Better Blood Transfusion
Level 3

ADVERSE EFFECTS OF TRANSFUSION

Knowledge Base

Effective Use of Blood Group
Scottish National Blood Transfusion Service
2006

Disclaimer

Whilst the information and advice included in this pack is believed to reflect current best clinical practice, neither authors nor publisher can accept any legal responsibility for any errors or omissions.

Effective Use of Blood Group
Scottish National Blood Transfusion Service
Ellen's Glen Road
Edinburgh EH17 7QT
Tel: 0131 536 5962
E-mail: EUB@snbts.csa.nhs.uk

Contents

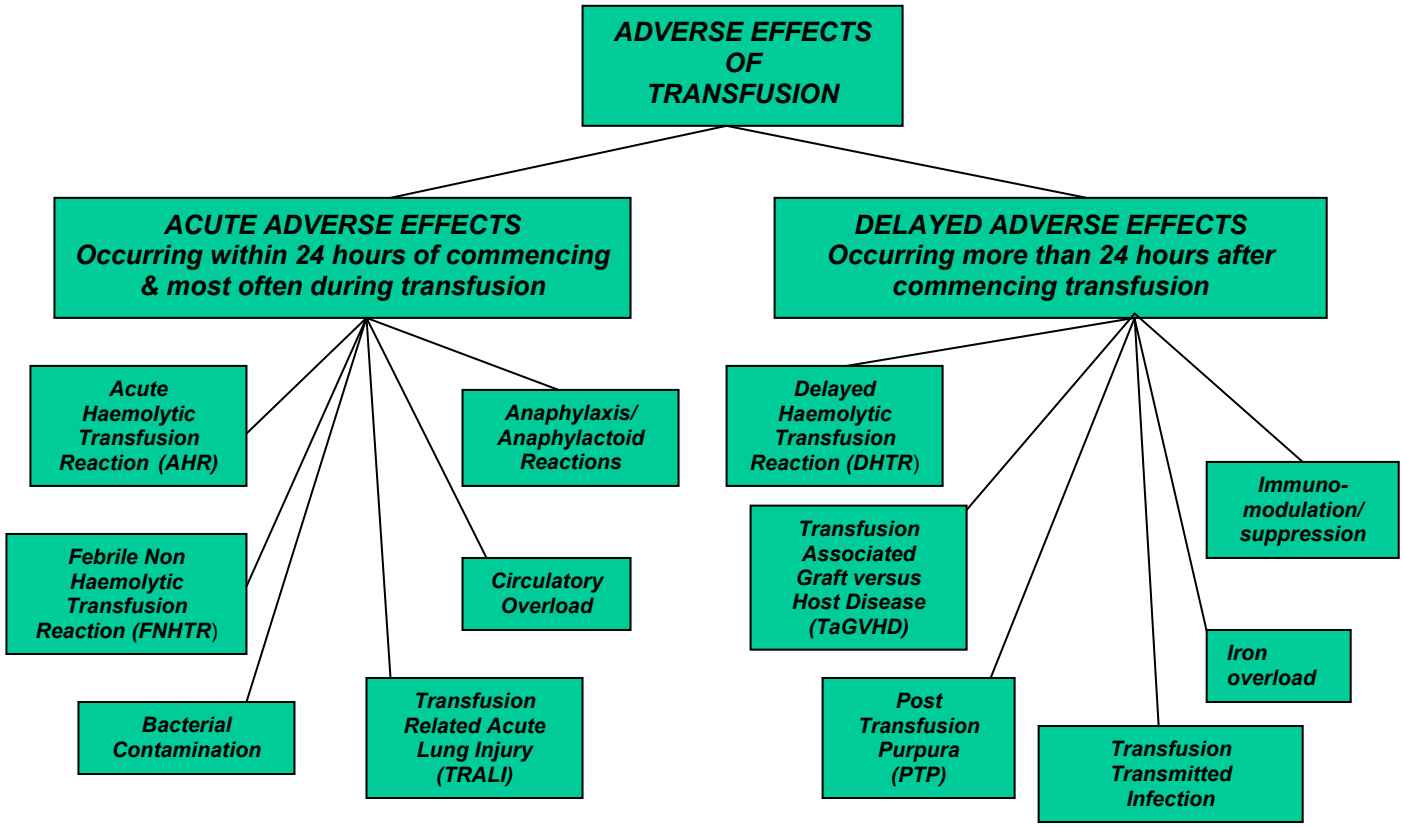
Acknowledgements

Introduction

Transfusion-transmitted infection such as HIV or Hepatitis B or C is perceived by patients to be the greatest risk associated with blood transfusion. In reality, however, SHOT data demonstrate that there is a much greater risk of an individual receiving an incorrect blood component (IBCT) i.e. transfusion of a blood component or plasma product intended for another individual or products which fail to meet patient-specific requirements such as irradiation. Such events are preventable and almost always result from failure to ensure positive patient identification at some point in the transfusion process. These errors usually occur at the time of pre-transfusion sampling or at the collection/administration of the blood components and strict adherence to patient identification procedures throughout the transfusion process undoubtedly reduces such mistakes and improves patient safety.
Transfusion practise can however never be completely risk free as the immunological complications, with the exception of ABO incompatibility, are unpredictable and difficult to prevent.

Any acute transfusion reaction may be life threatening and recognition of early symptoms and signs is crucial as prompt intervention may help reduce the associated morbidity and mortality. When a transfusion reaction does occur, not only is early clinical intervention required, it is also imperative that the Hospital Transfusion Laboratory and, where appropriate, the supplying transfusion centre are informed immediately so that any other potentially affected components can be quarantined and investigated in order to ensure that other patients are not placed at risk.

Figure 1: Adverse effects of transfusion



A

Acute Adverse Reactions

1. Acute Haemolytic Transfusion Reaction (AHR)

1.1 Incidence

ABO incompatible transfusions remain the main cause of severe haemolytic transfusion reactions with 23 reports made to SHOT in 2004, (equivalent to 0.69/100 000 components issued). Other antibody reactions result in an additional 0.4 incidents/100 000 components issued. All of these reactions resulted in significant morbidity with a reported mortality of around 10%.

1.2 Pathogenesis

Several factors influence the course and severity of transfusion reactions:

a. Antibody class and subclass (for IgG).
b. Ability of the antibody to activate complement – IgM is a more potent activator of complement than IgG.
c. Concentration of the antibody.
d. Thermal range of the antibody.
e. The number and density of red cell antigen sites (i.e. the amount of incompatible blood transfused).

A severe AHR due to ABO incompatibility results from intravascular haemolysis following rapid activation of complement. A similar clinical picture can occur with other red cell antibodies which also activate complement such as anti-Kidd (often difficult to detect in pre-transfusion samples) and anti-Duffy antibodies.

In intravascular haemolysis, incompatible transfused red cells react with the patient's anti-A, anti-B or other red cell antibody resulting in complement activation and the generation of C3a and C5a components.

This has two main consequences:

1. Direct interaction with smooth muscle, mast cells and endothelium leading to release of histamine and other vasoactive substances resulting in: platelet aggregation, smooth muscle contraction, bronchospasm, increased endothelial permeability and vasodilatation.
2. Formation of the Membrane Attack Complex (MAC) on the red cell surface. This results in direct intravascular red cell lysis which in turn generates thromboplastin-like substances and disseminated intravascular coagulation.

Antibodies which do not activate complement such as anti-D, anti-E, anti-c and anti-Kell antibodies cause extravascular haemolysis and as a consequence lead to less severe transfusion reactions.

Extravascular haemolysis may occur in the spleen or the liver. IgG_1 and IgG_3 antibodies do not usually fully activate the complement cascade. In this situation, phagocytic mononuclear cells which bear receptors for the Fc fragment of IgG_1 and IgG_3 bind the antibody coated red cells. Normal plasma IgG prevents phagocytic cells binding to IgG_1- and IgG_3-sensitised red cells whilst they are in the circulation. There is however no plasma IgG in the

spleen and splenic macrophages therefore bind to the Fc fragment of the antibody coating the red cells resulting in splenic destruction. On the other hand, cells coated by IgM or IgG antibodies which activate complement to the C3 stage only, adhere to C3b receptors on macrophages present in high concentration in the liver resulting in hepatic extravascular haemolysis

1.3 Symptoms and signs

The correlation between the possible causes of an ATR and the resulting symptoms and signs are shown in Table 1. Note that many of symptoms/signs are non-specific and can result from more than one potential trigger.

Table 1: Possible symptoms and signs of an acute transfusion reaction:

SYMPTOMS				
	Infusion site pain	Myalgia	Dyspnoea	Rigors
AHR	▲	▲	▲	▲
Bacterial Contamination		▲	▲	▲
TRALI			▲	▲
Anaphylaxis/ Anaphylactoid Reaction			▲	
Mild Allergic Reaction				
FNHTR				▲
Acute Circulatory Overload			▲	

SIGNS						
	Pyrexia	Tachycardia	Tachypnoea	Hypotension	Wheeze	Rash
AHR	▲	▲	▲	▲	▲	▲
Bacterial Contamination	▲	▲	▲	▲	▲	
TRALI	▲	▲	▲	▲	▲	
Anaphylaxis/ Anaphylactoid Reaction	▲	▲	▲	▲	▲	
Mild Allergic Reaction						▲
FNHTR	▲	▲				
Acute Circulatory Overload		▲	▲	▲ (hypertension possible)	▲	

In severe reactions exposure to the first few mls of incompatible blood can result in a rapid and very dramatic clinical deterioration due to complement activation and the liberation of anaphylotoxins C3a and C5a but cytokines such as Interleukin 1, Interleukin 8 and Tumour Necrosis Factor also play an important role.

Typically a severe reaction begins with pain at the infusion site and progresses to headache, chest tightness, lumbar pain and rigors. There is accompanying tachycardia, hypotension, pyrexia and tachypnoea.
Renal damage occurs due to a combination of hypotension and haemoglobinuria and may be limited or even prevented by hydration (and diuretic if required) to maintain urine output of >100ml/hr.

1.4 Investigation

Investigations are directed at establishing the cause of an acute severe transfusion reaction and also help in the assessment of severity. The recommended immediate laboratory investigations in a suspected severe acute transfusion reaction are shown in Table 2.

Table 2: Immediate investigations in a suspected acute severe transfusion reaction

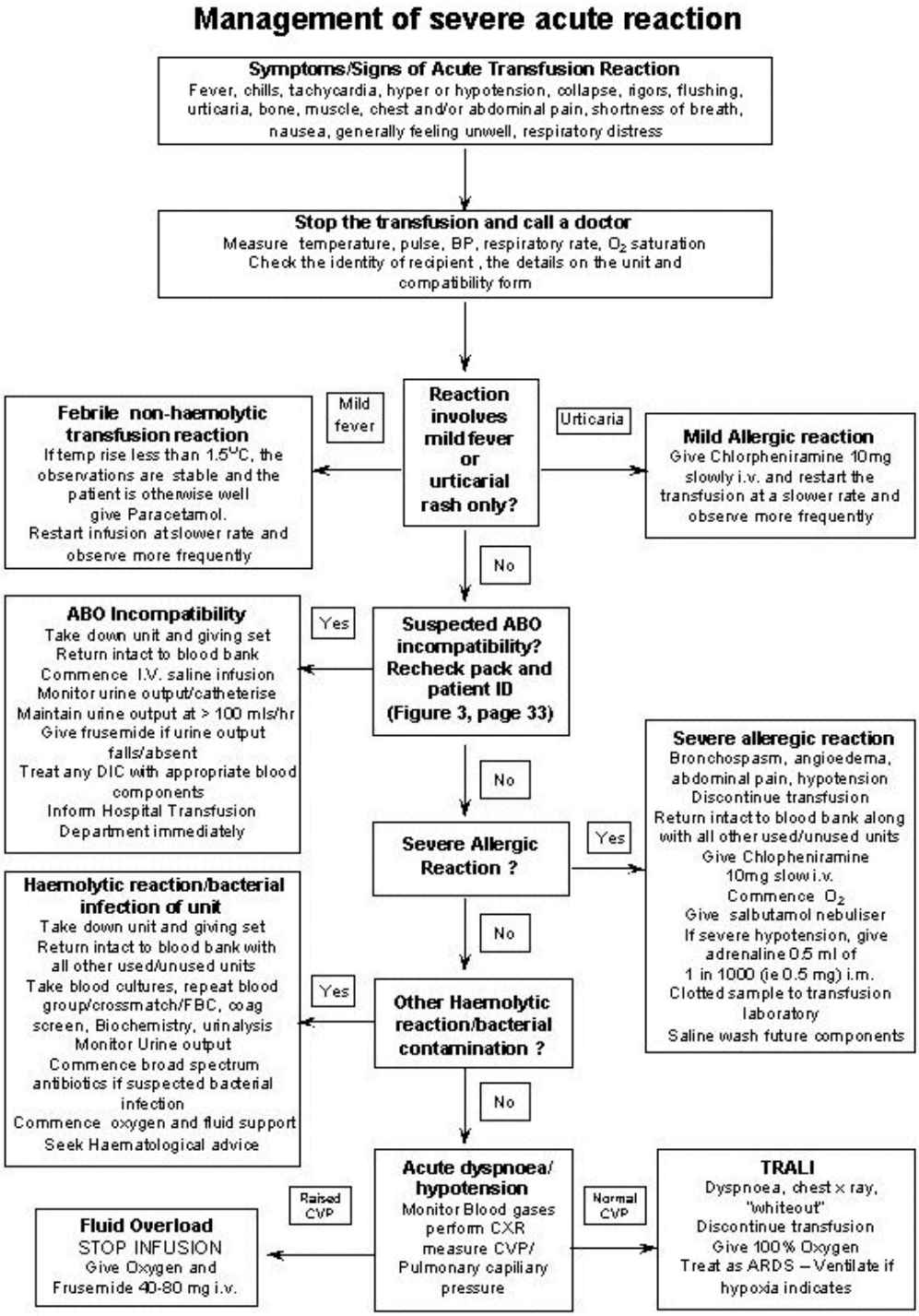
Haematology	Full blood count Coagulation screen including fibrinogen & D-dimers/ FDPs
Transfusion	Direct antiglobulin test (DAT) Repeat blood group, antibody screen & compatibility testing on pre & post transfusion samples
Biochemistry	Urea & Electrolytes Liver function tests Haptoglobins (sometimes performed in haematology lab) Plasma haemoglobin (sometimes performed in haematology lab)
Bacteriology	Blood cultures CRP
Immunology	IgA, anti-IgA and anti-Gm antibodies Mast cell tryptase (Not performed by most labs and not essential. May be useful if anaphylactic/toid reaction. Samples should be obtained at time 0, 3-6 hours & 12-15 hours if possible)
Urine	dipstick testing for haemoglobin (ideally the first voided sample) & if positive this should be formally quantified
Chest x-ray	Indicated if any respiratory symptoms/signs which have developed or progressed since commencing the transfusion

1.5 Management

The first action to be taken in the management of any suspected transfusion reaction is to stop the transfusion immediately and assess the patient. The identity of the patient should then be checked along with the component compatibility label and the transfusion prescription. If the correct blood is being transfused to the correct patient and any reaction is mild and not progressive, it may well be safe to resume the transfusion with an increase in observations.

The management of a suspected acute severe transfusion reaction is shown in Figure 2.

Figure 2: Management of a severe acute transfusion reaction



1.6 Prevention

Administration of the correct blood to the correct patient following positive patient identification is the most important factor in prevention of AHRs. It is therefore crucial that all staff appreciate the importance of positive patient identification, and that this message is reinforced by the development of guidelines and protocols as well as strategies such as the use of individual patient identification cards for transfusion-dependent outpatients. Barcode systems for patient identification and electronic blood release systems are undergoing evaluation and do appear to reduce wrong blood incidents however access within the NHS has been limited due to cost.

2. Bacterial Contamination

2.1 Incidence

This is a relatively rare complication of transfusion (approximately 2 cases/million components transfused). Twenty-nine confirmed instances of bacterial contamination were reported to SHOT between 1996 and 2003, 7 of which were thought to have directly contributed to the patient's death.

2.2 Pathogenesis

Staphylococcus from the skin flora of the donor's arm is the commonest source of bacterial contamination. Less commonly it can arise as a result of an asymptomatic bacteraemia in the donor such as Yersinia enterocolitica or rarely from environmental contamination of the collection pack or anticoagulant e.g. Pseudomonas species.

Platelet transfusions carry the greatest risk of bacterial contamination as storage at 18-22°C is more conducive to bacterial proliferation than the 2-6°C required for red cell storage. Furthermore, pooled rather than apheresis platelets are more likely to be implicated simple because of the greater donor exposure and the additional risk of contamination during the pooling process.

Table 3 shows the reports of transfusion transmitted bacterial contaminations in the UK made to SHOT between 1995 and 2003 by species and component type and age.

Table 3: Bacterial causes of adverse reaction to transfusion (From SHOT 1995-2003)

	Platelets; age (in days) at use:							Red cells
	1	2	3	4	5	NK	all	
All species	0	2	3	6	10	4	25	4
Bacillus cereus				3[a]		1	4	
Coagulase negative Staphylococci					1		1	1 (23 days)
Enterobacter aerogenes			1[a]				1	
Escherichia coli		1[a]	1[a]			1	3	
Group B Streptococcus			1	1		1 3		
Morganella morganii					1		1	
Serratia liquifaciens								1
Staphylococcus aureus					2	1[a]	3	
Staphylococcus epidermidis		1[a]		2	6		9	1 (32 days)
Yersinia enterocolitica								1[a] (33 days)

[a] Associated with death of one recipient (7/29)

2.3 Symptoms and signs

Patients frequently become symptomatic early in the course of a transfusion reaction resulting from bacterial contamination (see Table 1).

2.4 Investigations

Given the often non-specific early clinical picture, the initial steps in the investigation of any ATR should be broad as outlined in Table 2.

Many transfusion recipients are already at risk of sepsis, if bacterial contamination is considered a possibility it is crucial to obtain cultures from both the patient and the implicated component in order to determine whether the transfusion has been the source of the infection.

2.5 Management

Initial management is outlined in Figure 2. Clearly if bacterial contamination is suspected this should include broad spectrum intravenous antibiotics with adequate anti-staphylococcal cover.

2.6 Prevention

The incidence of bacterial contamination appears to be falling as there were no confirmed reports of bacterial contamination to SHOT in 2004. This may well reflect increased awareness as well as the introduction of improved preventative measures such as:

- more effective donor arm cleansing
- exclusion of donors at risk of bacteraemia e.g. dental surgery within 24hours
- use of diversion packs for blood collection (first 20-30mls of every donation are discarded in order to avoid collection of any contaminated skin plugs).
- Development of bacterial detection systems for platelet packs such as BacT/alert, although routine introduction is limited by cost.

3. Transfusion Related Acute Lung Injury (TRALI)

3.1 Definition

TRALI is an acute severe reaction characterised by acute dyspnoea with hypoxia and development of bilateral pulmonary infiltrates.

3.2 Incidence

TRALI is a potentially life threatening complication of transfusion, which is probably under diagnosed due to the non-specific nature of the respiratory symptoms and signs. The estimated incidence is 0.02% of all blood components issued and it is the second commonest cause of transfusion associated morbidity and mortality in the UK (SHOT).
The incidence of TRALI is equal in males and females.

3.3 Pathogenesis

The pathogenesis is unclear and there are two theories. The more common is the immune-complex theory which is based on the passive transfer of anti_ HLA and/ or anti-granulocyte antibodies in donor plasma. These antibodies react with the patient's leucocytes leading to leucocyte and complement activation. (Occasionally the patient may have the antibodies that react against a donor antigen).

The alternative theory, thought to explain cases where neither anti-HLA or anti-granulocyte antibodies are detected, is that neutrophils are primed/activated by cellular components such as lipids.
Both mechanisms result in a similar clinical picture although neutrophil priming leads to a milder illness. The end result, irrespective of the mechanism, is sequestration of activated leucocytes within the pulmonary vasculature resulting in increased pulmonary capillary permeability and pulmonary oedema. However, overt lung injury does not always occur even in proven immune-complex disorders. A predisposing clinical condition such as active infection, recent surgery or massive transfusion appears necessary for the development of TRALI, presumably because this results in cytokine release and 'pre-priming' of neutrophils. It is unclear why the pulmonary vasculature is especially susceptible but it may be due, in part, to the fact that this is the first microcirculation encountered by transfused antibodies.

3.4 Symptoms and signs

Most cases present within 4-6 hours of exposure to a plasma containing component i.e. platelets, FFP, cryoprecipitate or red cells, but symptoms and signs can appear up to 24 hours after transfusion. Clinical deterioration is often very rapid resulting in a need for ventilatory support.

The chest x-ray is abnormal with bilateral peri-hilar nodular shadowing extending to mid and lower zones which is often difficult to distinguish from acute circulatory overload. Unlike cardiac failure, pulmonary artery wedge pressure is normal or low. Initially TRALI is clinically indistinguishable from ARDS however TRALI may be self-limiting with clinical and radiological improvement occurring within 1-4 days. Changes can however persist for >7days in up to 20%. Mortality rates are of the order of 5-20% but the majority of patients have no long-term sequelae

3.5 Investigation

Initial investigations should follow the standard assessment of ATRs outlined in Table 2. More specialised investigations will be required to confirm a diagnosis of TRALI if suspected clinically. These include screening donors of the implicated components for the presence of anti-HLA and anti-neutrophil antibodies. Multiparous female donors (sensitisation during pregnancy) and previously transfused male donors pose the greatest risk, although individuals transfused after 1980 are no longer accepted as blood donors in the UK.

Any positive antibody screen requires further evaluation to determine whether the detected antibodies cross-react with patient leucocytes and whether the patient has the appropriate HLA or neutrophil antigens. Commonest detected antibodies are anti-HLA Class II followed by anti-HLA Class I and anti-neutrophil antibodies whilst the most frequently targeted antigens are HLA A2 and HNA 1a, 1b, 2a and 3a.
If no cross reacting antibodies are found between any of the donors and the recipient it may be worthwhile screening for inter-donor antibody-antigen interactions as these have been described as a cause of TRALI.

3.6 Management

Initial management of an acute severe transfusion reaction is shown in figure 2. The management of TRALI is largely supportive, the most important factor being prompt, adequate ventilatory support and admission to an intensive care unit if necessary.

3.7 Prevention

All donors implicated in proven cases of TRALI are removed from the donor panel.

In the UK all FFP and cryoprecipitate is now obtained from untransfused male donors and where possible such plasma is also used to resuspend pooled platelets. Female donors are still accepted as apheresis platelet donors.

Additional strategies to try and reduce the incidence of TRALI include dilution of the antibody by pooling plasma components. This however leads to an increase in donor exposures and has not been adopted in the UK. Reduction in the volume of plasma in red cell concentrates and platelets or the use of plasma substitutes have been explored but these options are logistically difficult and expensive.

4. Allergic Reactions

4.1 Incidence

Severe anaphylactic/anaphylactoid reactions are extremely rare but mild allergic/urticarial reactions are reported to occur in 1-3% of transfusions. This has however improved following the introduction of universal leucodepletion of components.

4.2 Pathogenesis

The precise aetiology of mild allergic reactions is unclear although cytokine release or an immune reaction causing complement activation are thought to be contributory factors.

In classical anaphylaxis the patient has developed an IgE antibody to a previously encountered allergen. On re-exposure to this antigen there is cross-linking of mast cell surface IgE followed by mast cell granule release. Anaphylactoid transfusion reactions may occur when the recipient has an IgG antibody to a transfused allergen. This results in leucotrine and cytokine release as well as complement activation with liberation of C3a and C5a and immune complex formation. C3a and C5a are anaphylotoxins which act directly on surface receptors on mast cells resulting in degranulation.

The most commonly identified cause of a severe transfusion-related allergic reaction is an anti-IgA antibody in an IgA deficient recipient. This is however rare, occurring in 1 in 20 000 – 47 000 transfusions. Anti-Gm (IgG allotype) antibodies may also rarely result in anaphylactoid reactions.

4.3 Symptoms and signs

Any allergic reaction (even if mild) usually begins early in the transfusion. Table 1 shows the correlation between the causes and possible symptoms and signs of an acute transfusion reaction.

4.4 Investigation

Again, initial investigation should follow the standard ATR protocol as shown in Table 2. If a severe allergic reaction is suspected samples can be obtained for mast cell tryptase at time 0, 3-6 hours and at 12-15 hours. It is transiently elevated in anaphylactic and anaphylactoid reactions and if positive, suggests further investigation for an allergic trigger is merited. This is however a relatively specialised investigation that is not universally available.

The recipient's IgA levels should be measured since as already indicated the 'commonest' cause of a severe transfusion-related allergic reaction is an IgA antibody in IgA deficient individuals. Partial IgA deficiency is relatively common with an incidence of 1 in 400 in the UK. Severe IgA deficiency is however, uncommon with an incidence of 1 in 20 000 – 45 000 and only a minority of these will actually experience transfusion-related anaphylactoid reactions. If IgA levels are normal then serum should be screened for anti-Gm antibodies.

4.5 Management

Initial management of an acute severe transfusion reaction is shown in Figure 2. In severe reactions deterioration can be very rapid and prompt intervention may be life saving. In mild reactions it is often possible to continue with the transfusion once the minor nature of the reaction is established and appropriate treatment with antihistamine has been administered.

4.6 Prevention

Mild allergic reactions are difficult to prevent as the underlying aetiology is unclear. The introduction of leucodepletion has resulted in significant reduction in their incidence.

Prevention of an initial anaphylactic/anaphylactoid reaction is difficult, but components from IgA deficient donors should be used for future transfusion support in patients with documented anti-IgA or anti-Gm antibodies. Saline washed red cells as this process removes IgA from the transfused component.

5. Febrile Non-Haemolytic Transfusion Reaction (FNHTR)

5.1 Definition

A rise in temperature ≥ 1°C above pre transfusion baseline without associated rigors, hypotension or chest or lumbar pain.

5.2 Incidence

Reported to occur in 1-2% of transfusions although the incidence has fallen dramatically since the introduction of universal pre storage leucodepletion.

5.3 Pathogenesis

The triggers for FNHTRs are multifactorial. The commonest cause is the presence of anti-granulocyte, anti-HLA or rarely platelet specific antibodies, formed as a result of pregnancy or previous transfusion. These react against leucocytes or platelets in the transfused component leading to complement fixation and formation of antibody-antigen-complement complexes that activate macrophages and result in pyrogen release. Cytokines release from leucocytes during storage can also trigger a FNHTR.

5.4 Symptoms/signs

Symptoms and signs usually develop towards the end of the transfusion although they can appear up to 2 hours after the transfusion is completed.

5.5 Investigation

Once a severe acute transfusion reaction has been excluded further investigation of a FNHTR does not usually yield any useful information.

5.6 Management

These reactions are usually mild and self-limiting and the transfusion can usually be completed after administration of an anti pyretic.

6. Circulatory Overload

6.1 Incidence

This is the commonest acute adverse reaction to blood transfusion.

6.2 Pathogenesis

Usually the transfusion is administered too rapidly or an excess volume is transfused and the patient's cardiovascular system is unable to compensate.

6.3 Symptoms and signs

Table 1 shows the correlation between the causes and possible symptoms and signs of an acute transfusion reaction.

Symptoms and signs are exactly the same as in any other cause of fluid overload and may develop at any time during the transfusion depending on the patient's cardiovascular reserve.

6.4 Investigation

In most instances fluid overload will be easy to identify however it may not be immediately apparent and in these instances investigation should proceed as in Table 2 until the cause of the patient's symptoms and signs is established.

6.5 Management

Initial management of an acute severe transfusion reaction is shown in Figure 1. Circulatory overload secondary to transfusion should be managed in the same way as that from any other cause with diuretics, oxygen and appropriate cardiovascular support.

6.6 Prevention

In patients with known significant cardiac disease, transfusion should be administered slowly and if necessary with diuretic cover. In severe cardiac disease it may be necessary to restrict the volume transfused to 1 unit of RCC in any 12 hour period.

Patients with chronic anaemia are at increased risk of circulatory overload as they have a normal circulating volume prior to commencing transfusion. There is also a particular risk associated with transfusion of 20% albumin solutions as a 100ml transfusion has an intravascular effect of approximately 300ml.

B

Delayed Transfusion Reactions

1. Delayed Haemolytic Transfusion Reaction (DHTR)

1.1 Definition

A haemolytic transfusion reaction occurring more than 24 hours after commencing transfusion. Delayed serological transfusion reaction (DSTR) is the term used when a new antibody is formed but no haemolysis occurs.

1.2 Incidence

DHTRs have an incidence of approximately 1 in 5400 units transfused. They are rarely life-threatening but may result in significant morbidity. DSTR occurs in approximately 1 in 2990 units transfused.

1.3 Pathogenesis

The recipient has been previously immunised either due to previous transfusion or pregnancy. The antibody has however, not been detected in a pre-transfusion sample because it is absent, present at sub-detectable levels or missed. Re-exposure to the relevant red cell antigen results in a secondary immune response. Antibody levels rise rapidly over the next few days and lead immune destruction of the transfused red cells.

Occasionally a DHTR occurs at the time of primary allosensitisation when a newly synthesised antibody reaches significant concentration whilst the sensitising red cells are still present in the circulation.

Antibodies typically fix complement only to C3 and haemolysis is therefore extravascular. Cytokines also contribute to DHTR especially in more severe cases with an increase in inflammatory mediators such as Tumour Necrosis Factor , Interleukin 6 and Interleukin 8.

1.4 Symptoms and signs

A DHTR usually occurs within 1-14 days of transfusion (mean 7 days). Patients may be asymptomatic with the DHTR detected following the discovery of a positive direct antiglobulin test (DAT) and a suboptimal increase in haemoglobin. In more severe cases, there is a significant fall in the haemoglobin and patients may occasionally become febrile and jaundiced and rarely develop haemoglobinuria. Around 6% of patients develop renal impairment and a proportion require dialysis.

1.5 Investigation

There is a suboptimal increment in haemoglobin and the blood film shows spherocytes and polychromasia. The DAT is positive with IgG and/or C3 coating on red cells.
Unconjugated bilirubin and LDH are increased and serum haptoglobins are reduced or absent. Renal function should be monitored as it may be affected if haemolysis is significant.

Serology should demonstrate a new red cell alloantibody in the post transfusion sample which occasionally will be identified on retesting of the pre-transfusion sample. Antibody identification may require red cell elution studies as well as confirmation that the recipient is antigen negative. Antibody levels tend to rise 7-10 days post transfusion and retesting at this time may also allow specificity to be established.

The implicated antibodies are most frequently Rhesus (E>C>c) followed by Kidd (Jk^a>Jk^b), Duffy (Fy^a>Fy^b) and Kell. Antibodies with Kidd and Duffy specificities are more frequently identified in DHTR rather than DSTR.
In 10% of cases more than one alloantibody is identified.

1.6 Management

Specific management is rarely required but the patient may require further red cell transfusion. If haemolysis is severe, management should be as for autoimmune haemolysis with steroid +/- intravenous immunoglobulin. Rarely red cell exchange transfusion using antigen-negative units is required. Future transfusions should be with antigen negative red cells if an antibody specificity is determined.

1.7 Prevention

Patient groups particularly at risk include those with Sickle Cell Disease or Thalassaemia who require long term transfusion support. This is due to the significant difference in the patient's red cell antigen profile compared to that of the mainly Caucasian donor population. Alloimmunisation can be reduced/prevented by extended red cell phenotyping and transfusion of compatible units where at all possible.

All identified red cell antibodies should be clearly flagged on the Hospital Transfusion Laboratory computer system to prevent any future anamnestic response to further exposure.

2. Post Transfusion Purpura (PTP)

2.1 Definition

PTP is a delayed transfusion reaction characterised by an acute severe thrombocytopenia due to a secondary immune response resulting in platelet destruction.

2.2 Incidence

PTP is a rare complication of transfusion (no cases reported to SHOT in 2004), which usually occurs in middle aged or elderly multiparous women.

2.3 Pathogenesis

The patient has formed a specific anti-platelet antibody due to either pregnancy or previous transfusion. Re-exposure leads to a secondary immune response with rapidly increasing antibody levels. This results in the destruction of both antigen-positive transfused platelets and, via an unknown mechanism, the patients own antigen-negative platelets.

2.4 Symptoms and signs

Patients present with symptoms and signs due to their profound thrombocytopenia including a widespread purpuric rash, bleeding and bruising.

2.5 Investigation

The patient should be screened for the presence of anti platelet antibodies. If detected the donor should then be screened for the relevant antigen by platelet ELISA and monoclonal antibody immobilisation of platelet antigen (MAIPA) assay. The most commonly implicated anti platelet antibody is anti HPA1a however it is still relatively rare since >95% of the UK population are HPA1a positive.

2.6 Management

Patients are at high risk of severe bleeding during the thrombocytopenic period and treatment is indicated in virtually all cases. Platelet transfusion may exacerbate the immune destruction and should be avoided other than in life-threatening bleeding. If required, antigen-negative compatible platelets should be administered (although this may not result in the expected increment in count and multiple doses may be required).

High dose intravenous immunoglobulin (2g/Kg body weight administered over 3-5 days) is the treatment of choice. More than 80% of patients respond over 4-5 days. The mechanism of action is thought to be Fc receptor blockade with or without non-specific binding of immunoglobulin to platelet surfaces.

Therapeutic plasma exchange is regarded as second line option as the response times are delayed compared to those of immunoglobulin. The role of steroids is unclear and splenectomy has been performed occasionally. This is however generally a self-limiting illness with recovery of the platelet count within 21 days even in those who fail to respond to first or second line therapies.

2.7 Prevention

There are no practical means to prevent the primary episode. Patients who have had PTP should, wherever possible, receive antigen-negative platelets and red cells to try to avoid recurrence.

3. Transfusion Associated Graft Versus Host Disease (TaGVHD)

3.1 Incidence

TaGVHD is an extremely rare but usually fatal complication of transfusion. (13 cases reported to SHOT between 1996 and 2004, all fatal. It may occur following transfusion of any blood component which contains viable T lymphocytes where there is a degree of disparity in histocompatibility antigens between donor and recipient. The risk appears to be related to the number of viable T lymphocytes infused, the susceptibility of the patient's immune system to their engraftment and to the degree of HLA disparity between the donor and recipient. Immunosuppressed patients are at greatest risk (although it is not described in patients with HIV) however it can also occur in immunocompetent individuals when the donor and recipient share an HLA haplotype e.g. transfusion from a first or second degree relative.

3.2 Pathogenesis

T lymphocytes may remain viable in stored red cells for at least 3 weeks. When transfused to a susceptible recipient these viable donor T lymphocytes engraft and proliferate, causing widespread tissue damage by a combination of T cell and cytokine effect (donor T cells recognise recipient cells as foreign due to differences in major and minor histocompatibility antigens). Major target tissues are skin, bone marrow, thymus, gastrointestinal tract, liver and spleen.

3.3 Symptoms and Signs

The clinical features generally begin 4-30 days following transfusion and include fever, diarrhoea, a maculopapular or erythematous skin rash which progresses to erythroderma and desquamation, hepatitis with or without jaundice and pancytopenia. Neonates may present with early hepatosplenomegaly followed by lymphoid regression. TaGVHD is nearly always fatal with mortality of >90%.

3.4 Investigation

The diagnosis is made based on the combination of clinical features in a recently transfused patient and is confirmed by histological and molecular analysis of a skin biopsy or other affected tissue in which there is an infiltrate of donor derived CD3+, CD4+ and CD8+ lymphocytes.

3.5 Management

Treatment is designed to reduce cytotoxic T lymphocyte mediated tissue injury and production of inflammatory cytokines such as Tumour Necrosis Factor however efficacy has not been formally demonstrated. Treatment options include high dose steroid therapy, intravenous immunoglobulin, azathioprine, cyclosporin and anti-thymocyte globulin. Newer treatments include anti CD3 antibody, Campath, chloroquine and serine protease inhibitors.

3.6 Prevention

The number of lymphocytes necessary for development of TaGVHD is unknown however leucocyte depletion alone has been shown to be inadequate. TaGVHD is only prevented by gamma irradiation of cellular blood components, (red cell, platelet and granulocyte concentrates), for at risk groups which are well defined It is imperative that the hospital transfusion laboratory is informed of any patients for whom irradiated products are necessary and the patients should also be made aware of their risk e.g. issued with a card and information sheet. Indications for gamma irradiation of cellular components are shown in Table 4.

Irradiation is necessary only for cellular components as plasma components contain no intact T lymphocytes only leucocyte fragments. The minimum dose of irradiation required is 25Gy with no part of the field receiving >50Gy.

Table 4: Current indications for the gamma irradiation of cellular blood components

Groups for whom gamma irradiation of cellular components is currently recommended

1. Red cells or platelets for intrauterine transfusion (IUT)
2. Exchange transfusion in neonates who have previously received an IUT.
3. Exchange transfusion in neonates who have not previously received an IUT (as long as irradiation does not unduly delay transfusion)
4. All congenital immunodeficiency states (apart from chronic mucocutaneous candidiasis) e.g. SCID, Wiskott Aldrich syndrome, Di George syndrome
5. All allogeneic stem cell transplant recipients from initiation of conditioning therapy and continued for as long as they remain on GVHD prophylaxis or until lymphocytes are $>1.0 \times 10^9$/l. (Longer for patients with chronic GVHD and for up to 2 years in patients with SCID)
6. Any cellular component transfusion should be irradiated in the 7 days prior to a patient undergoing an autologous stem cell collection
7. For 3 months following initiation of conditioning therapy in autologous stem cell transplant recipients (6 months if total body irradiation)
8. All patients with Hodgkin's Lymphoma
9. All patients who have received purine analogue therapy e.g. fludarabine, cladrabine
10. All transfusions of cellular components from a first or second degree relative
11. All granulocyte transfusions
12. All transfusions of HLA matched platelets

Groups for whom gamma irradiation of cellular components is not necessary

1. Top up transfusion in a neonate with no history of IUT
2. Patients with solid tumours
3. Solid organ transplant recipients

4. Transfusion Transmitted Infection (Excluding Bacteria)

4.1 Incidence

For HIV, Hepatitis C and Hepatitis B, JPAC figures estimate the risk of an infectious donation entering the UK blood supply to be 1 in 5.22 million donations, 1 in 29.03 million donations and 1 in 0.50 million donations respectively. (2003-2004 figures).

In 2004 the first probable case of transfusion-transmitted variant Creutzfeldt Jakob Disease (vCJD) was reported in which a donor developed vCJD 3-5 years following donation and one recipient developed vCJD 6.5 years after transfusion. The probability that the recipient did not acquire vCJD from transfusion is calculated at 1 in 15 000 –30 000. In a second report, a patient who had received transfusion from a donor who subsequently developed vCJD was found to have the abnormal prion protein in her appendix at autopsy . The patient died of unrelated causes however and there was no evidence of clinical vCJD at the time of death.

4.2 Pathogenesis

For an infection to be transmissible by transfusion it must have a blood-borne phase and remain viable throughout collection, processing and storage.

4.3 Symptoms and Signs

These depend on the pathogen however the disease may not follow a classical course as the infecting dose is often relatively large and it is administered directly into the blood stream (often an unnatural route).

4.4 Investigation

Detection is often hindered by factors such as asymptomatic infection (e.g. HCV), delayed onset of infection, lack of clinical awareness and by the potential for other sources of infection. If a TTI is suspected it is important to inform the supplying Blood Centre as soon as possible so that any untransfused components from the potentially implicated donor(s) can be withdrawn and the donors and components investigated as a possible source of infection. If possible it is important to demonstrate negativity in a pre-transfusion sample from the recipient

4.5 Management

This is dependant on the pathogen but standard management is generally no different than if the infection was acquired by a natural route.

4.6 Prevention

Strict donor selection criteria with exclusion of those at increased risk together with mandatory microbiological testing form the mainstay of prevention of TTI.

Table 5 shows the current microbiological testing of all blood donations in the UK.

Table 5: Mandatory microbiological testing of all blood donations in the UK

Mandatory
HbsAg
Anti HIV 1 & 2
Anti HCV
HCV Nucleic acid testing (NAT)
Anti HTLV I & II
Syphilis antibody
Under special circumstances the following may be necessary
CMV
Malaria antibodies
Trypanosoma cruzii antibodies
Serological tests for West Nile Virus
HbcAb

Strategies which have been introduced to prevent transmission of vCJD include universal leucodepletion, sourcing of FFP from non-UK donors for fractionation and for transfusion to children born after 31/12/95 (the point at which BSE is thought to have been eliminated from the food chain), exclusion of donors who have been transfused in the UK since 1980, and in many countries outwith the UK donors who have resided for a significant time in the UK are excluded. Other strategies which may be effective are specific filtration devices to reduce the concentration of prion protein in the transfused product

and reducing plasma in red cell and platelet concentrates (a large amount of prion protein is contained in plasma however platelets also express large amounts so this strategy may not be particularly effective).

A serological test for vCJD may soon be available and it may be that this is introduced as part of routine donor microbiological testing. However this will be very expensive and as its significance with respect to the possible development of clinical vCJD in the donor or in transfusion recipients will be undetermined its routine introduction may result in significant unnecessary anxiety.

5. Immunomodulation/Immunosuppression

Animal models have suggested that allogeneic blood transfusion may modulate the recipient's immune system resulting in an increased risk of tumour recurrence and of post-operative infection. Prospective trials have however failed to confirm this in vivo. No significant differences have been observed in the relative risk of tumour recurrence in transfused versus untransfused patients or in recipients of allogeneic versus autologous transfusion. The effect of transfusion on post-operative infection rates is controversial: some trials have shown an increased rate of post-operative infection in transfused patients, many other studies have however failed to confirm these findings.

6. Iron Overload

Each unit of red cells transfused contains approximately 250mg of iron. The maximum daily iron excretion is only of the order of 1mg in the absence of bleeding and iron overload is therefore a major risk in chronically transfused patients. Transferrin may become completely saturated after only 10-15 units of red cells, thereafter excess iron becomes bound to tissue parenchyma, the liver and heart being most affected

Chelation therapy can minimise iron accumulation in chronically transfused patients and it has been shown to be most effective when it is started early.

References

BCSH Guidelines for the Clinical use of Red Cell Transfusions.
British Journal of Haematology 2001; 113, 24-31

BCSH Guidelines for the use of Fresh Frozen Plasma, Cryoprecipitate and Cryosupernatant. British Journal of Haematology 2004; 126, 11-28

BCSH Guidelines for the use of Platelet Transfusions. British Journal of Haematology 2003; 122, 10-23

BCSH Guidelines on gamma irradiation of blood components for the prevention of transfusion associated graft versus host disease. Transfusion Medicine, 1996; 6, 261-271

Estimated frequency (or risk) of HIV, HCV or HBV infectious donations entering the blood supply.
Joint UKBTS/NIBSC Professional Advisory Committee Position Statement 05 (26 October 2005)

Donor arm cleansing and monitoring, diversion and bacterial detection.
Joint UKBTS/NIBSC Professional Advisory Committee Position Statement 06 (22 June 2005)

Serious Hazards Of Transfusion, Annual Report 2003
www.shotuk.org

Serious Hazards Of Transfusion, Annual Report 2004
www.shotuk.org

Bux, J. (2005). Transfusion related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sanguinis, 89, 1-10.

Kopko, P.M. (1999). Transfusion related acute lung injury. British Journal of Haematology, 105, 322-329

Ludlam, C. & Turner, M.L. (2005) Managing the risk of transmission of variant Creutzfeldt Jakob Disease by blood products. British Journal of Haematology, 132, 13-24

McClelland, D.B.L. & Contreras, M. (2005). Effectiveness and safety of blood transfusion: have we lost the plot? Journal of the Royal College of Physicians of Edinburgh, 35; 2-4

MacLennan, S. Transfusion related acute lung injury TRALI. NBS Transfusion Medicine Clinical Policies Group (March 2003)

Pamphilon, D.H. Transfusion associated graft versus host disease. NBS Transfusion Medicine Clinical Policies Group (February 2002)

Perrotta, P.L. & Snyder, E.L. (2001). Non-infectious complications of transfusion therapy. Blood Reviews, 15, 60-83

Pineda and Taswell, 1975