Red-cell transfusion – risks and benefits - part 1 of 2

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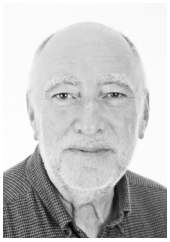

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Although often of life-saving benefit, transfusion of donated red cells is associated with considerable potential risk for the recipient patient.

This article, directed at healthcare professionals without any particular transfusion expertise, outlines these risks and the measures taken to minimize them.

Particular attention will be paid to the two most significant risks: transmission of serious blood-borne infection and the potentially fatal acute immune hemolytic reaction that occurs if patients receive ABO-incompatible red cells.

Other significant adverse effects will be discussed briefly. The focus of a second article will be the ongoing research that is defining more precisely those patients who are most likely to benefit from red-cell transfusion.

One aspect of this research, measuring outcome following transfusion, is providing evidence that many patients may be exposed to the risks of transfusion without any real benefit.

A list is abbreviations is found at the end of the article.

Transfusion of whole blood is rarely justified. Rather than whole blood, the components of blood are utilized individually.

Of all blood components, red cells are by far and away the most frequently prescribed, so that, although they are not strictly speaking synonymous, the terms blood transfusion and red-cell transfusion are often used interchangeably.

It is usual to classify the many adverse effects associated with transfusion of blood products to one of two broad etiological groups: immune and non-immune. In essence, the immune reactions result from transfusion

of donated blood products that the recipient patient's immune system "*sees*" as foreign.

Non-immune adverse events include those that result from transmission of an infective agent, present in donated blood. These are the transfusion-transmissible infections (TTIs).

Transfusion-transmissible infections

Viruses

The two most significant risks are: liver disease (viral hepatitis, evolving to cirrhosis and liver cancer) caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), and acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency viruses (HIV-1 and HIV-2).

Human T-cell leukemia viruses (HTLV-1 HTLV-2) can also be transmitted via blood.

Although infection with HTLV is usually asymptomatic and of little significance, a small proportion (around 5 %) of those infected develop serious illnesses, including adult T-cell leukemia, infective dermatitis and serious inflammation of the eye (uveitis) [1].

Cytomegalovirus (CMV) is a blood-transmissible virus. Infection with CMV is common and invariably asymptomatic. However, in neonates and those who are immunocompromised (e.g. AIDS patients) CMV infection is associated with serious morbidity (pneumonitis, hepatitis and retinitis progressing to loss of vision).

The only other two blood-transmissible viruses of note are Epstein-Barr virus, the cause of infectious mononucleosis and parvovirus 19, a common usually benign infection, except for those who are immunocompromised and those with sickle cell disease [2].

Novel viruses continue to emerge. In very recent times, the severe acute respiratory syndrome (SARS) virus and avian flu virus have provided cause for concern. Continued vigilance and research is necessary to identify and assess the significance of novel viruses for transfusion medicine [3].

West Nile Virus (WNV), a virus carried by mosquitoes and transmitted to humans by mosquito bite, provides a salutary lesson [4]. This virus was not present in the Northern Hemisphere before 1999, when the first cases of infection were identified.

Over the intervening five years the virus quickly spread and it is now endemic in many parts of North and Central America. By 2002 it was clear that the infection could also be transmitted via blood transfusion.

Although WNV infection is usually asymptomatic, some develop a self-limiting feverish illness. The condition has proved fatal in a small minority of predominantly elderly people. In just six years, WNV has emerged as a significant and permanent threat to the safety of the blood supply in the US, Canada and Central America.

Bacteria

The transfusion of blood infected with a significant virus (e.g. HCV, HIV) has no symptomatic effect in the short term; indeed, in some instances a clinical effect will not be evident for years.

By contrast, the effect of transfusing bacterially contaminated blood products is usually evident during the transfusion [5]. Early signs and symptoms include rigors, pyrexia and hypotension.

If sepsis intervenes, rapid clinical decline and death due to multiple organ failure may result.

Bacteria may be present as a result of low-grade, asymptomatic infection of the donor at the time of donation. Alternatively, environmental bacteria or bacteria normally present on the skin of the donor may be introduced during the collection process.

Many bacterial species, both Gram negative and Gram positive, have been implicated in particular cases [6].

Protozoa

Red-cell parasites of the Plasmodium species (P. falciparum, P. ovale P. vivax and P. malariae), which cause malaria, are the most significant protozoa to significantly threaten the safety of the blood supply [7].

If donated red cells containing these parasites are transfused, malaria is transmitted. In some parts of the world, other blood-transmissible protozoa (e.g. Trypanasoma cruzi, the cause of Chagas disease, and Toxoplasma gondi, which causes toxoplasmosis) are also significant.

Prion particles

Prion particles are the infective agent responsible for bovine spongiform encephalopathy (BSE) and its human counterpart, new variant Creutzfeldt-Jakob disease (nvCJD).

This is an untreatable neuro-psychiatric disease that invariably progresses to lethal dementia, and which is widely supposed to be caused by eating meat from cattle suffering bovine spongiform encephalopathy (BSE) [8].

The notion that prion particles are transmissible via blood and that nvCJD is therefore a transfusion-transmissible disease has been a concern for some years, particularly in countries like the UK where there have been serious outbreaks of BSE and where the prevalence of nvCJD is highest.

However, the real significance of prion disease for transfusion medicine remains unclear at the present time; two cases of "*probable*" transfusion-transmitted nvCJD have been described to date [9, 10].

Immune reactions to red-cell transfusion

ABO incompatibility – an acute immune hemolytic transfusion reaction

The surface of red cells is covered with inherited antigens. Immune hemolytic transfusion reactions occur if the recipient patient's plasma contains significant antibodies to antigens present on the surface of donated red cells. Antigen/antibody binding causes red-cell destruction (hemolysis). The reaction may be acute, i.e. arising during or very soon after the transfusion, or delayed. The most serious are the acute reactions, which can arise after transfusion of just a few milliliters of red cells.

In almost all cases these serious, potentially fatal reactions are due to ABO blood group incompatibility.

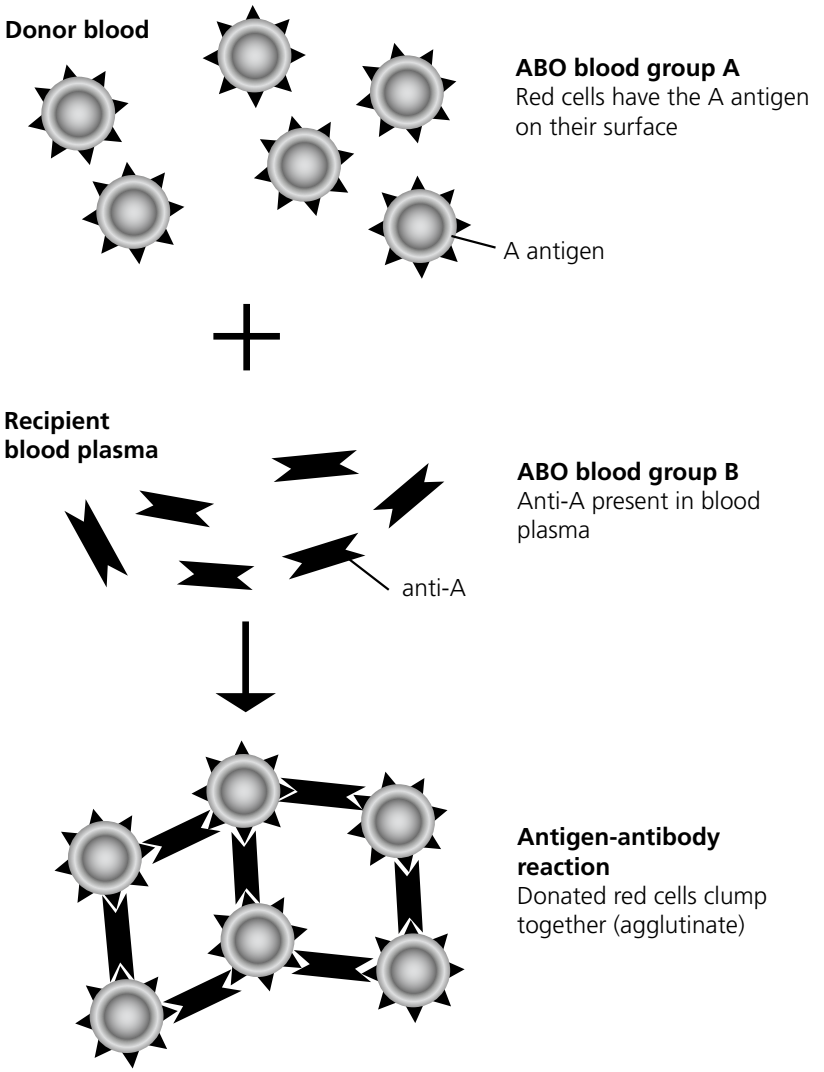
We all belong to one of four groups of the ABO blood group system determined by the presence or absence of two inherited red-cell antigens A and B. Those whose red cells bear the A antigen belong to blood group A, and those with the B antigen belong to blood group B. Those who belong to the third group, AB, have both A and B antigens on the surface of their red cells, whilst those who belong to Group O have neither A nor B antigens on their red cells.

The crucial importance of the ABO blood group system for transfusion medicine is that unlike nearly all other red-cell antibodies, those directed at the antigens of the ABO system are naturally occurring and also highly immunogenic.

This means that circulating in everyone's blood plasma are strongly reacting antibodies to the red-cell antigen(s) of the ABO system that we lack. Thus those who have the A antigen on the surface of their red cells and belong to blood group A have the antibody directed at the B antigen, anti-B, in their plasma. Those who are blood group B have anti-A in their plasma.

Those who are blood group O have anti-A and anti-B in their plasma and those who are blood group AB have neither anti-A nor anti-B in their plasma.

An ABO acute hemolytic transfusion reaction will inevitably occur if plasma of the recipient patient contains antibodies (either anti-A or anti-B) to A or B antigens present on the surface of the donated red cells. FIGURE 1 describes such a reaction.



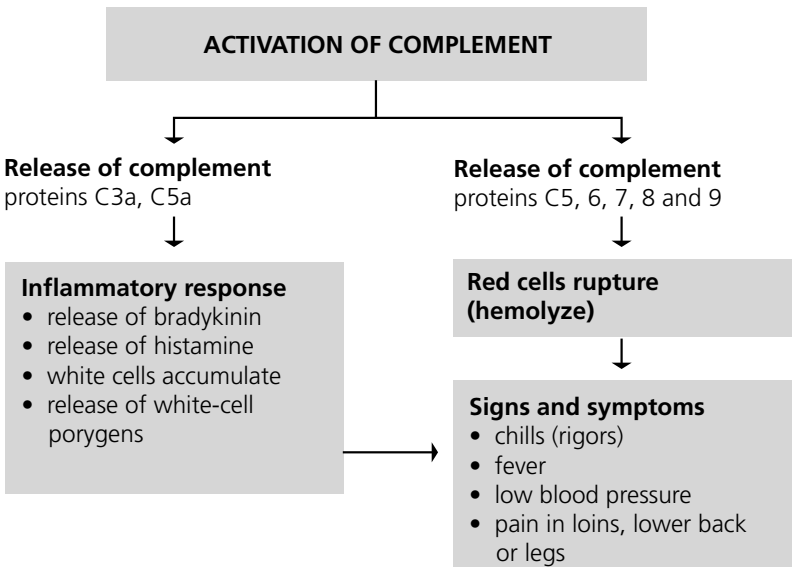


FIGURE 1

In this case, group-A red cells are transfused to a recipient patient who is blood group B and therefore has anti-A circulating in plasma.

Antigen/antibody binding causes red-cell agglutination and activation of the complement protein cascade.

Complement proteins C3a, C4a and C5a are released to plasma. These proteins are responsible for many of the systemic effects of AB-incompatible transfusion reaction, which include fever, rigors, breathlessness, reduction in blood pressure, flushing of the face and pain in loins and legs.

Pro-inflammatory cytokines (e.g. IL-1 and IL-6) released from activated white cells are a contributory cause of these florid signs and symptoms. Complement-mediated intravascular hemolysis (red-cell destruction) causes release of hemoglobin to plasma, which is excreted in urine.

The most significant clinical effects of ABO-incompatible transfusion are hypovolemic shock leading to acute renal failure, and disseminated intravascular coagulation (DIC), a condition characterized by depletion of plasma coagulation factors, which leaves affected patients at risk of severe life-threatening hemorrhages.

In short, ABO incompatibility causes an immediate (acute) severe transfusion reaction, which is potentially fatal if the transfusion is not halted and medical treatment started immediately [11].

Other immune hemolytid reactions

Unlike anti-A and anti-B, which are naturally occurring, almost all other significant red-cell antibodies are immune antibodies and are only present in the plasma of those who have been exposed to red cells bearing the relevant "*foreign*" antigen during previous transfusion or pregnancy.This means that those who have no

previous transfusion history and have never been pregnant are highly unlikely to suffer an immune hemolytic transfusion reaction, so long as they are given ABO-compatible red cells.

In general, hemolytic transfusion reactions caused by secondary or "*atypical*" red-cell antibodies are less severe because, in general, they are not associated with activation of the complement cascade. Destruction of red cells is thus not complement mediated.

Instead, antibody-coated red cells are removed from circulation and destroyed by macrophages in the spleen (extravascular hemolysis).

The reaction is delayed, so that typically there are no signs during the transfusion save possibly a slight increase in temperature. However, anemia and jaundice consequent on red-cell destruction occur during the ten days following transfusion [11].

A range of red-cell antibodies may precipitate such a reaction, including anti-D, anti-c, anti-E and anti-e, all directed at antigens of the Rh blood group system; anti-K (antibody directed at antigens of the Kell blood group system); anti-Dfy (antibody to antigen of the Duffy blood group system) and so on.

It is important that patients whose plasma contains any of these antibodies are not transfused with red cells bearing the relevant antigen.

Non-hemolytic immune effects

Febrile non-hemolytic transfusion reaction

This is a relatively common but mild reaction among patients who have had previous transfusions and as a result developed antibodies to HLA antigens present on the surface of transfused white cells.

If the same antigen is present on white cells subsequently transfused, antibody/antigen binding causes activation of white cells and release of cytokines, which cause mild and self-limiting symptoms (pyrexia, chills and headache) within 30-60 minutes of starting transfusion.

Transfusion-related acute lung injury (TRALI)

This is a much more serious condition with a mortality rate of around 10 %. It is caused by the presence of antibodies in donor plasma directed at antigens present

on recipient patient's white cells.

Agglutinated white cells, sequestered in the microvasculature of the lungs, release a range of toxic products that damage the endothelial lining of these vessels. The most significant consequence is pulmonary edema and acute respiratory distress, which can be either rapidly fatal or resolve almost as quickly.

Symptoms, which begin within an hour or so of transfusion, include breathlessness, coughing, rigors and fever. Severe hypoxemia is usual [12].

Allergic reactions

Mild allergic reactions to a variety of donated plasma constituents are common, occurring in 1-2 % of all transfusions. They are manifest as a red itchy skin rash within an hour of starting transfusion; anti-histamine treatment is effective in such cases.

Rarely, potentially fatal systemic allergic (anaphylactic) reactions occur; patients with IgA deficiency are particularly vulnerable. Dramatic effect may be seen after transfusion of just a few milliliters. Signs and symptoms include flushing of the skin, hypotension, nausea, abdominal pain, respiratory distress and cyanosis.

Rapid treatment response is vital for survival in these extreme, but rare allergy cases.

Other miscellaneous adverse effects of red-cell transfusion

Circulatory overload is a complication of transfusing blood products too rapidly to patients with pre-existing cardiac or pulmonary insufficiency. Resulting hypervolemia causes hypertension and pulmonary edema. Symptoms include breathlessness, cyanosis and coughing. A slow rate of transfusion prevents symptoms.

Iron overload is a potential problem for patients who require repeated red-cell transfusion over a prolonged period (years). Each unit of packed red cells contains 250 mg iron. Since there is no physiological means of excreting excess iron, it can accumulate in tissues causing long-term damage to many organ systems.

Such patients require preventative iron-chelating therapy.

Potassium leaks from red cells to plasma during storage, so that there is a transitory risk of raised plasma potassium (hyperkalemia) and consequent cardiac arrythmia (including cardiac arrest), particularly for patients who are given red cells that are close to expiry date.

Minimizing the risk of transfusion-transmitted infection

Measures taken to minimize the risk of transfusion-transmitted infection can be addressed under four main headings:

- Donor selection
- Laboratory testing of donated blood for evidence of infection
- Collection and storage of donated blood
- Leukodepletion

Donor selection

Rigorous exclusion from blood donation of all those whose clinical and lifestyle history indicate that they could be harboring a blood-transmissible infectious agent is the first and probably most significant measure taken to prevent transfusion-related infection.

All potential donors, for example, are given information about lifestyle activities that are known to be associated with high risk of HIV, HBV and HCV infection, and specifically asked to exclude themselves if they belong to a "*high-risk*" group.

Recent travel to parts of the world where blood-transmissible infections (e.g. malaria) are endemic may also preclude donation.

Those who have recently suffered symptoms suggestive of infectious disease may be deferred or permanently

excluded from donation. The criteria for selection are continuously reviewed in the light of perceived threats to the safety of the blood supply.

For example, last year in response to the threat that nvCJD poses to the safety of the blood supply in the UK, a decision was made to exclude from blood donation all those who had received a blood-product transfusion since 1980.

Laboratory testing of donated blood for evidence of infection

Every unit of donated blood undergoes mandatory testing for evidence of past or present infection with the most significant transfusion-transmissible viruses: HIV-1, HIV-2, HBV, HCV, HTLV-1 and HTLV-2.

In the US, WNV has recently been added to this list. The only other universally applied test is one for evidence of present or past infection with the bacteria that causes the sexually transmitted disease syphilis.

If testing proves positive, the affected unit is withdrawn and the donor permanently excluded from further donation.

Until recently, these tests have been based almost exclusively on detecting antibodies in blood plasma to the relevant virus. This approach has an important limitation: there is a time window of variable length between infection and measurable antibody response.

This, of course, means that in a very small minority of donors who have only recently been infected, the antibody test may be negative. A new generation of tests (nucleic acid amplification technology, NAT) based on detecting virus-specific RNA overcomes this problem.

NAT is technically more demanding and also considerably more expensive but is now being selectively used to supplement antibody testing of donated blood [13]. When applied, NAT testing has the effect of increasing the number of infected donations detected and thereby reducing the risk of viral-transmitted infection.

In the UK, mandatory NAT testing is only applied at the present time for detection of HCV infection, whereas in the US current policy is to use the new technology for detecting HCV, HIV and WNV infection.

Collection and storage of donated blood

There are currently no routinely performed tests for detection of bacteria in donated blood. The most significant measures for reducing the risk of transmitting a bacterial infection during transfusion are those protocols dealing with the collection and storage of donated blood.

Scrupulous aseptic technique during collection of blood reduces the risk of bacteria present in environment or on the skin of the donor infecting donated blood.

Recent research has demonstrated that by discarding the first 15 mL of donation, the risk of bacterial contamination is further reduced [14].

Such measures have no effect in preventing bacterial infection of blood that may be present as a result of transient asymptomatic bacteremia of the donor at the time of collection.

However, after collection, red-cell concentrates are stored at a temperature (4 oC) that inhibits growth of most bacterial species, and in any case blood has bactericidal properties that continue to operate during storage.

There are some species of bacteria (e.g. Yersinia, Pseudomonas) that can grow at the temperature blood is stored so that these pose a particular threat [15].

The longer red cells are stored, the greater the risk of bacterial contamination.

This is part of the reason that all blood products have an expiry date. Pretransfusion checks are important for prevention of bacteria-transmitted infection. These include: a visual inspection of the red-cell pack for signs (hemolysis, cloudiness) of bacterial contamination, and a check that the expiry date has not passed.

Leukodepletion

Leukodepletion is a filtering process by which most of the white cells (leukocytes) are removed from donated blood. Since 1999, leukodepletion has been applied to all donated blood products in the UK.

This safety measure was introduced in response to the then theoretical risk that nvCJD is transmissible via blood, specifically the white cells in blood. Leukodepletion has other safety-related advantages and has since been adopted by other transfusion authorities around the world.

The additional advantages include reduction in the risk of CMV, because this virus is present in the white cells of infected individuals, and reduction in the risk of non-hemolytic febrile reaction, which is mediated by donated white cells.

Preventing acute and delayed hemolytic reactions

Acute and delayed immune hemolytic transfusion reactions are prevented by pretransfusion tests of donor and recipient blood [16]. The object is to identify any significant red-cell antibodies in the recipient patient's plasma so that red cells bearing none of the relevant antigens can be selected for transfusion. The following tests are mandatory:

- ABO blood grouping of donor and recipient
- Rh D typing (either positive or negative) of donor and recipient
- Red-cell antibody screening of recipient blood plasma

For the vast majority of patients, naturally occurring anti-A and anti-B are the only significant red-cell antibodies likely to be present in plasma, so that of all laboratory tests, determination of ABO blood type of donor and recipient are the most important for the safety of the patient who requires red-cell transfusion.

It is vital that patients only receive red cells that are ABO identical or at least ABO compatible with theirs. ABO-incompatible reactions are potentially fatal and also entirely avoidable.

Apart from ABO testing, it is mandatory to test both donor and recipient for the presence or absence of the Rh D antigen on red cells. Those who are Rh D negative should not receive red cells which are Rh D positive, because they will develop immune antibodies (anti-D) that might cause a hemolytic reaction if they are given Rh D-positive red cells in the future.

A particular threat applies to Rh D-negative women of reproductive age because the presence of anti-D in the plasma of a pregnant woman can cause a condition called hemolytic disease of the newborn, which threatens survival of newborn babies.

An antibody-screening test allows identification of any other significant red-cell antibodies in patient plasma as a result of a previous immunizing red-cell transfusion or pregnancy.

Incidence of adverse effects of red-cell transfusion - how safe is red-cell transfusion

Transfusion-transmitted infection

Measures taken to minimize the risk of HBV, HCV, HIV and HTLV infection during transfusion have been highly successful. The blood supply has never been safer and the theoretical risk of contracting these viral infections during red-cell transfusion is now vanishingly small.

The chance that a unit of donated blood might transmit HIV in the UK is estimated at 0.014 per 100,000 units. The relevant figure for HCV is 0.024 and for HBV 0.176 [17].

In the UK, all incidents of blood-transfusion adverse events are collated in an annual Serious Hazards of Transfusion (SHOT) report. For the five-year period of 1999-2004, SHOT identified just 24 cases of probable transfusion-transmitted infection for all blood products, of which six were viral (two HBV, two HIV, one HTLV and one case of hepatitis E).

There was one case of malarial transmission and the remaining 16 were bacterial (15 during platelet transfusion and just one during red-cell transfusion) [18-22].

ABO incompatibility

The transfusion of ABO-incompatible red cells is avoidable and each case represents system failure invariably involving human error. Every year in the UK, around 2.6 million red-cell units are transfused and on average there are around 24 cases of ABO-incompatible red-cell transfusions (19 cases in 2004).

In most cases, these result in minor or no ill effects, but in up to a third, patients suffer serious morbidity requiring admission to intensive care and rarely (0-2 cases per year in the UK over the past 10 years), patients die as a direct result of receiving ABO-incompatible red cells.

The risk of an ABO-incompatible transfusion is currently estimated to be 1:100,000 and the risk of death caused by transfusing incompatible red cells is 1:1,800.000 [23].

Transfusion-related lung injury (TRALI)

Over the past 5-10 years, TRALI has emerged as a significant cause of transfusion-related morbidity and mortality and in this respect ranks second only to ABO mismatch. The estimated incidence of TRALI is 0.01-0.08 % per plasma-containing unit transfused; associated mortality is 5-14 % [12]. TRALI is more likely to occur as a result of transfusion of platelets and fresh frozen plasma than red cells. In 2004, SHOT identified 13 TRALI cases in the UK. Of these, just two involved transfusion of red cells. The remainder were due to transfusion of other blood products [22].

Summary

Red-cell transfusion is such a commonplace procedure that it is perhaps easy to overlook the risks involved. In the vast majority of cases, red-cell transfusion is completed with no ill effect, but a tiny minority suffer illness as a result of transfusion and very rarely, deaths occur.

All healthcare professionals involved in the complex multistep transfusion process should be aware of the risks involved and the ways in which best practice [24, 25] can prevent or ameliorate adverse effects.

Patients should not be exposed to the risks of transfusion unless best available information suggests that not transfusing poses a greater risk.

Abbreviations

TTI	Transfusion Transmitted Infection
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HTLV	Human T-cell leukemia virus
CMV	Cytomegalo virus
WNV	West Nile Virus
nvCJD	new variant Creutzfeldt-Jakob disease
BSE	Bovine Spongiform Encephalitis
IL-1	Interleukin 1
DIC	Disseminated Intravascular Coagulation
HLA	Human Leukocyte Antigen
TRALI	Transfusion-Related Acute Lung Injury
NAT	Nucleic Amplification Technology

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