# The hazards of blood transfusion

***Blood transfusion-related immunomodulation results in either immune activation, associated with a variety of transfusion reactions, or immunosuppression, associated with an increased predisposition to infections and post-surgical cancer recurrence. This article reviews the major complications associated with blood transfusion.***

In recent years red blood cell transfusion requirements in western nations has been increasing as a result of the increasing burden of chronic disease in an ageing population, improvement in life-support technology and blood-intensive surgical procedures (National Blood Data Resource Center, 2001; Wells et al, 2002). In the United States alone nearly 15 million units of blood are donated and 13 million units are transfused annually (National Blood Data Resource Center, 2001).

For much of the last century red blood cell transfusion has been viewed as having obvious clinical benefit. However, over the last 20 years red blood cell transfusion practice has come under increased scrutiny. Initially this was driven by concerns over transfusion-related infections, human immunodeficiency virus (HIV) in particular. While the risk of transfusion-transmitted infections has received considerable attention, the risk of this complication with modern blood banking techniques is now exceedingly remote (Busch et al, 2003). On the other hand, it is now becoming clear that there are other important, less recognized risks of red blood cell transfusion related to red blood cell storage effects and to immunomodulating effects of red blood cell transfusions that occur in almost all recipients (Raghavan and Marik, 2005) (*Table 1*). These immunomodulating effects may increase the risk of the recipient developing perioperative and nosocomial infections, acute lung injury and the possibility of cancer recurrence and the development of autoimmune diseases later in life (Raghavan and Marik, 2005). Nevertheless despite the increased awareness of the risk of blood transfusion, red blood cell transfusions remain common with many patients receiving blood with no good indications. This article reviews the complications associated with red blood cell transfusion.

## Infectious complications

Although rare, transfusion-transmitted infections resulting from a variety of agents remain a cause of concern in modern allogenic transfusion practice. With modern screening techniques the risks of transmission of hepatitis B (HBV), hepatitis C (HCV) and HIV are extremely low (Busch et al, 2003). Leukocyte contamination of blood products remain primarily the aetiological mode of transmission of various infectious agents. Transfusion-transmitted cytomegalovirus (CMV) occurs in approximately 4% of transfusions, and is caused by reactivation of latent CMV in leukocytes from healthy donors.

Besides CMV, other herpes-viruses such as Epstein–Barr virus, human herpes virus (HHV) -6, HHV-7 and HHV-8 are associated with leukocyte contamination during transfusion. Human T-cell leukaemia/lymphoma virus (types I and II) target T lymphocytes and are solely transmitted by cellular blood components (Sandler et al, 1991). Primary toxoplasmosis has been reported to be transmitted by whole blood (Siegel et al, 1971). Transfusion-transmitted West Nile virus infection occurred in the USA in 2002 among 23 patients from 14 donors and since then over 600 infected units of blood were identified from a 2.5 million donor pool (Pealer et al, 2003). TT virus is a novel newly discovered DNA virus transmitted by transfusion to approximately 30% of patients who undergo cardiac surgery (Wang et al, 2000).

## Transfusion-related immunomodulation

Allogenic blood transfusions introduce a multitude of foreign antigens including human leukocyte antigen (HLA)-class II bearing donor dendritic antigen-presenting cells (APC) in recipients. The immunogenicity of soluble, particulate or cellular major histocompatibility complex (MHC) antigens present on transfused allogenic blood products depend on the viability of APC, co-stimulatory molecules to present them to recipient T cells, and HLA compatibility between donor and recipient. Blood transfusions primarily induce immunomodulation in two opposite ways. They may either cause allo-immunization or tolerance induction.

Immunization is reflected by the induction of HLA alloantibodies and T cell activation, while the induction of tolerance is suggested by enhanced renal, hepatic, cardiac, pancreatic and skin allograft survival in transfused *vs* non-transfused recipients. Presence or absence of 'autologous' HLA-DR Ag on the leukocytes of the transfusion donor plays a decisive role as to whether immunization or immune suppression will ensue following allogenic blood transfusion (Lagaaij et al, 1991). Transfusions sharing at least one HLA-DR antigen with the recipient will induce tolerance while fully HLA-DR mismatched transfusions lead to immunization. Accumulation of various soluble bioactive substances occurs during storage and includes histamine, lipids, cytokines, fragments of cellular membranes, and soluble HLA class I antigens, many of which

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are white blood cell-derived and play an important role in transfusion-related immunomodulation. Stored red cells harbour potent pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, bactericidal permeability-increasing protein and tumour necrosis factor.

The specific constituents of red blood cell transfusions that mediate either or both of the immunomodulatory and proinflammatory effects remain unknown, however, it has been suggested that transfusion-related immunomodulation may be mediated by:

- Allogenic mononuclear cells
- Soluble biological response modifiers released in a time-dependent manner from white blood cell granules
- And/or soluble HLA class I peptides that circulate in allogenic plasma (Vamvakas and Blajchman, 2007).

It has been suggested that leukodepleted blood may have fewer immunomodulating properties and hence reduce the complications associated with the transfusion of non-leukodepleted blood (Raghavan and Marik, 2005). However, there is still some debate as to the benefit of leukoreduction (Corwin and AuBuchon, 2003). Removal of leukocytes from red cell transfusions may have a small but potentially important effect on clinical outcomes, however, cost-effectiveness of universal leukoreduction has yet to be proven, especially in lower risk populations.

The age of transfused red blood cells has been suggested as a possible explanation for some of the adverse effects associated with red blood cell transfusion. Numerous abnormalities have been associated with storage of red blood cells and some studies have suggested that transfusion of 'older' red blood cells may be associated with adverse effects (Marik and Sibbald, 1993). In a provocative study recently reported by Koch and colleagues (2008) cardiac surgery patients who received blood that was older than 14 days had a higher risk of sepsis and a reduced short- and long-term survival compared to patients who received fresher blood. If age of transfused red blood cells is in fact important, it would have major ramifications on the already limited blood supply. At this point only limited clinical evidence is available and thus a definitive clinical trial is necessary to answer this question.

## Clinical implications of transfusion-related immunomodulation

Clinical evidence for the existence of transfusion-related immunomodulation was first reported by Opelz and colleagues (1973) who showed that allogenic blood recipients had improved renal allograft survival. This observation was subsequently confirmed in prospective clinical trials. Clinical syndromes associated with immune activation in the recipient include a variety of transfusion reactions, transfusion-associated graft-*vs*-host disease, transfusion-related lung injury (TRALI), alloimmunization and possible development of various autoimmune diseases. Syndromes associated with tolerance induction and immunosuppression include: febrile non-haemolytic transfusion reactions; increased predisposition to nosocomial and postoperative infections; cancer recurrence; TRALI; delayed TRALI syndrome; microchimerism; and enhanced survival of various allografts in recipients. A number of these complications are reviewed below.

**Table 1. Complications associated with blood transfusion**

| | | |
|---|---|---|
| Infectious | Human immunodeficiency virus (HIV) | |
| | Hepatitis B, C, D | |
| | Cytomegalovirus | |
| | Parvovirus B19 | |
| | Epstein–Barr virus | |
| | Human T cell leukaemia or lymphoma virus | |
| | Human herpes virus 6, 7 and 8 | |
| | Toxoplasmosis | |
| | Malaria | |
| | West Nile virus | |
| | TT virus | |
| | Prion disease? | |
| Non-infectious | Immune activation | Non-haemolytic febrile reactions |
| | | Anaphylactoid allergic reactions |
| | | Acute haemolytic reaction |
| | | Delayed haemolytic reactions |
| | | Transfusion-related acute lung injury |
| | | Delayed transfusion-related acute lung injury syndrome |
| | | Transfusion associated graft *vs* host disease |
| | Immune tolerance | Nosocomial or postoperative infections |
| | | Multi-organ failure |
| | | Transplant tolerance |
| | | Cancer recurrence? |
| | | Autoimmune disease? |

### Febrile non-haemolytic transfusion reactions

Febrile non-haemolytic transfusion reactions, characterized by a rise in temperature usually associated with chills and rigours, are believed to be caused by pyrogenic cytokines produced by donor leukocytes and infused with the transfused blood. This reaction may be associated with a leukocytosis. The risk of febrile transfusion reactions is reduced with the use of leukoreduced blood.

### Increased risk of postoperative complications and nosocomial infections

Multiple observational studies have demonstrated that blood transfusion is associated with an increased risk of postoperative and nosocomial infections, increased length of hospital stay and increased mortality. While sicker patients in general receive more blood transfusions, multivariate analysis consistently demonstrates

that blood transfusions are independent predictors of morbidity and mortality.

A meta-analysis was carried out of 45 cohort studies that assessed the effect of red blood cell transfusion on patient outcomes (Marik and Corwin, 2008a). These studies included postoperative, cardiac and intensive care unit patients. Twenty-two studies examined the association between red blood cell transfusion and nosocomial infection; in all these studies blood transfusion was an independent risk factor for infection. The pooled odds ratio for developing an infectious complication was 1.8 (95% confidence interval = 1.5–2.2). Hill and colleagues (2003) performed a meta-analysis of studies investigating the risk of postoperative infections in patients receiving a blood transfusion. In this study the odds ratio of the association between red blood cell transfusion and postoperative infection was 3.45 (range 1.43–15.1). These studies provide overwhelming evidence that red blood cell transfusions increase the risk of postoperative and nosocomial infections. Transfusion-related immunomodulation-associated immunosuppression has been associated with a decrease in the helper:suppressor T-lymphocyte ratio, a decrease in natural killer cell function, defective antigen presentation and suppression of lymphocyte blastogenesis. These findings may partly explain the mechanisms by which red blood cell transfusions increase the risk of infectious complications in hospitalized patients. These data are supported by the Canadian Critical Care Trials Group study (TRICC study) in which patients randomly assigned to a restrictive transfusion strategy and who received significantly fewer blood transfusions had reduced morbidity (Hébert et al, 1999).

## Cancer recurrence

As blood transfusions may result in immune tolerance and interfere with immune surveillance it has been suggested that perioperative blood transfusions may increase the likelihood of tumour recurrence. Evidence for a possible deleterious effect of allogenic blood transfusion has been reported in the context of tumours of the colon, rectum, breast, head and neck, lung, prostate, stomach, kidney, cervix and vulva (Vamvakas, 1995). However, as many of these studies are observational with multiple cofounders the association between perioperative blood transfusion and cancer recurrence is suggestive but not proven. However, a meta-analysis of randomized controlled studies of patients undergoing curative resection of colorectal cancer by the Cochrane group reported a pooled odds ratio of cancer recurrence of 1.42 (95% confidence interval = 1.20–1.67) associated with blood transfusion (Amato and Pescatori, 2006).

This topic remains controversial as does the use of leukoreduced blood in patients undergoing surgery. However, considering the overall risks associated with blood transfusion the use of this human product should be limited in patients undergoing surgery.

## Transfusion-related acute lung injury

TRALI is a clinical syndrome characterized by the sudden onset of respiratory distress in patients receiving a transfusion of blood products. Symptoms typically develop within 1–2 hours after initiation of the transfusion and may include sudden onset of dyspnoea and tachypnoea (Toy et al, 2005; Rana et al, 2006). The clinical features are identical to those of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

The reported incidence of TRALI indicates it is rare, although its overall occurrence is almost certainly more common than the quoted estimate of one case in 5000 U of transfused blood (Popovsky and Moore, 1985). It is likely that many cases of TRALI have been misdiagnosed or confused with circulatory overload, cardiac failure or as an 'anaphylactic' type reaction. TRALI is now considered the leading cause of death in the United States that is directly related to the transfusion of blood products. Although the pathophysiology of TRALI is poorly understood two causes of TRALI have been proposed: anti-leukocyte antibodies; and biologically active substances such as lipids and cytokines that have neutrophil priming activity (Toy et al, 2005; Rana et al, 2006). These two mechanisms may not be mutually exclusive and a patient may have TRALI as a result of one or both mechanisms. When a case of TRALI is suspected the transfusion should be stopped immediately and the blood bank contacted to screen the donor units for anti-leukocyte antibodies.

## Delayed TRALI syndrome

While massive transfusion has long been identified as a risk factor for ALI and ARDS, transfusion of a smaller blood volume has until recently not been well studied and has not generally been considered a risk factor for ALI. However, several studies reported over the last 5 years have demonstrated that in patients with other risk factors for ALI, even a single unit of blood increases the risk for developing ALI or ARDS. In these studies, the transfusion of blood or blood products was an independent risk factor for the development of ARDS with a pooled odds ratio of 2.13 (95% confidence interval = 1.75–2.52). The term 'delayed TRALI syndrome' has been coined to describe ALI occurring in this setting (Marik and Corwin, 2008b).

Patients who develop the delayed TRALI syndrome characteristically have additional risk factors for developing ALI, most notably sepsis, trauma or burns. The observation that blood transfusion increases the risk of ALI in critically ill patients is supported by the results from the TRICC study (Hébert et al, 1999). In this study, a liberal transfusion strategy was associated with an increased risk of ALI or ARDS (odds ratio 1.5; 95% confidence interval = 0.97–2.49). In addition to increasing the risk of developing ALI or ARDS, blood transfusions are associated with an increased risk of death in patients with established ARDS (Gong et al, 2005; Netzer et al, 2007).

## The risks and benefits of blood transfusion

Considering that over 100 million units of red blood cells are transfused annually worldwide, one would expect to find published literature demonstrating a benefit from blood transfusion. Unfortunately, no such literature exists. Indeed, the published literature strongly suggests that blood transfusions are harmful. Marik and Corwin (2008a) performed a systematic analysis of the literature to identify those studies that have investigated the impact of blood transfusions on patient outcome. Only in a single subgroup from a single study was there evidence that blood transfusion was beneficial (Wu et al, 2001). While this study has been criticized for methodological problems (Hébert et al, 2007), it suggests that elderly patients who suffer a myocardial infarction and whose baseline haematocrit is below 33% may benefit from a blood transfusion.

Overwhelming evidence strongly supports the notion that blood transfusions are harmful. It should, however, be noted that the studies included in the meta-analysis were performed with non-leukocyte reduced blood. While the benefits of leukoreduction remain controversial, it is possible that the infections complications, risk of ARDS and effect on mortality may be reduced with leukoreduction. Not withstanding this, there are at present scarce data to support the idea that blood transfusion is beneficial, and therefore this intervention should be avoided unless absolutely indicated (i.e. patients with ongoing haemorrhage).

## Conclusions

Blood transfusions are associated with numerous complications associated with both immune activation and suppression, TRALI, an increased risk of infections and tumour recurrence complications, which increase the likelihood of death. The classical 30/10 (haemoglobin 10 g/dl and haematocrit of 33%) transfusion) transfusion trigger can no longer be supported. In every patient in whom a blood transfusion is considered, the risks *vs* the potential benefits should be carefully evaluated. **BJHM**

*Conflict of interest: none.*


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### KEY POINTS

- The risks of transmission of hepatitis B, hepatitis C and HIV are extremely low with modern banking techniques.
- Cytomegalovirus, Epstein–Barr virus, human herpes virus (HHV)-6, HHV-7 and HHV-8 transmission may occur with leukocyte contamination during transfusion.
- Transfusion-related immunomodulation is common and may result in immune activation or immune suppression.
- Transfusion-related immunomodulation-associated immune activation results in a variety of transfusion reactions, transfusion-related lung injury, alloimmunization and possible development of various autoimmune diseases.
- Transfusion-related immunomodulation-associated immunosuppression results in an increased predisposition to nosocomial and postoperative infections, cancer recurrence and enhanced survival of various allografts in recipients.
- The classical 30/10 transfusion trigger can no longer be supported. In every patient in whom a blood transfusion is considered, the risks *vs* the potential benefits should be carefully evaluated.