Red cell transfusion and the immune system

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Summary
Understanding the complex immunological consequences of red cell transfusion is essential if we are to use this valuable resource wisely and safely. The decision to transfuse red cells should be made after serious considerations of the associated risks and benefits. Immunological risks of transfusion include major incompatibility reactions and transfusion-related acute lung injury (TRALI), while other immunological insults such as transfusion-related immunomodulation are relatively underappreciated. Red cell transfusions should be acknowledged as immunological exposures, with consequences weighed against expected benefits. This article reviews immunological consequences and the emerging evidence that may inform risk-benefit considerations in clinical practice.

Introduction
The decision to transfuse red cells should be made after serious considerations of the associated risks and benefits. Immunological risks of transfusion include major incompatibility reactions and transfusion-related acute lung injury (TRALI), while other immunological insults such as transfusion-related immunomodulation (TRIM) are relatively underappreciated.

Immunological risks of red cell transfusions may be classified according to host and donor interactions. In this review, we discuss these complications and strategies to reduce them.

Red cell antibodies
The International Society of Blood Transfusion recognises > 300 red cell antigens from > 30 systems [1]. The most important points of compatibility lie within the ABO system [2, 3]. Many of these antigens may provoke acute or delayed haemolytic transfusion reactions, as well as haemolytic disease of the foetus and newborn, while others are clinically insignificant despite their potential to corrupt compatibility tests [4, 5].

In 1901, Karl Landsteiner established that not all blood was the same, identifying what is now known as the ABO system; he received a Nobel prize for this discovery in 1930. These antigens consist of precursor H-substance on carrier molecules; the highest density is on the red cell membrane, and lower densities are present on other tissues. The A and B genes encode enzymes that add N-acetylgalactosamine (A) or galactose (B) respectively to H-substance. Plasma contains antibodies formed against these antigens after confrontations with similar moieties on bacteria in the gastrointestinal tract and food substances [6].

Group O individuals (unmodified H-substance alone) develop anti-A and anti-B re-activities, while group AB individuals do not. The A types are further classified serologically as A1 (80%) and non-A1 (typically A2, 20%). The latter may naturally gain anti-A1 activity, which is not usually reactive at 37 °C, but can rarely result in a haemolytic transfusion reaction [4, 7, 8].

The Rhesus system includes up to 50 different antigens, of which D, C, c, E and e are the most clini-
cally significant. Rh factor or positivity refers to the D antigen, which is a large membrane protein (MW 30 000 Da). Numerous polymorphisms account for the RhD-negative (non-expression) state. The RhD+ phenotype is most frequent (85% in Caucasians, 95% in Sub-Saharan Africa, 99.5% in Eastern Asia) [9]. An increasing number of variants are also now recognized, including ‘weak D’, ‘partial D’ and ‘Del’. A second gene encodes the RHCE protein (expressing C/c and E/e antigens) [9].

**Haemolytic transfusion reactions**

The goal of the group, screen and cross-match is to prevent haemolytic incompatibility with red cells, but the importance of adhering to transfusion protocols and positive patient identification to avoid incompatible transfusion cannot be overstressed (Table 1) [7]. Transfusion reactions due to ABO incompatibility would occur in 1/3rd of transfusions without ABO typing [3]. Haemolytic transfusion reactions can be acute, delayed or serological, without clinical manifestations, and range from mild to severe and possible death.

The group and screen is conducted differently in different countries, but the objective of insuring a safe red cell transfusion is the same. It has three components: ABO and RhD grouping; antibody screening; and review of historical records. Patients’ red cells are examined with commercially prepared anti-A, anti-B and anti-D, and agglutination is assessed by visual inspection on forward typing [10, 11]. Known A and B group red cells are then added to the patient’s plasma, and again checked for agglutination on reverse or back-typing, therein also verifying conformity with Landsteiner’s Law [10, 11].

Other antibodies are identified by adding patient plasma to commercially characterised red cells for evidence of immune recognition of approximately 20 significant minor antigens relevant to cross-matching. If antibodies appear, then specificity investigations are performed. In some conditions at higher risk of screen positivity (allo-immunisation), matching beyond ABO and RhD may include typing for Kell and RHCE type [12, 13].

The antibody screen may miss dynamic seroconversions or antibody re-activations that are relevant to forthcoming cross-matches if not re-assessed (e.g. every three days) after recent red cell exposure, for example during pregnancy or after transfusion in the previous three months. Re-examination intervals may be extended in the chronically transfused or those with no history of recent pregnancy or transfusion, according to local blood bank policy [11].

Cross-matching is the final step in assuring red cell compatibility. It may either be abbreviated or represent a full serological cross-match. Abbreviated testing may be either an immediate spin or electronic cross-match, depending on the established laboratory protocols.

- Immediate spin: donor red cells are mixed with recipient plasma at room temperature for 5 min. This is unpopular due to sensitivity to insignificant IgM (cold) antibodies and insensitivity to significant IgG antibodies already discoverable by screening [11], or
- Electronic/computer cross-match: institutions with approved information systems favour virtual cross-matching. This relies on confirmed ABO and RhD typing with serially negative antibody screens (on at least two independent samples) [10, 14]. However, some centres issue units to some patients despite known antibodies [15].

A manual or serological cross-match should be performed if screening is positive, or the patient is

<table>
<thead>
<tr>
<th>Blood group</th>
<th>%</th>
<th>Antigen on red blood cell</th>
<th>Antibodies in the plasma</th>
<th>Can receive blood from</th>
<th>Can receive plasma from</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>44</td>
<td>0</td>
<td>Anti-A</td>
<td>O</td>
<td>All</td>
</tr>
<tr>
<td>A</td>
<td>43</td>
<td>A</td>
<td>Anti-B</td>
<td>O, B</td>
<td>All, AB</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>B</td>
<td>Anti-B</td>
<td>B, O</td>
<td>B, AB</td>
</tr>
<tr>
<td>AB</td>
<td>4</td>
<td>A and B</td>
<td>None</td>
<td>All</td>
<td>AB</td>
</tr>
</tbody>
</table>

**Table 1** Summary of ABO frequency and transfusion compatibility.
known to have had red cell antibodies in the past. This includes an indirect antiglobulin test that is sensitive to IgG, not detectable otherwise or at room temperature [11]. Some laboratories perform this serological cross-match prior to issuing any red cells [15].

**Acute haemolytic transfusion reaction**

This is a potentially life-threatening event and occurs within 24 h of a transfusion; it is due to red cell immune destruction. Destruction affects incompatible red cell antigens or comes from haemolytic antibodies in plasma-containing products. The incidence is 1 in 38–76 000, with fatalities rare at <1 per million [16–18]. Between 2008 and 2012, the US FDA reported 53 deaths due to haemolytic transfusion reaction, acute and delayed, representing 27% of transfusion-related deaths (second after TRALI), however the incidence is decreasing [19]. AB- incompatibility accounted for three out of eight cases of acute haemolytic transfusion reaction in 2012. Of the remaining five cases, three were acute reactions by laboratory error (misinterpreted screen/misfiled records), and two were emergency transfusions given to patients with known antibodies and insufficient preparation time. Australia reported 14 cases between 2008 and 2011, with no fatalities, representing 1.8% of all events reported [18]. In the UK, there were nine cases in 2012, all after red cell transfusion, with no deaths [20].

Acute haemolytic transfusion reactions commonly stem from clerical error or other lapses in patient identification, culminating in administration of properly labelled blood to the wrong patient [16].

The pathophysiology involves complement-fixing antibodies in recipient plasma binding to mismatched red cells, thereby activating the classical complement pathway, with membrane attack complex-mediated intravascular haemolysis over a period of minutes. Recipient IgG may also bind to incompatible red cells to induce antibody-dependent cell cytotoxicity, wherein splenic and hepatic macrophages engage in extravascular haemolysis. The acuity of the reaction may reflect the level of preformed antibody in the plasma. It may occur if these antibodies are missed in error or by the urgent need for uncross-matched blood [21].

Plasma antibodies in products may conversely react with recipient red cells, and while the amount of plasma in packed red cells is limited, other blood products such as group O platelets may be suspended in plasma with high isohaemagglutinin titres that may bind to recipient red cells to induce haemolysis. Some blood banks assess titres in platelets, so that high-content concentrates are given only to matched recipients or undergo plasma volume reduction [22, 23]. Titres may increase after vaccination or probiotic ingestion [24].

The reaction itself manifests typically with fever, chills, chest or flank pain, shortness of breath, tachycardia, hypotension, and haemoglobinuria/haemosiderinuria. Progression to renal failure, disseminated intravascular coagulation (DIC) and death may occur. Laboratory evidence includes a failure of increase or even a fall in haemoglobin, with an increase in bilirubin and lactate dehydrogenase, while haptoglobin reciprocally falls. Management includes stopping the transfusion and providing supportive care. Fortunately, mortality is <10% [16], and correlates with the volume of incompatible blood transfused.

**Delayed haemolytic transfusion reaction**

The onset of delayed haemolytic reaction is >24 h after transfusion, and arises most often because of the missed detection of an antibody on screening [25, 26]. Antibodies are usually IgG isotypes, with some more prone than others to severe delayed reactions and/or waxing and waning expression (e.g. Kidd-Jkα [27], Duffy-Fyα, and Kell-K [28]). After the first confrontation, antibody levels eventually dissipate. On re-exposure, the anamnestic response manifests a prompt rise in antibody levels. These antibodies bind to the red cell, with haemolysis occasionally following. Frequency is 1 in 2500–11 000 [18, 28]. The FDA reported two fatal cases in 2012 – both failed to determine the implicated antibody before transfusion.

Delayed reactions present 1–4 weeks after transfusion with fever, chills, jaundice and laboratory evidence of haemolysis. The post-transfusion screening and/or direct antiglobulin test reveals the allo-antibody, which in the early stages may only be detected by blind eluates from the recipient’s circulating red cells. To varying degrees, alloantibodies may be adsorbed onto the incompatible subpopulation of red cells. These reactions are usually less severe than an acute reaction, and may be missed entirely, especially with reduced hospital length of stay [28]. Severity depends on antibody quality.
(subclass, affinity, thermal range), quantity (titre), and
target antigen density.

Treatment is usually unnecessary, although further
red cells should be selected for their antigen- negativity.
Archiving and review of serologic records in cen-
tralised databases mitigates risk [29–31]. Delaney et al.
noted that >13% of patient records were amended
with historical data that otherwise would have been
unknown to the primary care staff had there not been
data centralisation in King County, Washington [32].

Serological transfusion reaction and
allo-immunisation
A serological transfusion reaction describes the positive
screen or direct antiglobulin test after transfusion, and
may or may not correlate with a delayed transfusion
reaction. It spans not only the post-red cell reaction, but
the subclinical primary sensitisation that may be inci-
dentially detected in the laboratory 1–3 months later
[33]. These antibody-only responses are between two
and five times more common than delayed transfusion
reactions, featuring specificities such as anti-E or -K [34,
35]. Allo-immunisation, as a term, encompasses all sero-
conversions, including, but not limited to, those discov-
ered as a serological reaction through testing, although
many authors use the terms interchangeably [20, 36].

Serological reaction rates vary, being as low as
0.2–0.4% in healthy donors and soldiers [21, 37], 4% in
inpatients [32] and up to 76% in transfusion-depen-
dent patients [21, 38–40]. Harm et al. [29] found
screen-positivity in 44% of sickle cell patients, and in
63.3% of these at least one of the detected antibodies
evanesced over the study period of 15 years.

Allo-immunisation risk depends on red cell quan-
tity, presence and antigenicity of foreign antigens, and
whether the host is prone to seroconversion or not.
Rhesus D is one of the most immunogenic antigens.
Post-exposure seroconversion rates as high as 80%
have been reported in healthy volunteers [41],
although others suggest lower rates of 30% [42]. Rates
have decreased significantly since the use of anti-D im-
munophylaxis for RhD-negative pregnant women.

Allo-immunisation can be minimised by more
extensive matching in transfusion-dependent popula-
tions at high seroconversion risk. LaSalle-Williams et al.
[12] reported reduced allo-immunisation rates from
34% to 4% (7% if RhD mosaics were included) with this
approach. Immune provocation is important in sickle
cell disease, as a delayed transfusion reaction may pre-
cipitate a vaso-occlusive crisis or potentially fatal hyper-
haemolysis syndrome [43, 44]. Broadening the ‘better
match’ strategy is not yet known to be cost-effective in
lower-risk populations. Meanwhile, leukoreduction has
not affected red cell allo-immunisation rates [45].

Allo-immunisation to other blood product anti-
gens, such as human leukocyte antigen or human
platelet antigen, may provoke other sequelae such as
platelet refractoriness, post transfusion purpura, febrile
non-haemolytic transfusion reactions, TRALI, and allo-
graft rejection [46].

Non-haemolytic immunological
response to transfusion
A febrile non-haemolytic transfusion reaction is
defined as a >1°C rise in temperature and/or rigors/
chills with or without other symptoms such as nausea
or discomfort not attributable to other causes. These
were the most frequent adverse events reported in
Australia and New Zealand [18, 47]. Reporting rates
vary widely, but occur in approximately 1 in 300 red
cell transfusions and 1 in 20 platelet transfusions [48].

Two mechanisms may account for such a response
to transfusion. Soluble factors in the supernatant may
be pyrogenic, including cytokines released during stor-
age, particularly at room temperature [49, 50]. Lin
et al. [51] demonstrated higher levels of IL-6 and -8 in
post-red cell patients, including baseline IL-6 levels in
cases vs controls, although cytokine levels did not vary
accordingly in transfused products. Alternatively, reci-
pient leuko-agglutinins interact with donor antigens
[50], thereby explaining lower rates with pre-storage
leukoreduction [52, 53]. Febrile non-haemolytic
transfusion reactions are not dangerous, but are
uncomfortable for the patient and may result in the
early discontinuation of a transfusion.

King et al. [52] demonstrated a reduction of feb-
rile non-haemolytic transfusion reactions following
pre-storage leukodepletion from 0.37% to 0.19%. Yazer
et al. [53] also observed a reduction in red cell and
platelet responses (0.33% to 0.19% for red cells and
0.45% to 0.11% for platelets). Many centres premedi-
cate the patient to further decrease risk, although this
practice may be declining [54] as many question its benefit [48].

**Allergic reactions**

Allergic reactions vary from mild urticarial skin rashes to life-threatening anaphylaxis. Their incidence varies between 1% and 3% [48]. In a single-institution series examining adverse events, 17% were allergic with 1.3% anaphylactic [55]. Overall, severe allergic reaction frequency was 1 in 53 612 components (highest for platelets and lowest for red cells). Anaphylaxis accounted for 5% of transfusion-related fatalities in the US between 2009 and 2013 (nine cases overall and none in 2013 [19]).

Several mechanisms can explain allergic reactions: passive donor allergens or anaphylatoxins; passive donor IgE, host or donor anti-IgA IgG; and other activators, such as biologic response modifiers, of complement or mast cells [56]. Wild-type plasma proteins may sensitise recipients with inherited deficiencies or variations therein. For example, IgA-deficient recipients may develop anti-IgA IgG antibodies capable of reacting with IgA [57, 58]. It is unclear why anti-IgA IgG sensitisation occurs in those without known exposures [59]. IgA deficiency varies in different populations; up to 1 in 300 in the US or Canada and 1 in 32 000 in Japan [59]. IgA-mediated anaphylaxis is rare, with incidence estimates hampered by the lack of standardized diagnostic criteria or laboratory tests relevant to allergy testing [60], such as histamine and tryptase quantification or assays for basophil activation [61]. Analogous inherited protein deficiency that may act as a passive donor allergens include haptoglobin [62, 63], C4 and Von Willebrand factor [64].

Transfused anti-IgA IgG within IgA deficient donors could theoretically cause reactions in non-IgA deficient recipients. However, increased rates of allergic reactions have not been seen when IgA deficient donor products are used, implying that dilution of IgG in the recipient reduces the risk [65, 66].

Methylene blue has been reported to cause anaphylaxis [67], and this is relevant in countries using this agent for pathogen inactivation. Food allergens conveyed by the donor may also play a role, as suggested in a case [68] of peanut protein initiating anaphylaxis in a recipient with the allergy, although the protein was not tested for and some refute the veracity of this claim [69]. Transfusion of allergens may be more likely to induce an allergic reaction in atopic recipients via primed mast cells and basophils [70].

Conversely, passive transfer of IgE from donor to recipient can occur, with harm if the protein is subsequently ingested. The half-life of IgE in plasma is relatively short (1.1 days), but once bound to a mast cell or basophil it may persist for up to 7 weeks [71]. Arnold et al. [72] describe this scenario in a recipient of two units of plasma, whose peanut ingestion 2 days later met with anaphylaxis. Peanut-specific IgE was found, with a normalising disappearance 3 months later and a non-reactive peanut re-exposure. The donor was found to be peanut allergic and further product collection/component preparation demonstrated that the IgE level was unaffected by storage. Similar reports followed [73]. IgE antibodies to common food substances were found in 2.2% of Norwegian and 11.1% of Swedish blood donors. Note was made in this study of peanut allergy frequency and quality, in that over a quarter of those with anti-peanut IgE had moderate to high levels [74].

Domen et al. [55] found storage-dependent biological response modifiers associated with allergic reactions after observing five events in autologous donations and a disproportionate amount in platelet transfusions [75]. However, Savage et al. [76] concluded that recipient and donor factors are more important than product factors in allergic pathogenesis. Indeed, rates have not changed with leukoreduction [52].

**Transfusion-related acute lung injury**

Transfusion-related acute lung injury was once thought to be a rare complication, but it is now recognised as a leading cause of transfusion-related morbidity and mortality [20, 77–80]. In 2004, the US National Heart, Lung and Blood Institute Working Group formulated a definition for TRALI (Table 2) [77, 78]. Transfusion-related acute lung injury remains under-reported due to incomplete acceptance of this definition and the voluntary nature of haematovigilance [81–83]. UK case review also incorporates correlative serology [84].

The incidence of TRALI is between 0.08% and 15% [85]. It has decreased in the UK, with 11 suspected cases in 2012 (none fatal), compared with 36 suspected cases and 7 deaths in 2003 [34]. However, it remains a leading cause of US transfusion fatalities [80].
A proposed mechanism for TRALI is the 'two hit' model [86, 87]. The first hit lies in the extent to which host neutrophils are activated and marginated on pulmonary endothelium. Transfusion introduces the second 'hit' in an antibody- or non-antibody-mediated manner. In the former, passive transfer of donor antibodies against Human Leukocyte Antigens (HLA) or Human Neutrophil Antigens (HNA) react with targets in the recipient or, less commonly, leuko-agglutinins in the recipient react with donor leukocytes (revers-TRALI). There are several reported cases of reverse TRALI, but this is now rare through pre-storage leukoreduction [86]. High-titre, cognate encounters do not guarantee TRALI, and antibody-negative TRALI cases occur, thereby suggesting alternative mechanisms, such as pro-inflammatory mediators, as the second hit.

The second hit arises from transfusion factors. It is dose-dependent and typically associated with plasma, although low volumes of plasma, such as the quantity within red cell units (2–100 mL), cryoprecipitate, and intravenous immunoglobulin [88] may be sufficient to cause TRALI. A threshold model [86] describes who does, or does not, develop TRALI [88, 89].

Manifestations of TRALI include dyspnoea, hypoxaemia and hypotension. There may be a transient leukoneutropenia and then leucocytosis. Nearly all patients require supplementary oxygen and up to 70% require ventilatory support [90]. Symptoms usually resolve within 72–96 h. Mortality is estimated at 10–15% [84, 91].

The mainstay of prevention is transfusion avoidance. Given that anti-HNA and anti-HLA antibodies occur at higher frequency in multiparous females [92, 93], implementation of male-only plasma in component therapy began in the early 2000s, with the UK starting in 2003. The incidence of TRALI has decreased markedly in these risk-mitigating nations [94], prompting attempts to minimise plasma in cellular components. Because male-only plasma restrictions may reduce supply, some propose either reactive exclusions (only excluding donors implicated in TRALI) or proactive exclusions (multiparous females, those previously transfused or those with leukocyte antibodies). Most often, female plasma is subjected to fractionation (except in the UK [84]) for production of albumin and immunoglobulin. Leukoreduction reduces TRALI incidence [95], as does solvent detergent plasma [94, 96]). Controversially and less practically, washed and/or fresh products may be considered.

Transfusion related immunomodulation

Transfusion related immunomodulation is often cited as a non-infectious consequence of transfusion and yet its mechanism remains unclear. It was first deliberately exploited in renal transplantation through the anti-rejection effects of non-leukoreduced red cell transfusions [97]. Subsequently, observations of immunosuppression and/or cancer recurrence led to abandonment of this tactic [98].

Transfusion related immunomodulation probably results from cell-mediated and humoral hits in stored red cells. There may be limits to what factors can be attenuated by pre-storage leukoreduction due to other byproducts in red cells (e.g. lipopolysaccharides and free iron) [99]. Postoperative clinical consequences of TRIM may result in increased morbidity due to infectious complications and cancer recurrence [100].

Red cell storage lesion

Red cells can be stored at 4 °C for 21–42 days according to preservative solution. This allowable duration of storage is based on FDA-defined criteria for red cell
integrity, i.e. free hemoglobin < 1% and 75% ± 9% of re-transfused red cells recoverable 24 hours later in healthy volunteer blood donors [101]. The storage lesion reflects changes that occur during refrigeration with biochemical membrane changes (i.e. phospholipids, proteins and lipid peroxidation), and increased red cell fragility, as well as biochemical changes within the red cell rendering it less capable of its own maintenance (e.g. 2,3 DPG depletion, ATP depletion, loss of nitric oxide). Additionally, free iron and leukocyte-derived inflammatory cytokines accumulate (e.g. IL-6 and TNF) [99].

Older red cells may be less effective at oxygen delivery, while introducing immunological stress. Evidence for detrimental outcomes with older blood include observational data in critical care [102], trauma [103], liver transplantation [104, 105], breast reconstruction [106], cardiac surgery [107, 108] and cardiology [102, 109]. However, there is evidence challenging this association [110–112] and other data showing that fresh red cell-associated harm [113]. The temporal relationship between transfusion and morbidity is complicated and storage effects are best resolved by randomised trials. Ongoing studies include those on inpatients [114], cardiac surgery (www.clinicaltrials.gov NCT00458783, NCT00991341, and NCT00458783), abdominal surgery (NCT01914328), paediatric intensive care (NCT01977547 and NCT01586923), and adult intensive care (NCT01638416 and NCT01638416).

**Prestorage leukoreduction**

Prestorage leukoreduction leaves a leukocyte count of < 5 x 10^6 per unit (99.9%, or a 3 log, reduction). This nearly eliminates the risk of leukotropic virus transmission such as cytomegalovirus [115] or Epstein-Barr virus [116], while reducing HLA allo-immunisation [117]), and bacterial or parasitic contamination [118, 119]. Some evidence suggests a decrease in the risk of TRALI and transfusion-related acute circulatory overload [95]. It may also reduce TRIM, although the association with postoperative infections, multi-organ dysfunction and death is less clear [120, 121]. Whilst prestorage leukoreduction is mandatory in Canada and most of Europe, it is only recommended by the FDA in the USA, reflecting the lack of definitive risk-cost benefit evidence [122].

**Infectious complications**

Postoperative infections are a major burden to the healthcare system and patient recovery. Reducing the risk of hospital-acquired infections is considered very important today, with measures including appropriate antibiotic prophylaxis, hand-washing, and minimising use of urinary catheters and drains. Such efforts are included in programs dedicated to enhancing surgical recovery [123, 124]. Early retrospective evidence showed a strong association between infectious complications and red cell transfusion [125]. One explanation for such findings is confounding by the indication for transfusion, e.g. anaemia in a patient with tachycardia and pre-existing infection. The most compelling evidence for an association derives from a meta-analysis of restrictive vs liberal transfusion strategies that included 18 randomised trials with 7593 patients [100]. Restrictive protocols usually withhold transfusion until Hb < 70 g.l^-1 while liberal ones maintain Hb > 100 g.l^-1. With serious infection, the risk ratio for association between restrictive protocols and severe infection was 0.82 (95% CI 0.72–0.95). The number needed to treat as such to avoid a serious complication was 38 [100]. Interestingly, the benefit of restrictive transfusion practice was not lost by leukoreduction, suggesting that it is either ineffective or that leukocyte-independent mechanisms of immunomodulation also play a role.

**Cancer recurrence**

It is difficult from retrospective surgical populations to determine how red cell transfusion affects cancer recurrence because of confounding factors related to resection and transfusion need [126]. The more difficult the resection, the greater the need for red cells and the greater the odds of an extensive or residual cancer. A Cochrane review found a pooled estimate of cancer recurrence at 1.42 (95% CI 1.20–1.67), although whether transfusions suppress anti-cancer immune-surveillance remains speculative [127].

**Solid organ transplantation**

Human leukocyte antigens (HLA) allo-immunisation with red cells in those awaiting transplantation is an important concern. However, red cells are inconsistently immunogenic with 10–30% developing HLA antibodies with ≤ 20 transfusions [128]. In contrast, the rate is
< 2% in male donors regardless of transfusion history [129, 130]. Despite low seroconversion risk with red cells, once present, HLA antibodies call for complex and cumbersome desensitisation to minimise allograft rejection.

**Transfusion-associated graft vs host disease**

Transfusion-associated graft vs host disease is a rare, but usually fatal complication of blood transfusion. Three factors are important in its pathogenesis: immune integrity of recipient; degree of HLA similarity between donor and recipient; and number of active T-cells introduced – it is higher with fresh and/or non-leukoreduced blood [131]. Donor T-cells are usually destroyed by host defense mechanisms and cleared within days [132]. However, destruction of donor T-cells may not occur if the recipient is immunocompromised or if the donor T-cells are not recognised as foreign because of their similarity with recipient epitopes. In either case, failure to recognise identifiable foreign epitopes, as in the case of HLA homozygous haplosimilar donors in relation to heterozygous recipients, permits donor lymphocyte escape. The donor T-cells recognise the recipient’s tissues as foreign and mount an attack on the recipient. This may be seen with directed donation between relatives, with HLA-matched platelets, or in populations with reduced genetic diversity where a close HLA match is more likely between a recipient and a random donor, e.g. in Japan [133]. The incidence is unknown, especially in the immunocompetent, but is estimated to be between 0.1% and 1% in susceptible individuals [132–134]. Transfusion-associated graft vs host disease is probably under-recognised and misdiagnosed as sepsis or a drug reaction [135, 136]). The UK SHOT report reported 13 cases between 1996 and 2001, with no further cases until 2009 [34]. Virtually no cases were reported since pre-storage leukoreduction was introduced in the UK in 1999, despite mitigation failures such as missed irradiation [34, 84]. Clinical manifestations include fever, rash, hepatitis, and diarrhea 1–2 weeks after transfusion, although onset may be delayed by as much as three months [137]. Pancytopenia follows, and mortality is high (>90%), due to overwhelming sepsis. Management options are few and successful treatment is rare [138]. The emphasis is therefore on prevention by avoidance or irradiation of cellular products in at-risk patients (Table 3) [134]. Increasing regulation regarding caesium source irradiators because of concern over terrorist activity has led to a search for alternative strategies, such as pathogen reduction [139].

### Table 3 Risk factors for transfusion-associated graft vs host disease.

<table>
<thead>
<tr>
<th>Significantly increased risk</th>
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<tbody>
<tr>
<td>Congenital immunodeficiency syndromes</td>
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<td>Bone marrow transplantation (allogeneic and autologous)</td>
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<tr>
<td>Transfusions from blood relatives (directed donations)</td>
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<tr>
<td>Intra-uterine transfusions</td>
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<tr>
<td>HLA-matched platelet transfusions</td>
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<tr>
<td>Hodgkins disease</td>
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<td>Patients treated with purine analogues</td>
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<table>
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<td>Acute leukaemia</td>
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<td>Non-Hodgkin’s lymphoma</td>
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<td>Solid tumour treated with intensive chemotherapy or radiotherapy</td>
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<td>Exchange transfusions</td>
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<td>Preterm infants</td>
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<td>Solid organ transplant recipients</td>
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<table>
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<tr>
<th>No perceived increased risk</th>
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<tbody>
<tr>
<td>Healthy newborns</td>
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<tr>
<td>Patients with AIDS</td>
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HLA, human leukocyte antigen; AIDS, acquired immunodeficiency syndrome.

### Conclusion

Immunological consequences of blood transfusion may not be trivial. The risk of harm and inventory stewardship compel increasingly conservative practices. Measures to reduce transfusion include pre-operative optimisation, intra-operative blood conservation, and postoperative considerations. Immunological consequences of transfusion should be factored into all transfusion decisions and subsequent review of any post-transfusion sequelae.

### Competing interests

No external funding or competing interests declared.
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