Sirchia reported one case each of PTH resulting from CMV and EBV in a four-year prospective surveillance of 2959 surgical patients, accounting for 3.8% of the total cases of PTH in the series reported.[14] Koziol labelled CMV as the responsible agent in seven cases of PTH, accounting for 12.5% of the cases and occurring in 1.4% of patients who received transfusion.[16] Transfusion-associated CMV infections are usually benign and self-limited but may result in serious, even fatal, infections in immunocompromised patients.[21] Recipients of bone marrow transplants and premature infants have been described as groups at risk for serious transfusion-associated CMV infections and CMV seronegative units have been recommended for these two groups.[21,22]

Hepatitis B virus continues to be an important aetiological factor in PTH. Hepatitis B develops in 0.3 to 1.7% of transfusion recipients and accounts for 7 to 17% of PTH cases although screening of blood donations for hepatitis B surface antigen has been carried out since 1972.[23] The reported incidence of HBV-associated PTH varies and is probably accounted for by the varying prevalence of the carrier state in the donor populations.[13,23,24] The incidence of HBV-seropositivity in donated blood in Canada (1990–91) is 0.03% of all donated units (personal com-

munication, National Office, Canadian Red Cross Society). It is not clear why PTH type B continues to occur despite screening but Hoofnagle has proposed the following hypotheses: (1) mistakes are made in the screening of blood, missing HBV+ve units; (2) transmission occurs by means other than transfusion and the transfusions are inappropriately implicated because of a temporal relationship; (3) an infectious donor is in the incubation period of acute hepatitis B (one to six weeks from infection until appearance of HbsAg); and (4) a seronegative infectious donor who is a carrier of low-level HBV donates blood.[23] Antibody to hepatitis B core antigen (anti-HBC) appears in the serum of patients eight weeks after infection with hepatitis B virus, and hepatitis B is more frequent after transfusion with anti-HBC positive blood than with anti-HBC negative blood.[13,23,25,26] The recent implementation of screening for anti-HBC may further reduce the incidence of PTH secondary to HBV.

The dominant aetiological agent in PTH is non-A, non-B virus (NANB). Once again, there are regional differences in the reported incidence of PTH in patients receiving blood transfusions with recent series documenting incidences of 2.4–4.6% in Scandinavian countries, 4.3% in Italy and 7.2% in the United States.[13,14,16] The variability in the incidence is likely a reflection of the background prevalence in the population. The majority of the cases will be both anicteric and asymptomatic and diagnosis is based on prospective studies of serum levels of alanine aminotransferase (ALT) and the documentation of persistently high or high fluctuating levels of ALT. Despite its relatively mild presentation during the acute infection, NANB PTH has a disturbing tendency to progress to a chronic state marked by a persistent carrier stage. Persistent hepatitis occurs in about 50% of patients and cirrhosis occurs in 10–20% of patients with persistent hepatic disease.[13,19] NANB hepatitis has been recently renamed hepatitis C because both a viral particle and a plasma antibody to that virus have been identified. Blood banks are now routinely screening for hepatitis C. The incidence of HCV-seropositivity in donated blood in Canada (1990–91) is 0.08% of donated units (personal communication, National Office, Canadian Red Cross Society). Concern remains that NANB hepatitis may be a result of more than one virus and because the hepatitis-C screening test does not become reliably positive during periods of peak elevation of hepatic enzymes, there continues to be a role for surrogate NANB screening (serum transaminases) in order to eliminate donor units capable of transmitting NANB hepatitis. However, the recent report by Sirchia documenting a 50% reduction in the incidence of PTH, following the implementation of HCV screening in their institution, is encouraging.[14]

HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Blood banks discouraged blood donation from individuals at high risk for the acquired immunodeficiency disorder (AIDS) in 1983 and, in 1985, following identification of HIV, began screening for the virus. Although there are 3,345 cases of transfusion-associated AIDS in the United States, excluding haemophiliacs (Center for Disease Control, Atlanta, April 30, 1990) and 226 in Canada,[27] since the implementation of HIV-1 screening there have been only 14 cases of transfusion-associated AIDS in the United States.[28] The National Office of the Canadian Red Cross Society is aware of two possible HIV seroconversions associated with transfusions (personal communication, National Office, Canadian Red Cross Society). This must be measured against the 15 million blood and blood products transfused since the implementation of HIV screening in Canada. Ward investigated 13 patients, seropositive for HIV, who had received blood from seven donors screened as seronegative for HIV at the time of donation.[28] The seven donors were found to be infected with HIV on subsequent testing. Six of the seven donors reported risk factors for HIV infection and five had engaged in high risk activities within four months of their HIV-seronegative donation. Ward concluded that these donors had been infected only recently before donation, were seronegative at the time of donation and seroconverted thereafter. It was further concluded that the reasons for deferral of donation need to be communicated more effectively to blood donors who are at high risk for HIV infection. Based on the incidence of HIV antibody of 0.012% in repeat donors and 0.04% in first time donors (USA) and an eight week incubation period for development of HIV antibody, Ward estimated that the rate of HIV transmission by seronegative blood would be 26 instances per million transfusions.[28] This estimate is much larger than the number of reported cases of HIV infection linked to seronegative blood transfusion at this time. For comparison, the incidence of HIV-seropositive blood donations in Canada (1990–91) was 0.004% of donated units (personal communication, National Office, Canadian Red Cross Society).

It has been demonstrated previously that antibody to HIV appears in the blood between six and fourteen weeks after infection with HIV.[28] However, Wolinsky reported that HIV infection could remain silent for up to 42 mo and Imagawa recently reported persistent seronegativity in patients at high risk for HIV infection, from whom the virus itself could be recovered.[29,30] Haseltine has hypothesized that this may occur when the virus fails to stimulate the immune system to elaborate antibody or when a brief period of seropositivity is followed by an absence of antibody.[31] The phenomenon of delayed seroconversion

has been reported only in individuals at high risk for HIV infection and transfusion-associated HIV infection has not resulted in such circumstances.[30,32] However, there have been 11 reported cases of transfusion-associated AIDS from screened blood where there were other recipient risk factors not related to blood transfusion or where the donors were confirmed to be seronegative.[28] While the presumption has been that another mode of transmission was responsible in these cases, the possibility that some donors were antibody-negative but infected with HIV remains. It should be acknowledged that appropriate self-disqualification among high-risk donors would have prevented virtually all of the documented cases of HIV transmission by seronegative donors to date and that aggressive educational programmes may be of more value in reducing or eliminating the problem than more extensive blood testing.[28] Finally, it should be recognized that, because of aggressive donor screening and blood testing by the blood banks, HIV transmission by blood transfusion is negligibly small and that hepatitis remains the dominant clinical concern.

Human T-lymphotropic virus 1 and 2 (HTLV-1, HTLV-2) belong to the same family of viruses as HIV but cause cell proliferation (leukemia and lymphoma) rather than cell lysis and death as seen in AIDS. The neurological disorders tropical spastic paraparesis (TSP) and HTLV-1 associated myelopathy (HAM) have also been associated with the virus. Although HTLV can be transmitted by blood, no HTLV-1 infected transfusion recipients have been reported to have developed clinical disease.[33] However, the incubation can be long and the clinical risk of transfusing HTLV-1 positive blood is difficult to assess. The Canadian Red Cross began screening for HTLV-1 in April of 1990 and the incidence of HTLV-1 seropositivity in donated units is 0.003% (personal communication, National Office, Canadian Red Cross Society).

Parasites are rarely transmitted by blood transfusion and the likelihood of transmission is further reduced by careful donor assessment rather than by blood testing. Transfusion of bacterially contaminated blood products is not common but has been implicated in 26 transfusion-associated deaths.[4] Such reactions are characterized by Walker as rare, occurring in less than one in 150,000 transfusion events.[3] Although platelets are commonly felt to pose a greater risk for transfusion-associated sepsis because they are stored at room temperature, blood products implicated in transfusion-associated sepsis were evenly divided between red cells and platelets in Sazama's review.[4] Morrow reviewed 29,738 platelet transfusion events in his institution and documented transfusion-associated sepsis in seven (one per 4200 platelet transfusions).[34] Sepsis was associated with long storage periods with most of the septic units having been stored for five days, the longest storage period permissible by the US Food and Drug Administration and the Canadian Red Cross. Bacterial contamination was presumed to have occurred at the time of collection of the blood.

Complications related to large volume blood transfusions

There are a number of complications related to the transfusion of large volumes of blood (> one blood volume) at rates of infusion of 90 ml · min^{-1} or greater. These complications result from the constituents of the preserving solutions used in blood banking and the temperature (4° C) at which blood is stored as well as the effects of storage on solutions of red cells, most notably progressive hyperkalaemia and acidosis of the plasma fraction. Hypothermia may result from rapid transfusion of large volumes of cold blood. Hypothermia has been associated with increased mortality in traumatized patients and preservation of normothermia may enhance survival in critically ill trauma patients.[35] This topic will be discussed under the heading of blood warmers. Progressive hypocalcaemia, hyperkalaemia and acidosis may result from the transfusion of large volumes of stored blood. Clinically important metabolic acidosis as a result of transfusion is seen only in patients who have received blood at rapid rates of transfusion (1.2 ml · kg^{-1} · min^{-1}).[36] Although it is difficult to separate the component of the metabolic acidosis that is a result of the rapid transfusion from that caused by lactate production in injured patients with hypotension and inadequate tissue oxygenation, rapid transfusion and restoration of circulating volume and blood pressure is likely to reduce endogenous lactate production and improve the outcome in critically injured patients.[35,37] The exogenous lactate administered with the blood is likely to be well tolerated if circulating volume and blood pressure are maintained.[36]

There is considerable excess calcium-binding capacity given the current volumes of citrate anticoagulant added to stored blood and following rapid transfusion of large volumes of stored blood, serum hypocalcaemia may result.[36,38] The hypocalcaemia is transient and there is little evidence that it is an important clinical concern in most patients.[36] However, myocardial dysfunction has been reported during rapid transfusion and has been attributed to low serum calcium concentrations.[39] Hyperkalaemia has long been recognized as a potential but uncommon complication of rapid transfusion.[40,41] However, recent reports have documented considerable, albeit transient, hyperkalaemia during rapid blood transfusion for hypovolaemia and lethal arrhythmias have been attributed to the elevated serum potassium concentration.[36,42–44] It is likely that these complications were not commonly reported in

the past due to the technological limitations which prevented very rapid blood transfusion. However, technology has progressed so that it is possible to transfuse 500–1000 ml · min^{-1} and to replace greater than four blood volumes per hour.[44,45] These rates are well in excess of the 90–120 ml · min^{-1} that have been reported to be associated with hyperkalaemia.[36,46] In a recent case report of a lethal hyperkalaemic intraoperative arrest it was documented that the patient received blood replacement of packed cells containing 23.6 mmol · L^{-1} to 34.4 mmol · L^{-1} of potassium at infusion rates of 420 ml · min^{-1} or greater.[44] It was later calculated that the patient received 9.9 mmol · min^{-1} of K^+. At the time of arrest the serum K^+ concentration was 10.7 mmol · L^{-1}. This suggested that such rapid infusion rates of hyperkalaemic packed cell solutions fail to provide sufficient time for redistribution of the potassium load throughout the extracellular space which results in high potassium concentration in the central compartment, myocardial toxicity, and cardiac arrest.[42–4] Wall has suggested that hypothermia, shock, acidosis and aortic crossclamping may decrease the volume of the central compartment and promote further elevations in serum potassium as well as enhancing the toxicity of the hyperkalaemia.[42] This potential fluctuation of the central compartment and the resulting modification of the volume of distribution may explain the lack of a consistent correlation between the rate of transfusion and the degree of hyperkalaemia in patients receiving rapid and massive transfusion.[36,42] Linko has demonstrated that the hyperkalaemia is transient, that potassium redistribution occurs rapidly, and that serum potassium concentrations measured following rapid transfusion events (>90 ml · min^{-1}) have returned to normal, baseline values.[36]

A number of conclusions may be drawn from these reports. A sustained rate of blood transfusion greater than 90 ml · min^{-1} is probably required to produce clinically important hyperkalaemia and hypocalcaemia. The hyperkalaemia is transient but will produce characteristic ECG changes and if extreme (>9 mmol · L^{-1}) can produce lethal myocardial toxicity. Hypothermia, shock and acidosis are likely to enhance hyperkalaemic toxicity, are often present in patients requiring such massive transfusions and contribute to the high mortality.[35,37] It is recommended that the EGG be monitored closely in such circumstances and if hyperkalaemia occurs, that it be treated aggressively. There are no good data to support the routine use of calcium supplements during or following massive transfusion.

The immnosuppressive effects of blood transfusion

There are abundant data to show that blood transfusion alters host defences. It is generally recognized that homologous blood transfusions exert nonspecific immunosuppressive actions.[47] In patients who have received blood component transfusions, there are impairment of natural killer cell and phagocytic cell function and decreases in helper/suppressor cell ratios.[48–50] A role has been postulated for natural killer cells in host resistance against tumours.[51] There is a correlation between the degree of functional impairment and the amount of blood transfused and the duration of functional impairment appears to be more prolonged with subsequent donations.[50,52] The principle of the blood which results in the immunosuppression has yet to be defined although it is recognized that plasma alone contains factors capable of modifying the immune response. The clinical importance and extent of these alterations in host defences has yet to be determined. That this immunomodulation has some clinical significance was first demonstrated in the field of renal transplantation and more recently in the areas of cancer recurrence following surgical excision of solid tumours and postoperative septic complications.

Transplant survival and blood transfusion

Medawar demonstrated in 1945 that blood shared antigens with other tissues and that animals could be immunized to donor skin grafts by previous blood transfusion, resulting in graft rejection.[53] However, in 1972 Opelz conducted a large review of renal graft survival and demonstrated that blood transfusion was associated with increased graft survival.[54] The benefit seemed to increase with larger numbers of units transfused. This "transfusion effect" led to the widespread practice of deliberate preoperative transfusion of kidney transplant recipients. Although graft survival was increased about 20% by this manoeuvre, some patients did become immunized to their designated organ and were unable to be transplanted.[55] Over the last decade the benefit of blood transfusion before transplant has become steadily less demonstrable and this is primarily because of improved graft survival in non-transfused patients.[56–8] This is presumed to be related to the widespread use of the immunosuppressant agent, cyclosporine-A, after organ transplantation. With equivalent outcomes now being demonstrated in the non-transfused but cyclosporine-treated patients compared with transfused patients there is reduced emphasis on pre-transplant blood transfusion.[56–8]

Cancer recurrence and blood transfusion

Burrows and Tartter first reported an association between perioperative blood transfusion and adverse outcome in the treatment of patients with colorectal cancer.[59] They documented a lower five-year recurrence-free survival rate in patients who had received perioperative blood transfusions than in patients who had not been transfused. Subsequent reports have noted poorer outcomes in patients who

TABLE III Cancer outcome* and blood transfusion

Cancer	*Variable*	*Reference*
Colorectal	5YS - DF	59
Colorectal	5YS - DF, 5YS	48
Colorectal	5YS	60
Colorectal	5YS	61
Colorectal	5YS - DF	62
Colorectal	5YS	63
Colorectal – metastatic	S, DFS	64
Gastric	5YS	65
Lung	5YS - DF	66
Lung	5YS	67
Breast	5YS-DF	68

*Peer-reviewed studies in which multivariate analysis demonstrated a statistically significant and independent association between blood transfusion and early cancer recurrence.
S = survival, DFS = disease-free survival, 5YS = five-year survival, 5YS-DF = Five-year disease-free survival.

have been transfused perioperatively and have undergone surgery for cancers of the lung, breast and colon and metastatic cancer of the colon.[48,60–68] Studies in which multivariate analysis was employed to reduce the likelihood that a confounding variable, rather than blood transfusion, was responsible for the earlier cancer recurrence and which demonstrated an effect of blood transfusion on adverse outcome are presented in Table III.[48,60–68] In these studies blood transfusion was linked to earlier recurrence of cancer independent of: duration of surgery; histological tumour stage; tumour location; level of preoperative anaemia; and age. However, caution must be exerted in the interpretation of multivariate analyses in which a high degree of intercorrelation among variables exists. The question whether blood transfusion is a surrogate marker for one or more clinical factors predisposing to tumour recurrence remains unanswered. For example, preoperative anaemia, a state likely to result in an increased requirement for perioperative blood transfusion, is independently associated with a decreased five-year survival rate.[60] Transfusion is associated with longer operations, higher blood loss and lesser preoperative haemoglobin concentrations.[62,69] Thus, transfusion cannot be termed an independent variable in predicting recurrence risk in such circumstances.

Not all studies have reported an increased incidence of adverse outcomes following blood transfusion[63,70–80] and in some studies there were different outcomes registered among subgroups within the study populations.[68,81] Adjuvant therapy was more often given to patients with breast cancers who had been transfused and these patients had more advanced disease than those patients who were not transfused.[68] Increased recurrence rates in patients with high grade sarcomas were seen only in those transfused patients who received adjuvant chemotherapy as well.[81] The increased use of adjuvant chemotherapy in these subgroups may imply either higher grade or more extensive tumours and again this may be the relevant variable predicting outcome, rather than the blood transfusion *per se*. Patients with colorectal, cervical or prostatic cancers who received three or less units of packed red cells had similar outcomes to patients receiving no blood transfusions.[82] Both groups had better outcomes than those patients, with similar cancers, who had received more than four units of packed red cells or even one unit of whole blood. Patients with Duke's B or C colorectal carcinoma who received plasma-containing blood products, either whole blood or plasma, had an increased rate of recurrence compared with patients receiving either no blood or packed red cells.[83] Administration of red cells alone did not appear to confer a higher risk of recurrence than no blood transfusion.

Although the association between perioperative blood transfusion and earlier cancer recurrence does not prove causality, it provides information convincing enough to be applied in clinical practice. The data do not support the avoidance of transfusion where warranted nor do they support limiting surgical resection to avoid blood transfusion but they do suggest that transfusion should be restrained to optimize clinical outcome following cancer surgery. Small volumes ($\leq$3 units) of packed red cells do not appear to increase the risk of early cancer recurrence.[82,83] However, the immunosuppressant effect of blood transfusion is cumulative and limiting the use of blood components given during each transfusion is to be encouraged.[49,50] Also, the use of packed red cells rather than whole blood is recommended.[82,83] The use of plasma should be restricted to well-defined clinical circumstances where it is recognized to be indicated.

Postoperative infections and blood transfusions

There are now a number of studies reporting an increased incidence of postoperative septic complications in patients who have received perioperative blood transfusion (Table IV).[84–93] As in the cancer outcome studies, interpretation of the results is complicated by their retrospective nature and by the lack of consistent patient populations, methodology and outcome variables across the studies. These analyses are further limited because many of the independent variables are not independent at all. Variables that demonstrate associations with both blood loss and postoperative infection include age, length of operation, trauma index or injury severity, number of organs injured and reoperation. Once again, the question whether blood transfusion is a surrogate marker for other variables that increase the incidence of postoperative septic complications remains unanswered.

TABLE IV Blood transfusion and postoperative septic complications*

Surgery	*Reference*
Colorectal cancer resection	84
Regional ileitis bowel resection	85
Trauma	86
Abdominal trauma	87
Bowel trauma	88
Hip replacement	89
Gastric carcinoma resection	90
Intraabdominal operations	91
Coronary artery bypass grafting	92
Coronary artery bypass grafting	93

*Studies reported an association between postoperative septic complications and blood transfusion.

Although there is no proved causal relationship between earlier cancer recurrence, postoperative septic complications and blood transfusions, the body of evidence which demonstrates that transfusion inhibits immune function nonspecifically, makes the argument for causality plausible. It is prudent, as we await further data, to promote haemostatic surgical techniques, restrained and judicious use of blood products emphasizing the use of components rather than whole blood and to increase the use of autologous transfusion and blood salvage where feasible.

Special topics in blood transfusion

Microaggregate filtration in blood transfusion

Early blood bankers recommended the use of filters of 140–300 μm pore size during transfusion of stored blood to eliminate large blood clots. Although smaller particles of debris or microaggregates (MA) were not removed by such filters, these MA were not felt to be harmful to the patient. As a result of adverse outcomes attributed to MA-induced lung damage, especially after open heart surgery and following massive transfusion (defined as >10–12 units in 24 hr), filters capable of removing MA were introduced.[94,95] However, the role for MA blood filters (MABF) has yet to be defined.

Microaggregate formation occurs early in stored blood. Early MA are formed primarily of degenerating platelets with granulocyte debris and fibrin strands being added subsequently. Screen filtration pressures can be measured to determine the extent of MA formation. Blood is passed through a screen of 20 μm pore size at a constant flow rate. As particulate matter accumulates on the screen, the pressure required to maintain constant flow across the screen increases. Screen filtration pressure doubles after 24 hr and is too high to be measured after a week of storage.[96] The MABF are capable of reducing screen filtration pressures in stored blood to control levels (those seen immediately after donation) and are capable of reducing MA content to less than 10% compared with unfiltered blood.[96] Filtration through MABF causes no appreciable change in haematocrit or white cell count, no release of fibrinolysins and no reduction in clotting factors except for platelets. The reduction in platelet count is a result of removal of platelet aggregates which do not function in clotting.

The available MABF can be classified as either screen-type or depth type. The screen filters remove debris by interception whereas the depth type remove MA by absorption. Retardation of flow rates was seen with early models of MABF and the surface area has been increased such that it is now possible to achieve flow rates comparable to those attained with large pore filters. However, the MABF may retard flow during the transfusion of viscous, packed red cells unless the units are diluted before transfusion. The capacity of most MABF is 3–6 units of blood with reductions in flow being registered as the filter is exhausted.[97] Older stored units have a tendency to exhaust the MABF more rapidly.

The MA are removed primarily in the pulmonary capillary bed although blood administration through aortic cannulae during cardiopulmonary bypass may allow systemic embolization of MA. Reports of MA-induced lung injury resulting in adverse patient outcomes (ARDS, mortality) after cardiopulmonary bypass and massive transfusion are controversial. Studies performed during the Vietnam War suggested that MA contained in transfused blood resulted in pulmonary embolization and lung injury and played a role in the genesis of severe acute respiratory distress syndromes (ARDS) following massive transfusion.[95,98,99] However, not all studies reported an association between the volume of blood transfused and pulmonary MA embolization nor in an increased incidence of hypoxemia or ARDS after massive transfusion.[100–102] Snyder and Collins, after reviewing the Vietnam data, concluded that the occurrence of fatal pulmonary injury following trauma and multiple transfusion may be, but was not always, associated with demonstrable microemboli to the pulmonary circulation.[103,104] The pulmonary injury and the occurrence of ARDS were more often related to the type and magnitude of the trauma than to the amount of blood transfused. The incidence of severe ARDS in civilian trauma units has decreased appreciably over the last decade.[103] This may be attributable to early and more aggressive treatment of hypotension and sepsis, both aetiogical factors in ARDS causation. When transfused volumes exceed ten units of blood, particulate debris can be readily identified in autopsied lung.[96] Pepe reported that when massive transfusion was the sole risk factor for the development of ARDS in trauma patients, it was only seen in patients who had received more than 22 units in 12 hr.[105]

The level of injury was high in these patients and this finding is not inconsistent with Snyder's conclusions that it is the severity of injury and not the blood transfusion that represents the most important factor in the development of ARDS.

In submassive transfusion events (≤ eight units in 24 hr) the use of MABF did not provide a clinical benefit compared with patients who received transfusion through a standard blood set without a MABF.[106–110] The patients studied included patients with preexistent pulmonary dysfunction who might be expected to be more sensitive to the MA-induced pulmonary injury.[110] In this subgroup, as well, no clinical benefit was derived from the use of the MABF for blood transfusion. There are no reports in patients with severe or end-stage pulmonary disease regarding the use of MABF in transfusion.

The MA contain both platelet and granulocyte debris, both of which play a role in febrile transfusion reactions. This reaction is felt to be a dose-related phenomenon and any reduction in MA content of the donor blood will presumably decrease the incidence or severity of these reactions.[111] The use of MABF for transfusion of components to patients who have experienced febrile reactions in the past should be encouraged. However, there are no data to support the routine use of MABF during transfusion. During massive transfusion events, the use of MABF may limit the rate of transfusion, especially as the filters progressively exhaust and there would appear to be little role for MABF in circumstances where aggressive volume resuscitation is required.

Crystalloid for dilution of packed red cells

In clinical practice, units of packed red cells are often diluted with crystalloid solution to improve the rheological characteristics and increase flow rates during infusion. Although the flow rate ($ml \cdot min^{-1}$) of the diluted unit will be increased compared with the undiluted state, the time required for transfusion of 90% of the red cell mass is unchanged.[112] Dilution of the packed cells would be most useful in patients who require both increased intravascular volume and red cells. In those patients requiring only red cells, crystalloid dilution of the packed unit is unnecessary and will not result in a more rapid transfusion rate of the entire unit. Concerns have been expressed regarding the use of calcium-containing crystalloid solutions for diluting packed red cells.[46,113–115] Citrate is employed as a chelating agent in stored blood to remove calcium, an essential cofactor in the clotting cascade, and prevent clot formation during storage. It has been hypothesized that the use of calcium-containing diluent solutions will saturate the citrate, that the excess calcium will then be available to initiate the clotting cascade and that clot formation will result.

Rock has demonstrated that there is considerable excess calcium-binding ability given the current volumes of citrate added to blood for storage.[38] Therefore calcium could be added to stored blood during dilution without necessarily exceeding the calcium-binding capacity of the citrate contained in the unit. In fact, it would require the calcium contained in the equivalent of 900 ml of Ringer's lactate (RL) to saturate the citrate present in a unit of packed red cells, an amount of crystalloid far in excess of that used clinically to dilute packed cells (100–200 ml).[116] Edwards reported that blood-RL solutions containing up to 70–90% RL by volume developed clot only after 45 min at 37° C.[114] Parlow demonstrated that blood-RL mixes have to be greater than 70% RL by volume before clot formation occurs and that it takes 30 to 60 min for clot formation.* Cull documented clot formation when blood-RL mixtures containing 50 vol% or greater of RL were made but noted that 15 minutes or more were required for clot formation. There was no clot formation for more than two hours if less than 50 vol% of RL was contained in the final mixture. It can be concluded from the available data that there is an increased likelihood for clot formation if RL is used as a diluent compared with normal saline. This clot formation is most likely to be seen when the final blood-crystalloid mixture contains more than 50 vol% of RL and will require 15–120 minutes to become manifest. Little clot formation can be expected in the setting of rapid transfusion when less than 1:1 ratios of blood:crystalloid are used. Use of normal saline as a diluent will result in no measurable clot formation. The residual blood in the intravenous set following transfusion could form clot if RL is subsequently infused through the same set.[113] Flushing the system with a volume of normal saline sufficient to clear the system or changing the intravenous set after blood administration effectively eliminates the problem of clot formation.[113] Finally, there is no evidence that the clot formation that occurs when RL is used as a diluent for red cells results in any pathophysiological sequelae in patients during or after the transfusion.

Use of blood warmers

Packed red blood cells are stored at 1–6° C for preservation of red cell functional integrity. Administration of cold stored blood to patients results in cooling of the intravascular space and necessitates energy expenditure on the part of the patient to restore and maintain normothermia. In the case of an elective transfusion of 1–2 units of stored red cells, each administered over two to four hours, the energy

**Parlow JL, Johnson GD, Adams MA.* Compatibility of Ringer's lactate solution with packed red cells for rapid infusion. Presented at the University of Ottawa Annual Review Day in Anaesthesia, May, 1989.

TABLE V Techniques for warming blood for transfusion.

Pretransfusion warming
1 ambient temperature (slow transfusion)
2 water bath
3 electromagnetic warmers
4 radiowave warmers
5 microwave warmers
6 heated saline admixture
In-line warming
1 water baths
2 countercurrent warmers
3 dry heat warmers

Reference 121.

expenditure will be minor (15–20 kcal) and can be easily met by most patients. This is very different from the shocked and bleeding patient receiving 20 units of packed cells over 60–90 minutes. If this transfusion occurs with cold stored blood, energy expenditures as great as 300 kcal may be required to maintain normothermia. The patient will not be capable of maintaining normal blood temperatures and hypothermia with its attendant physiological perturbations will occur. Patients who become hypothermic during major transfusion events have a higher mortality than patients whose body temperature is maintained more closely to normal.[35,118–120] Current resuscitative practices dictate and technology allows for transfusion flow rates in the order of 500–1000 ml · min^{-1}. Unless techniques are employed to maintain body heat during such transfusion events, patients will rapidly become hypothermic. With decreasing body temperature, there is a simultaneous reduction in cardiac output and an increase in metabolic acidosis. A vicious cycle is established and the end-results are cold, shocked and moribund patients with a higher mortality than that seen in similar patients with more normal body temperatures.[35,118–120]

Iserson and Huestis have recently reviewed current techniques of blood warming to which the reader is referred (Table V).[121] Although they do not recommend the use of warmers for routine, minor transfusions (1–2 units) on the ward or in the operating room, they encourage the use of warmers for all more intensive transfusion events. However, because heat loss in the operating room is a multifactoral problem, any and every effort should be made to conserve patient energy and maintain normal body temperature.[122] For this reason, this author recommends the use of blood warming techniques even for minor (1–2 units) intraoperative blood transfusions. Maintaining normothermia reduces the incidence of postoperative shivering thermogenesis and although, for most patients, this will be little more than an unpleasant postoperative experience, in some it can cause morbidity.[122]

A problem in the preoperative care of the traumatized patient is that blood warmers are often not used during the early resuscitative phase, the result being that the patients arrive in the operating theatre already hypothermic. A technique of mixing cold stored blood with warmed (45–70° C) saline has been described that allows for rapid warming of stored blood and requires only an incubator to warm and store the saline.[123–125] Saline temperatures as high as 70° have been demonstrated to be safe, not only with respect to red cell integrity but also with respect to the final temperature of the admixture. Saline temperatures greater than 70° result in increased osmotic fragility and higher supernatant concentrations of both free haemoglobin and potassium. An advantage of the saline admixture technique is that the use of an in-line warmer is not required and thus very high flow rates may be achieved even without the use of a high capacity blood warmer. This makes the technique ideal for the early resuscitative phase of trauma patient care. Further, the fact that no equipment or set-up is required means that this technique can be rapidly established and used on multiple patients in a busy emergency room without significantly increasing team efforts. In situations where lesser flow rates are adequate, Zorko has described a technique of saline admixture where the cold stored blood is mixed with saline warmed only to 45° C, then passed through an in-line warmer.[125] The end-product is nearly normothermic, being warmer than blood that has been either admixed or passed through an in-line heater and achieving a higher flow rate than blood that has not been admixed. Whatever the technique employed, it is clearly advantageous to warm all stored blood either before or during transfusion. As the magnitude of the transfusion event increases, blood warming may move from being desirable to being life-saving.

Informed consent and blood transfusion

The recent reexamination of the indications for and risks related to blood transfusion has motivated physicians to provide more information to patients with respect to blood products. A natural evolution of this process is the obtaining of informed consent from the intended recipients of blood products before transfusion. In fact, standard texts in anaesthesia recommend that informed consent be obtained before any transfusion event and that a notation be made in the patient's chart that the risks of transfusion have been discussed with a patient.[46] Written informed consent has been recommended by some authors and it has been suggested that the following elements be contained in the consent: the nature of the proposed procedure (blood transfusion); the alternatives available, including no transfusion; the expected benefits resulting from the transfusion; and the risks of blood transfusion.[126–128]

Although the American Association of Blood Banks (AABB) Standards do not specifically address the issue of written informed consent, an AABB memorandum, dated July 10th, 1986 recommended "that patients who receive non-emergency transfusions be informed of the risks and benefits of blood products and consent to their use."

Informed consent has been deemed unnecessary in the past if the patient waived the right to be informed, if the physician felt that it was not in the patient's interest to be informed (the doctrine of "therapeutic exception"), if the patient was incompetent or if the emergency nature of the procedure precluded obtaining written informed consent.[127] The first two are probably no longer valid and it is increasingly accepted that incompetent patients are best represented by a surrogate other than the treating physician. The emergency nature of a procedure remains the only reason for not obtaining informed consent before administering blood products.

There are a number of positive aspects to informed consent before blood transfusion. It affords the patient an opportunity to talk with the physician and become informed regarding the risks and benefits of blood transfusion. There is some evidence that the physician may be less inclined to transfuse in borderline cases if informed consent is required.[126] Finally, in the past, legal suits against physicians have usually centred on malpractice but failure to discuss risks of transfusion and the allegation of unnecessary transfusion have been the focus of recent suits following transfusion-associated HIV transmission.[127] Although such legal considerations should not dissuade physicians from ordering transfusions when indicated, they do focus attention on the need to evaluate clearly the indication for the transfusion and discuss the situation with the patient.

It might be argued that the nature of anaesthetic practice, with many transfusions being given during operation, does not allow for consent discussion before blood product administration. However, the use of blood schedules allows for the estimation of the likelihood that blood will be required during elective surgery. Once it has been determined that there is a possibility that blood will be required intraoperatively, the patient should be informed. The indications, risks and benefits of blood transfusion as well as the alternatives available to the patient in that particular institution should be outlined and the patient should have the opportunity to respond. That this discussion took place should be documented on the anaesthetic record. In the event that an intraoperative transfusion is felt to be warranted, the anaesthetist should document the considerations underlying the decision to transfuse.

Legal considerations aside, it is the author's opinion that preoperative discussions with the patient, documentation of patient informed consent on the anaesthetic record to blood transfusion is necessary. An entry on the anaesthetic record reflecting the considerations resulting in the decision to transfuse will validate clinical decision-making and enhance the quality of transfusion medicine. This opinion was presented to the Canadian Medical Protective Association (CMPA) who stated that a physician should obtain informed consent before an elective blood transfusion. The physician should explain to the patient the reasons for the transfusion, the relative risks and benefits as well as the alternatives available to the patient. A note should be entered in the record about the discussion having taken place. It is the CMPA position that a separate written consent is not necessary.

Summary

The risk to the patient from a homologous blood transfusion is probably lower now than in the past. However, a zero-risk blood supply is not achievable for practical and technical reasons.[129] This must be factored into the decision whether to transfuse and, in order to do so appropriately, the transfusing physician must have accurate data of transfusion risks. In this review, an attempt was made to provide as accurate an estimate of transfusion risks as is feasible in such a changing field. Finally, it would seem prudent to involve the patient, whenever possible, in the decision to transfuse and the concept of informed consent for blood transfusion is supported.

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