Blood transfusion

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Abstract

The term 'blood transfusion' refers to therapeutic use of whole blood or its components (red cells, platelets, fresh frozen plasma, cryoprecipitate). Careful donor selection and stringent testing by the blood service is required to ensure a safe blood supply. Blood transfusion can be life-saving. However, donated blood is a limited resource, and hospital blood transfusion practice must focus on ensuring safe and appropriate use. Patient blood management is an evidence-based multidisciplinary approach aimed at optimizing the care of patients who might need transfusion, to reduce avoidable use of blood components. Clinical transfusion guidelines are essential, supported by education and training with regular practice audits. To minimize errors, particular emphasis must be placed on accurate patient identification from the initial blood sample, through laboratory testing and transfer of blood to clinical areas, to the final bedside check before transfusion. The reporting and monitoring of adverse events via national haemovigilance schemes has highlighted key areas for action and improved transfusion safety. Transfusion medicine must be practised within a strict regulatory framework; the Blood Safety and Quality Regulations 2005 based on European Union blood directives have had particularly far-reaching implications for UK Blood Services and hospital transfusion laboratories.

Keywords Blood components; haemovigilance; patient blood management; transfusion

Key points

- Blood transfusion safety is continually improving, but avoidable and unavoidable adverse events still occur
- The risk of transfusion-transmitted infection can be reduced by careful donor selection, microbiological testing and treating components to inactivate pathogens
- The greatest risk in the transfusion process continues to relate to human error (particularly 'wrong blood in tube')
- Strategies such as patient blood management have placed an emphasis on minimizing the need for transfusion, reducing the potential risks and costs, and sparing a finite resource
- Haemovigilance schemes require reporting of adverse events to identify themes to direct new safety initiatives

Introduction

Transfusion medicine is continuing to evolve, with scientific and clinical advances. The introduction of more advanced serological and molecular techniques for microbiological testing and stricter criteria for selecting donors have greatly reduced the risks of transfusion-transmitted infection. Additional steps during the processing of blood and components, including leucodepletion and, where feasible, viral inactivation, have further improved safety.

The key priorities for clinical transfusion practice include avoidance of unnecessary transfusion, following the principles of patient blood management (PBM) and reducing avoidable transfusion errors wherever possible. A robust clinical governance infrastructure within a hospital, including an active hospital transfusion team (HTT) and hospital transfusion committee (HTC), is essential for implementing key activities to ensure safe transfusion practice and appropriate use of blood.

Blood donation and processing

Blood donation

All donors in the UK are unpaid volunteers. They are carefully selected using a donor health questionnaire to ensure that they can donate safely, and to exclude anyone at risk of transmitting infection. Donors can give around 450 ml of whole blood up to three times a year; this is separated into red cells, platelets and plasma. In 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) undertook a comprehensive review of the evidence on the safety of UK plasma for the manufacture of immunoglobulins. The Commission on Human Medicines (CHM) considered the evidence and recommended that UK-sourced plasma can safely be used for the manufacture of immunoglobulins subject to a number of robust safety standards and risk mitigation measures.

The ban remains in place for the production all other plasma-derived medicines. The Department of Health and Social Care (DHSC) have accepted CHM's recommendations to update this specific vCJD risk reduction measure. This means that for the first time in over 20 years, UK plasma can again be fractionated to increase the availability of immunoglobulin medicines for the benefit of NHS patients in the UK.

Testing of donor blood

Transfusion-transmitted infection: the epidemiology of infection in a particular country's population can help guide the testing required to maximize the safety of the blood supply. Every blood donation in the UK is screened for hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus, human immunodeficiency virus (HIV) and syphilis. Human T cell lymphotropic virus is screened for in donations from new blood donors, and infections

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such as malaria are screened for depending on the donor's travel history. A separate bacterial screening process is in place for platelets as there are differences in the storage requirements for this blood product. The risks of a potentially infectious HBV, HCV or HIV window-period donation not being detected on testing in the UK are very low, at <1 per million donations tested (see https://www.shotuk.org/wp-content/uploads/myimages/SHOT-REPORT-2019-Final-Bookmarked-v2.pdf Table 20.2, page 162).

Some donations are also tested for cytomegalovirus (CMV) antibody to help provide CMV-negative blood for particular patient groups. In the UK, the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) has reviewed the available evidence and recommended that leucodepletion of all blood components (other than granulocytes) provides adequate reduction of CMV risk for almost all clinical situations; however, CMV-seronegative red cell and platelet components should be provided for intrauterine transfusions, for neonates, and for pregnant women requiring elective transfusions during the course of pregnancy.

Variant Creutzfeldt–Jakob disease (vCJD): three vCJD cases in the UK in which blood transfusion was implicated took place before the introduction of leucodepletion and other measures taken by the UK Blood Services to reduce the risk of vCJD transmission by blood, plasma and tissue products. All these measures were reviewed and were endorsed by SaBTO in 2013. One of the measures, the provision of imported plasma for individuals born on or after 1 January 1996, was withdrawn in September 2019. This followed a recommendation by SaBTO based on evaluation of the risk of transmission of vCJD. Other risk reduction measures, such as leucodepletion, remain in place.

Other novel infections: the UK Blood Services' Standing Advisory Committee on Transfusion Transmitted Infection (SACTTI) reviews data on new infectious threats, carries out risk assessments and issues recommendations to the Blood Services. UK Blood Services have put cautionary safety measures in place in relation to the global COVID-19 pandemic. The Epidemiology Unit, SACTTI and Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) have been, and will continue to be, closely monitoring this outbreak, risk-assessing the potential impact on the safety of the UK blood supply and responding appropriately.

Processing of blood

Donor blood is collected into plastic packs containing citric phosphate dextrose, an anticoagulant that helps to support red cell metabolism. All units are then transported without delay to the blood centre for processing, with initial leucodepletion to remove white cells. Further processing is then undertaken to produce red cells, platelets and plasma under stringent quality control standards.

In the standard unit of red cells available in the UK, most of the plasma has been removed and replaced by a saline solution containing saline, adenine, glucose and mannitol, also known as optimal additive solution. Red cells are stored at 4°C and have a shelf life of 35 days.

An adult therapeutic dose or 1 unit of platelets can be produced either by single donor apheresis or by centrifugation of whole blood followed by separation and pooling of the platelet-rich layer from four donations suspended in plasma. Platelets are stored at 20–24°C with constant agitation to maintain optimal platelet function. Bacterial screening of platelets before release has been standard practice in the UK since 2011. This reduces the risk of bacteriological contamination and has allowed extension of the shelf life of platelet units to 7 days. Platelet components must not be placed in a refrigerator.

Fresh frozen plasma (FFP) is produced by separation and freezing of plasma at −30°C. Once thawed, FFP must generally be used within 24 hours, but it can be stored at 4°C for up to 5 days for use in major haemorrhage.

Cryoprecipitate is prepared by undertaking controlled thawing of frozen plasma to precipitate high-molecular-weight proteins including factor VIII, von Willebrand factor and fibrinogen. Cryoprecipitate consists of the cryoglobulin fraction of plasma containing the major portion of factor VIII and fibrinogen. It is obtained by thawing a single donation of FFP at 4°C ± 2°C. The cryoprecipitate is then rapidly frozen to −30°C. It is available as pools of 5 units.

Blood transfusion regulations and European Union (EU) blood directives

The EU blood directive on blood safety set standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and components. This was written into English Law as the UK Blood Safety and Quality Regulations and was implemented in 2005.

Impact of the Blood Safety and Quality Regulations in hospitals

The chief executive of each hospital with a transfusion laboratory has to submit a formal annual statement of compliance to the Medicines and Healthcare products Regulatory Agency (MHRA). Hospital transfusion laboratories can be inspected by the MHRA and, in the event of significant deficiencies, can be given the order to 'cease and desist from activities'. Hospital transfusion laboratories undertaking any processing activities such as irradiation must have a licence from the MHRA indicating blood establishment status.

All hospitals must have an HTC with multidisciplinary representation. These committees are responsible for overseeing the implementation of guidelines, clinical audit and training of all staff involved in transfusion. The HTC has an essential role within the hospital clinical governance framework and must be accountable to the chief executive. The HTT, which comprises the transfusion practitioner, transfusion laboratory manager and consultant haematologist in transfusion, undertakes various activities on a day-to-day basis to achieve the HTC's objectives.

Patient blood management

PBM is an evidence-based, patient-focused initiative involving an integrated multidisciplinary multimodal team approach. By optimizing the patient's own blood volume, minimizing blood loss and optimizing the patient's physiological tolerance of anaemia, it aims to reduce unnecessary transfusion. This includes transfusion avoidance strategies such as preoperative correction of anaemia, intraoperative cell salvage,

antifibrinolytics (tranexamic acid) to reduce blood loss, use of restrictive transfusion triggers and giving a single red cell unit in patients who are not bleeding, followed by reassessment of the need for further transfusion. PBM builds on ideas previously laid out in 'Better Blood Transfusion' health circulars and is also a focus of the guidance issued by the National Institute for Health and Care Excellence (NICE) in 2015.

Laboratory transfusion

Blood group serology – ABO groups

There are four different ABO blood groups, which are determined by whether or not an individual's red cells have the A antigen (group A), the B antigen (group B), both A and B antigens (group AB) or neither (group O).

Depending on the ABO group, individuals produce anti-A or anti-B antibodies in early life that are mainly immunoglobulin M and can rapidly attack and destroy incompatible cells, with activation of the full complement pathway; this results in intravascular haemolysis (acute haemolytic reaction). It is therefore essential that only red cells of a compatible ABO group are transfused.

Rhesus D (RhD) group and antibodies

Individuals who lack the RhD antigen are called D-negative and account for about 15% of the white British population (far fewer in some ethnic groups), with the majority, who do have the RhD antigen, called D-positive. D-negative individuals can become 'sensitized' and develop anti-D after being exposed to D-positive cells during transfusion or pregnancy. The clinical complications include haemolytic disease of the fetus and newborn (HDFN), the risk of which can be minimized by using anti-D immunoglobulin prophylaxis in D-negative mothers. Transfusion of D-positive red cells to a D-negative individual who is already sensitized can result in a 'delayed transfusion reaction', in which the red cells become coated with immunoglobulin G and are removed by the reticuloendothelial system by extravascular haemolysis. This can result in a failure of the haemoglobin to increase, together with jaundice, and may only manifest 4–7 days after transfusion.

There are around 300 human blood groups that belong to 30 separate red cell antigen systems as recognized by the International Society of Blood Transfusion. The ABO and RhD antigens are particularly important, but there are many other antigens on red cells that can result in the formation of antibodies after pregnancy or transfusion, such as Kell, other rhesus (c, C, E, e), Duffy (Fya, Fyb) and Kidd (Jka, Jkb) antigens, and these antibodies can also cause delayed transfusion reactions or HDFN.

Blood group and compatibility testing

The patient's red cells are grouped for ABO and RhD type, and the plasma is tested for anti-A and anti-B antibodies. Most UK laboratories now use automated blood grouping and antibody testing, with advanced information technology systems for documentation and reporting of results.

Because errors related to having the 'wrong blood in tube' are relatively common, with potential risk of ABO-mismatched transfusions, British Society for Haematology (BSH) guidelines recommend that a second sample should be requested for confirming the ABO group in any new patient, provided this does not impede the urgent delivery of red cells or components.

The hospital transfusion laboratory can readily provide red cells that are ABO- and RhD-compatible using electronic issue (or 'computer cross-match'), with no further testing needed, provided the patient does not have any antibodies and that there are robust automated systems in place for antibody testing and identification of the patient. If a patient has red cell antibodies, electronic issue should not be used and a full cross-match must be carried out. Certain other patient groups are not suitable for electronic issue, such as those who have had a stem cell or solid organ transplant.

Special requirements

The hospital transfusion laboratory also needs to ensure that appropriate blood and components are provided for patients with special requirements, such as CMV-negative (see above) or irradiated blood. The latter is needed for immunocompromised patients to minimize risk of transfusion-associated graft-versus-host disease. In addition to providing RhD-compatible blood, it is important to avoid transfusing Kell-positive red cells to Kell-negative girls and women with childbearing potential, to prevent the formation of anti-K antibodies that can cause severe HDFN.

Certain patient groups, such as those with sickle cell disease, are at very high risk of forming red cell alloantibodies, which increases the risk of delayed haemolytic transfusion reactions. Patients with haemoglobinopathy should therefore be given blood that is matched for the patient's full extended rhesus (c, C, D, E, e) and K types, to prevent their forming antibodies to these highly immunogenic antigens.

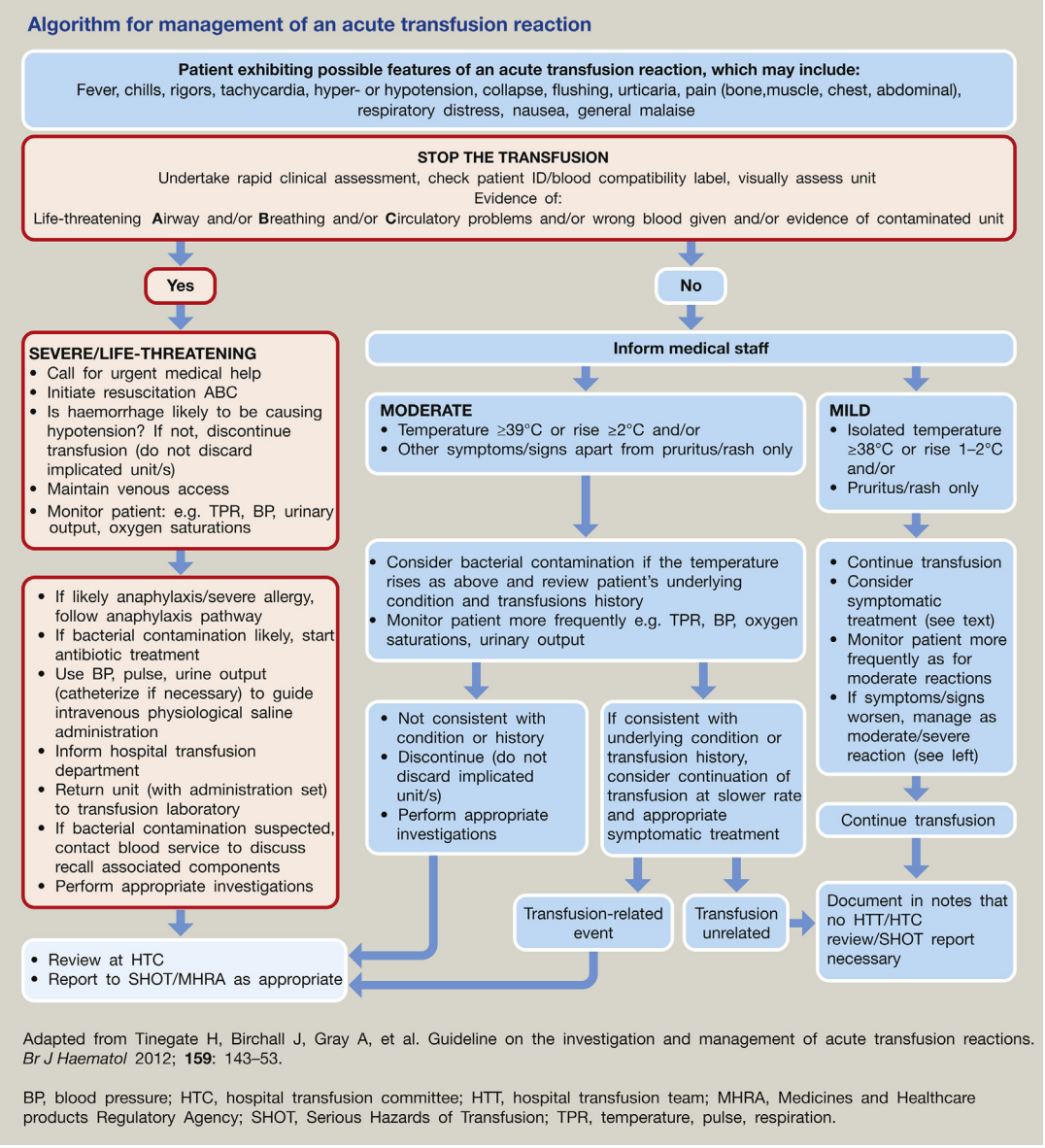
Clinical transfusion practice

Procedural safety

All hospitals must have a transfusion policy with clear guidance on correct patient identification and safe administration of blood and components, including the detection and management of adverse reactions. All hospital staff involved in the transfusion process, including phlebotomists, porters, medical and nursing staff, must undergo training and competency testing. It is particularly important that junior doctors, as key prescribers of blood components, be given training in the principles of PBM.

The decision to transfuse must be based on a thorough clinical assessment of patients and their individual needs; the indication for transfusion and confirmation of patient consent should be documented in their clinical records.

Errors in requesting, collecting and administering blood components (red cells, platelets, plasma components) can lead to significant risks. The Serious Hazards of Transfusion (SHOT) scheme (www.shotuk.org), launched in 1995, has repeatedly shown that 'wrong blood into patient' episodes are an important reported transfusion hazard; these are mainly the result of human error that can lead to life-threatening haemolytic transfusion reactions and other significant morbidity. In 2019, 84.1% of reports to SHOT, including four ABO-incompatible red cell transfusions, related to human error. This may be because systemic factors were not properly identified or



Adapted from Tinegate H, Birchall J, Gray A, et al. Guideline on the investigation and management of acute transfusion reactions. *Br J Haematol* 2012; **159**: 143–53.

BP, blood pressure; HTC, hospital transfusion committee; HTT, hospital transfusion team; MHRA, Medicines and Healthcare products Regulatory Agency; SHOT, Serious Hazards of Transfusion; TPR, temperature, pulse, respiration.

Figure 1

rectified, leading to short-term results rather than sustained improvement.

All patients given a blood transfusion must wear an identification band (or risk-assessed equivalent), with the minimum patient identifiers including last name, first name, date of birth and unique patient number. Positive patient identification is essential at all stages of the blood transfusion process, including blood sampling, collection of blood from storage and delivery to the clinical area and administration to the patient.

The detection and clinical management of acute transfusion reactions is outlined in Figure 1. Adverse events or reactions related to the transfusion should be appropriately investigated and reported to local risk management, SHOT and the MHRA via the Serious Adverse Blood Reactions and Events system.

Use of red cells

Red cells are indicated to increase the haemoglobin concentration and hence oxygen-carrying capacity of the blood after acute haemorrhage or in chronic anaemia (e.g. bone marrow failure, inherited anaemia, haemolytic disease of the newborn). The 'Blood Components' App, created by the National Blood Transfusion Committee (NBTC) based on national guidelines for transfusion, incorporates NBTC indication codes and is a useful resource to help appropriate use.

There has been a trend in favour of lowering the haemoglobin threshold used as a 'trigger' for red cell transfusion (e.g. haemoglobin trigger of 70 or 80 g/litre for most patients, with a trigger of 80 or 90 g/litre if there is a history of cardiac disease). This is based on evidence from patient populations in intensive care, after cardiac and hip surgery, in acute gastrointestinal bleeding and in sepsis, showing that a restrictive transfusion strategy resulted in equivalent clinical outcomes. However, individual patient factors must be taken into account. The initial assessment should include evaluation of the patient's age, body weight and any co-morbidity predisposing to transfusion-

associated circulatory overload, such as cardiac failure, renal impairment or hypoalbuminaemia. Fluid overload should be considered when prescribing the volume and rate of transfusion, and in deciding whether diuretics should be co-prescribed.

The generalization that transfusing 1 unit of red cells gives a haemoglobin increment of 10 g/litre applies only as an approximation for a 70–80 kg patient. In small, frail adults, prescription in millilitres, as for paediatric practice, is recommended. Patients who are not bleeding should be transfused a single unit followed by a reassessment of haemoglobin increment and clinical response, avoiding the prescription of multiple units.

Blood for planned procedures

Patients undergoing surgery in which transfusion may be required should have a 'group and screen' sample taken in the preoperative assessment clinic. Providing the antibody screen is negative, the transfusion laboratory can provide blood components quickly as needed, without the need to reserve cross-matched units. A maximum surgical blood-ordering schedule should be agreed, particularly in hospitals where electronic issue is not used as routine. This specifies how many blood units will be reserved (in the blood bank or satellite refrigerator) for standard procedures, based on audits of local practice.

Guidelines should also include strategies for blood conservation, including preoperative assessment (to detect and correct iron deficiency anaemia or bleeding disorders) and cell salvage. Routine preoperative autologous donation and storage of blood before surgery is no longer recommended in the UK.

The use of erythropoietin is now well established in chronic renal anaemia, but NICE does not support its routine use in patients with anaemia secondary to cancer.

Use of platelets

Platelets are indicated for the treatment or prevention (prophylaxis) of bleeding in patients with thrombocytopenia (low platelet counts) or with platelet dysfunction in a number of situations. The NBTC 'Blood components' App details indications to transfuse platelets.

Platelet refractoriness – a failure to obtain a satisfactory increment from platelet transfusions can have an immune or non-immune cause. The main immune cause is human leucocyte antigen (HLA) alloimmunization, which occurs after previous pregnancy or transfusion. Non-immune clinical factors include infection (and its treatment with antibiotics and antifungal drugs), disseminated intravascular coagulation and splenomegaly. HLA-matched platelet transfusions are indicated if no obvious non-immune cause is present and HLA antibodies are detected.

Use of fresh frozen plasma and cryoprecipitate

FFP is primarily given for three indications: to prevent bleeding (prophylactic), to stop bleeding (therapeutic) or for plasma exchange. Prophylactic transfusions are mainly used before surgery or invasive procedures. Many possible indications in patients without major bleeding are not substantiated by robust trial data. Further detail regarding indications is available in the NBTC 'Blood Components' App.

In adults, the therapeutic dose of FFP is 15 ml/kg body weight. Plasma should not be used for volume replacement. FFP should not be used to reverse of oral anticoagulation (warfarin); for this, prothrombin complex (prothrombin complex concentrate) is indicated (BSH anticoagulation guidelines) (see *Acquired disorders of coagulation* on pages 221–224 of this issue). The coagulopathy of liver disease is also complex, with many studies showing a lack of evidence of clinical benefit from prophylactic FFP transfusion in this setting.

Solvent-detergent plasma is prepared commercially from pools of 300–5000 plasma donations that have been sourced from non-UK donors and treated with solvent and detergent to reduce the risk of viral transmission. Solvent–detergent-treated plasma is indicated for patients undergoing plasma exchange for thrombotic thrombocytopenic purpura.

The main indication for the use of cryoprecipitate is in massive haemorrhage for replacement of fibrinogen if the concentration is <1.5 g/litre (or <2 g/litre in major obstetric bleeding). The adult dose is two pools of cryoprecipitate with 5 units in each pool. Fibrinogen concentrate is widely used in Europe for major haemorrhage but not licensed for this indication in the UK. Cryoprecipitate must not be used for replacement of coagulation factors in inherited conditions such as haemophilia or von Willebrand disease as specific factor concentrates are available for the treatment of these conditions.

Patient information and consent

Patients should be provided with timely information regarding the indication for transfusion, the risks and benefits of blood transfusion and any alternatives available. There is also a need to increase patient awareness regarding the importance of correct identification.

In October 2011, SaBTO in the UK reinforced the recommendation that valid consent for blood transfusion should be obtained and documented in the patient's clinical record. ◆

FURTHER READING

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