The use of blood and blood components in clinical medicine

1. Introduction

1.1 Following early, but often ill-fated, attempts at blood transfusion in the 17th century, the first well-documented successes were those of the Edinburgh and London obstetrician Dr James Blundell (1790-1873) who, "...appalled at my own helplessness at combating fatal haemorrhage during delivery...", reported 10 direct donor to patient transfusions between 1819 and 1829. However, the equipment was primitive, the volumes transfused were small and, with no knowledge of blood groups, serious reactions were common. Indeed, the Obstetrical Society of London in its *Enquiry into the merits of blood transfusion (1873)* concluded that "*...because of its inherent dangers, it should only be used as a last resort*". Despite the discovery of the major (ABO) blood group system by Landsteiner in 1901, transfusion using donor blood advanced little until introduced into military practice towards the end of the First World War However, it was not widely used in civilian practice during the next two decades despite the establishment of a number of local private or voluntary Blood Banks. It was only during the Second World War that a network of Blood Transfusion Centres and panels of volunteer blood donors in the modern sense were established in the UK. Donations of whole blood collected into glass bottles containing citrate anticoagulant, became sufficiently available in the 1950s and '60s to underpin medical developments such as open heart surgery, kidney dialysis and the treatment of haemolytic disease of the newborn. The next major technical advance was the replacement of glass bottles by plastic transfusion packs from the mid-1970s, making the separation and storage of individual constituents of the blood (red cells, platelets and plasma) much easier and opening the way to modern blood component therapy. War has always been a major promoter of advances in transfusion technology and medicine, and the recent conflicts in Iraq and Afghanistan have seen important improvements in survival after massive traumatic haemorrhage.

1.2 From these foundations in the work of Blundell, blood transfusion has become an essential component of modern medicine and surgery, built on the

altruism of volunteer donors. During 2008-2009, the UK Blood Transfusion Services issued 2.2 million units of red cells, more than 250,000 units of platelets and more than 400,000 units of plasma[1].

2. Blood components

2.1 The rationale for the separation of the major blood components after donation is that the main constituents of the blood – red cells, platelets and plasma – all have different storage requirements if they are to remain useful in treating patients. For example, red blood cells survive for at least 35 days if stored in a refrigerator at 4°C whilst platelets are damaged by refrigeration and have to be stored at room temperature. Some of the important blood clotting proteins present in the liquid part of blood (plasma) quickly become inactive unless frozen soon after donation (a process that destroys both red cells and platelets). Therefore, it makes both clinical and economic sense to separate and store the individual blood components in ideal conditions. Furthermore, most patients needing transfusion require only one particular part of the blood replacing, such as red cells for anaemia, and separation of the components allows several patients to benefit from a single whole blood donation.

2.2 Traditionally, individual blood components are prepared from whole blood by centrifuging (spinning) the plastic bag into which the volunteer has donated. The dense red cells move to the bottom of the bag, with plasma above and the platelets forming a layer in between. The individual components can then be squeezed out into separate storage packs. Special "multiple packs", connected by plastic tubing, are used for this process, ensuring the components remain sealed in a sterile environment.

2.3 In recent years, it has become increasingly common to collect individual blood components directly from the donor by a process known as "apheresis". The blood donor is connected to a machine, called a cell-separator, which centrifuges the blood and takes out only the particular component that is needed. The rest of the blood is immediately returned to the donor. This improves the efficiency of blood donation by allowing the blood services to

collect just those components they need for the treatment of patients. Furthermore, those healthy volunteers who are, for instance, only donating platelets or plasma, can donate more frequently (up to monthly) than those donating red blood cells (once every 4 months) as the body replaces platelets and plasma much more quickly than red cells without harmful affects. More than 80% of platelet donations are now collected by apheresis. With conventional collection methods, the platelets from four donations have to be pooled to make an *adult therapeutic dose (ATD)* for transfusion to a patient. However, using apheresis, a full ATD can be taken from just one blood donor, thus reducing the number of *donor exposures* for the patient and helping to reduce the small risk of transfusion transmitted infection.

3. Why is blood transfused?

3.1 Red Cells

3.1.1 Red cells are the most commonly transfused blood component. Like all blood cells, red blood cells ("erythrocytes") are made in the bone marrow. Normal red cells live for about 120 days after entering the bloodstream and their function is to transport oxygen from the lungs to vital organs and tissues, carried by the iron-containing red pigment haemoglobin (Hb) that gives the cells their characteristic colour. When patients have a very low level of haemoglobin, known as "anaemia", their ability to carry oxygen to vital organs is reduced and this can be improved by transfusion of red cells.

3.1.2 The most clear cut indication for red cell transfusion is in the patient who has dangerous bleeding ("haemorrhage") after trauma, surgery or childbirth, when prompt replacement of red cells can be life-saving. The other major causes of anaemia are due to failure of the bone marrow to make enough healthy red cells or the production of red cells that have a shortened lifespan in the circulation. The non-bleeding causes of anaemia are very many, ranging from genetic diseases of the blood such as thalassaemia and sickle cell disease, a lack of essential nutrients such as iron or vitamin B12, serious bone marrow diseases such as leukaemia or aplastic anaemia and anaemia caused by inflammation or cancer. The use of red cells in specific diseases is considered in more detail in Section 5. In

general terms, although transfusion is essential to maintain life in patients with massive bleeding or complete failure of the bone marrow, many of the "medical" causes of anaemia can be improved in varying degrees by other measures, such as iron therapy or treatment of the underlying disease and the indications for red cell transfusion, including the balance of risks and benefits, are less clear cut. This is the subject of much recent research, feeding into guidelines for clinical practice. Improvements in surgical and obstetric techniques in western countries have reduced the use of blood for these purposes and in most modern hospitals more than half of all red cells are transfused to "medical" patients.

3.2 Platelets

3.2.1 Platelets are also made in the bone marrow and they are an essential part of the body's clotting system. Patients with very low platelet counts are at increased risk of bleeding and, at extremely low levels, may die of serious internal bleeding such as brain haemorrhage. Low platelet counts ("thrombocytopenia") are seen in diseases of the bone marrow such as leukaemia but are also often a temporary affect of essential medical treatments such as cancer chemotherapy or cardiac bypass surgery (damaged in the "heart/lung machine"). Thrombocytopenia is also commonly seen in patients on intensive care units and in sick newborn babies, often caused by serious infection.

3.2.2 Platelet transfusions only became readily available from the late 1970s. Although they may be transfused to specifically treat an episode of bleeding, the large majority of platelet transfusions in modern medical practice are given to try and *prevent* bleeding in patients with low platelet counts ("prophylaxis") while recovery is awaited[2]. The relative benefits and merits of prophylactic, as opposed to *therapeutic* use of platelets is a subject of current clinical research (see below).

3.3 Plasma components

3.3.1 Plasma is the liquid component of the blood, in which the blood cells are suspended. Among its many constituents are the essential blood clotting

proteins ("clotting factors") and antibodies to fight infection ("immunoglobulins"). Because some of the clotting factors start to break down quickly after blood donation, plasma for clinical use is separated from the blood cells and quickly frozen for storage – this is known as "fresh frozen plasma" (FFP). FFP can be stored for up to two years at -30^{0}C. A derivative of FFP, cryoprecipitate, can be prepared that contains a higher concentration of the clotting factors fibrinogen, Factor VIII and von Willebrand's factor.

3.3.2 The main use of FFP is to treat patients who are bleeding because of a reduction in several of the many different clotting factors in normal blood. This is most commonly seen in patients where the natural clotting system is activated by major tissue trauma (accidents, military trauma, obstetric complications) or serious infection, with "consumption" of clotting factors as blood clots are made faster than new clotting factors can be produced. This is often known as "disseminated intravascular coagulation" (DIC) and is a potentially life-threatening complication of many acute illnesses. DIC is also commonly seen in very sick newborn babies on neonatal intensive care units. As most clotting factors are made in the liver, patients with severe liver disease, such as cirrhosis, are also at risk of bleeding.

3.3.3 FFP, or cryoprecipitate, is no longer used to treat inherited clotting factor deficiencies, such as haemophilia, as much more effective and convenient clotting factor concentrates are available (eg Factor VIII concentrate for Haemophilia A). Similarly, FFP is no longer recommended in the UK for the treatment of bleeding due to the anticoagulant drug warfarin as a specific antidote is readily available[3,4].

3.3.4 As a precautionary measure to reduce the risk of transmitting variant CJD, FFP for use in children below the age of 16 is now derived from imported donations from countries with a low incidence of bovine spongioform encephalopathy (BSE) – mainly the USA. This measure was introduced by the Department of Health in 2004. Similarly, since 2002, UK

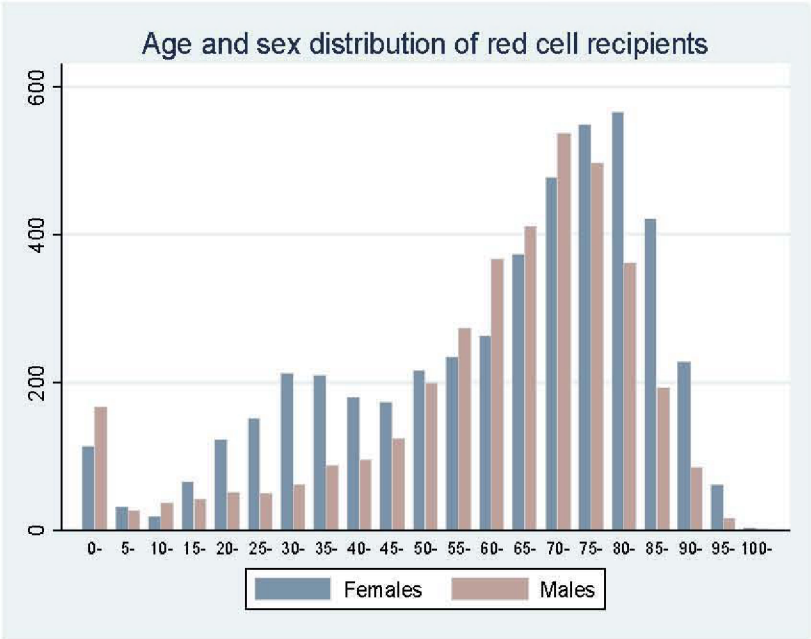
plasma has not been used to manufacture *blood products* such as Factor VIII concentrate used in the treatment of haemophilia.

3.3.5 National audits[5] show that the majority of FFP is used *to* try and *prevent* bleeding (prophylaxis) in patients with abnormal laboratory tests of coagulation but no actual bleeding. Again, this is a current area of controversy and ongoing research.

4. Who gets blood transfusion?

4.1 In the UK, we have useful data on the types of patient receiving blood transfusions from audits and epidemiological studies. The EASTR study[6] for example, collected data on all transfusions performed in 29 representative UK hospitals over a 12 month period in 2001/2002 and linked them to the hospital records to determine the reason for transfusion. Detailed transfusion data from 18 hospitals in the North of England have been published for comparable 28 day periods in 2000 and 2004[7]. The findings for the main blood components are discussed below:

4.2 Red Cells



EASTR Study 2001/2002

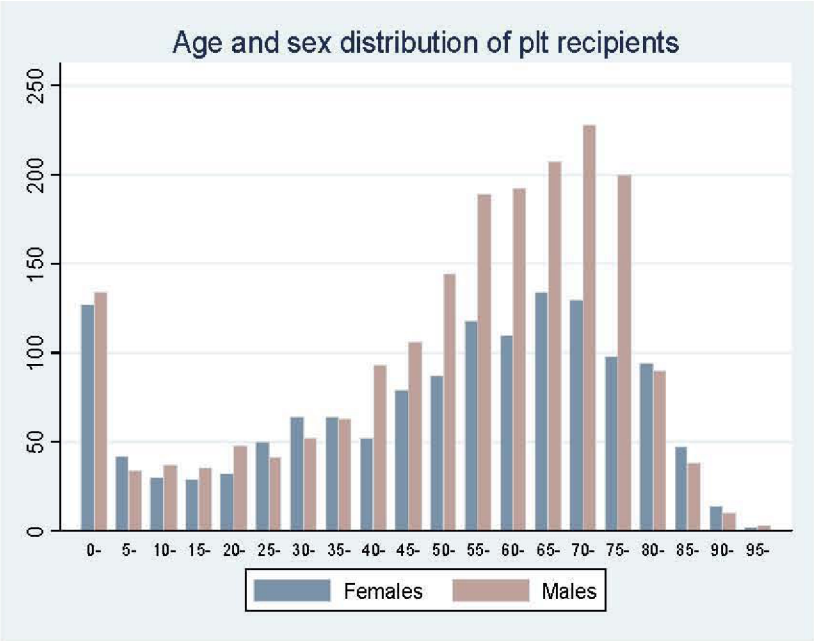
The EASTR data showed an early peak of transfusions in sick newborn babies (mainly in the first month of life). Red cell transfusion is more common in females than males in the 20-40 year age group because of obstetric and gynaecological indications (bleeding). As in all such studies, the risk of needing a transfusion increases sharply over the age of 60 and the median age of patients receiving red cell transfusion was 69 years.

The large prospective observational study of nearly 9,000 red cell transfusions issued over a 28 day period by 18 hospitals in the northern region of England in 2004[7] showed that 62% went to medical patients (compared to 52% in 2000), 33% to surgical patients (41% in 2000) and 5% to obstetrics and gynaecology patients (6% in 2000). The most common surgical indications for transfusion were orthopaedic surgery, such as hip or knee replacements (6.0% of all red cells transfused), gastrointestinal and liver surgery (5.5%) and cardiac surgery (5.2%). 5.9% of red cells were used in patients with trauma, such as road traffic accidents. Of non-surgical indications, haematology patients (including leukaemia treatment) used 18.2% of all red cells, 13.8% were used for patients with gastrointestinal bleeding (such as bleeding peptic ulcers) and cancer patients (8.8%). Transfusions to newborn babies only used 0.9% of red cells. The average age of patients receiving red cells was 63.6 years and nearly 60% were transfused to patients over 65 years of age. Compared to 2000, the number of red cells used in surgery had fallen by around 25% despite significant increases in activity in both orthopaedic and cardiac surgery. However, the number of red cells used for medical indications had risen by 10% since 2000.

Following the *Better Blood Transfusion* initiatives promoted by the Chief Medical Officers of the UK countries in a series of Health Services Circulars between 1998 and 2007[8], there has been a significant reduction in the use of red cells in most hospitals. In England and N Wales, red cell issues to hospitals fell by 19% between 1999 and 2010. This coincides with the appointment of Transfusion Practitioners, the establishment of Transfusion Committees in most hospitals and a range of national and regional initiatives to engage clinical staff in blood conservation. As noted above, most of this

reduction in red cell use is in the surgical specialties. Efforts are underway to study the more complex use of blood in medical specialties and develop better treatment guidelines based on research evidence.

4.3 Platelets



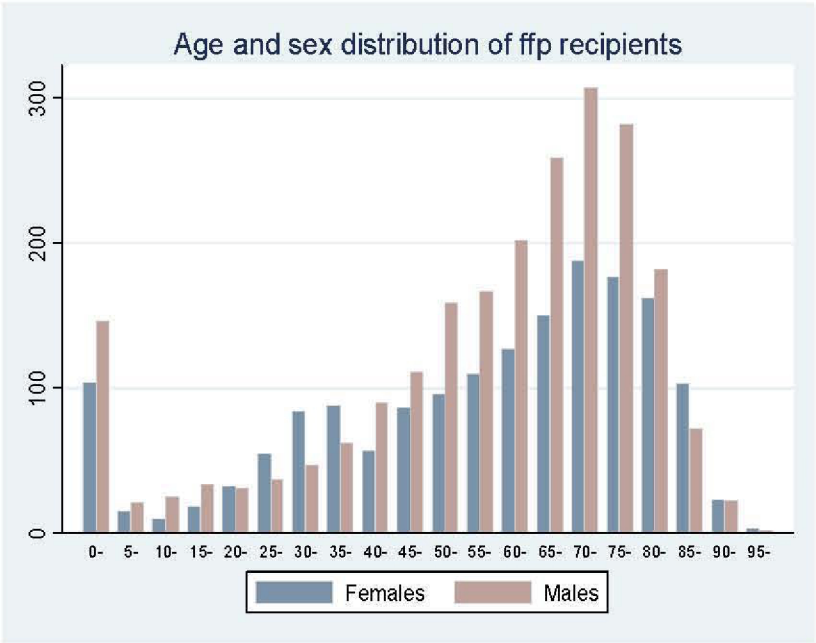
EASTR Study

Again, the EASTR study shows a peak of platelet transfusions in the first month of life and then an increasing incidence of transfusion in mid- to late life. The higher rate in older males may relate to cardiac surgery.

The major users of platelets in the EASTR Study were haemato-oncology (such as leukaemia treatment) (27%), cardiac surgery (17%), babies and children (13%) and liver disease (10%). The median age of platelet recipients was 59 years.

The number of platelet transfusions in UK hospitals has increased by 10% in recent years and the reasons for this are currently being investigated.

4.4 Fresh Frozen Plasma



EASTR Study

The EASTR study showed a similar pattern to platelet transfusion, with peaks in the newborn period and in later life. Around 45% of recipients of FFP had a surgical diagnosis and there was a large excess of older male recipients related to cardiac and vascular surgery. The median age of FFP recipients was 64 years.

A National Comparative Audit of the use of FFP was carried out in England in 2009 (NHS Blood & Transplant and Royal College of Physicians of London). 5053 FFP transfusions in 183 hospitals were studied. The biggest users were “surgery” (20%), liver disease (18%), cardiac surgery (12%) and treatment of major haemorrhage (12%).

Issues of units of FFP fell by 12% in England between 2000 and 2007 but have risen by around 5% in the last 3 years.

5. Current indications, contraindications and specific risks of blood component transfusion

5.1 Introduction

Until recently, public and professional concerns about the risk of receiving blood component transfusion centred on the transmission of infectious diseases, particularly viruses such as Hepatitis B and C and HIV. The risk of transmission of these "classical" transfusion transmitted infections has fallen significantly in the last two decades because of improvements in donor selection and better and more sensitive screening tests using molecular techniques such as the polymerase chain reaction (PCR). In 2009, the estimated risk of acquiring a viral infection from single donor blood components in the UK was 1.09 per million donations for Hepatitis B, 0.19 for HIV and 0.01 for Hepatitis C[1].

Since the inception of the UK voluntary Serious Hazards of Transfusion (SHOT) scheme in 1996[9], it has become clear that, although transfusion is a very safe process compared to many medical or surgical interventions, the highest risks are now related to misidentification of patients at the time of blood sampling or transfusion. SHOT has also identified that bacterial transmission by certain components, especially platelets, remains a significant, albeit rare, risk and has highlighted previously poorly recognised risks such as transfusion-related acute lung injury (TRALI). A particular strength of the UK SHOT scheme has been the ability to suggest interventions at Blood Service or hospital level to improve transfusion safety and monitor subsequent success. To keep this in context, the 2009 Annual SHOT Report[1] identified only one death in the UK definitely attributable to transfusion, compared to 12 in 1996, despite a 6-fold increase in reporting activity by hospitals during this time period. There have been no confirmed reports of viral or parasitic (such as malaria) transfusion transmitted infections to SHOT since 2005. However, the emergence of variant CJD as a new, but as yet highly uncertain and poorly understood, risk of transfusion in the last decade has underlined the need for continuing vigilance and clinical research to refine the indications for blood component transfusion in

individual patients. Technologies to remove vCJD prions from blood components by filtration are also under evaluation by UK blood services.

5.2 Red blood cells

Red cells are stored in special blood refrigerators at 4°C and can be transfused up to 35 days after collection. Much of the recent research into their use has focused on understanding the balance between the benefit – increasing the delivery of oxygen to vital organs – and the potential harm of transfusing stored red blood cells in the many different types of patient. The benefits of transfusion are most clear in patients who would otherwise quickly die from severe bleeding whereas any harmful effects are more important in less acute situations or where alternative treatments are possible.

Safety issues

There is no doubt that stored red cells undergo a number of changes (*storage lesion*) that impair their ability to flow and function normally after transfusion. These include a reduced ability to release oxygen that takes up to 24 hours after transfusion to normalise. Laboratory research shows that stored red cells may, at least temporarily, reduce blood flow in organs and tissues with already low oxygen levels. All of these effects are most likely to be harmful in patients who already have compromised organ function, such as intensive care patients and patients recovering from major surgery. A very influential randomised controlled trial of intensive care patients in N America[10] (the *TRICC* trial) showed that a *restrictive* red cell transfusion policy (ie only transfusing at lower Hb levels) was associated with improved survival, especially in patients with severe infection. Recent, although controversial, studies of patients having heart surgery have shown a possible association between risk of death or serious complications and the transfusion of older stored red cells[11]. A number of prospective clinical trials have been started around the world to see whether this is a true effect as it would have big implications for the provision of blood.

Clinical guidelines

Much research has focused on identifying *transfusion trigger* levels of Hb to guide clinical practice. The normal concentration of Hb is above 11.5g/dl in women and above 13.5g/dl in men. For many years it was traditional to use a trigger Hb concentration of 10g/dl for red cell transfusion after surgery and for transfusions to medical patients, but this was simply based on custom and practice. However, evidence from animal studies and observation of Jehova's Witnesses who declined blood transfusion for major surgery showed that healthy individuals, with good heart and lung function, can safely tolerate much lower levels of Hb without harm, although complications and mortality increased with Hb levels below 5g/dl. Older individuals and those with impaired blood flow to the heart (ischaemic heart disease) may not tolerate such low Hb levels safely. The ability to tolerate low Hb levels also depends on factors such as the speed of onset of anaemia (more dangerous with sudden bleeding) and the presence of other medical problems that affect the individual's ability to overcome the effects of anaemia. In patients who need long term transfusion support, the best indicator of the need for transfusion may well be measures of quality of life, rather any single Hb level. Therefore, it clearly does not make sense to have a *universal transfusion trigger*. Research is in progress to find better clinical and laboratory indicators of exactly who needs transfusion, and when, and to *individualise* treatment. In the meantime, current guidelines try to provide a sensible balance between risk and benefit in different patient groups although much controversy and variation in clinical practice persists.

Current consensus guidelines for red cell transfusion in the major patient categories can be summarised as follows:

- Major haemorrhage – rapid transfusion based on clinical parameters, such as blood pressure, pulse rate and estimated blood loss following a major haemorrhage protocol

- Slow onset "medical" anaemia such as those due to iron, vitamin B12 or folic acid deficiency – avoid transfusion and give the appropriate replacement therapy
- Anaemia following surgery – keep a comfortable margin above any *critical point*

  Hb 7g/dl for younger, otherwise healthy patients

  Hb 9g/dl for older (>60 years) patients and those with known heart disease
- Patients in critical or intensive care – 7g/dl (9g/dl if cardiac disease)
- Transfusion dependent patients:

  Thalassaemia major – 10g/dl (to suppress bone marrow production of red cells)

  Other indications – transfuse to optimise quality of life measures, such as fatigue

5.3 Platelets

Platelets are stored at "room temperature" (22°C) and quickly become inactive if refrigerated. They have a much shorter shelf life before transfusion (normally 5 days) than red cells. The normal adult dose is the platelets collected from 4 donations (or the equivalent dose from a single donor collected by apheresis) and platelets have to be transfused at least daily to maintain treatment levels in the patient.

Safety issues

Although there is some reduction in platelet function during storage, the main reason for the short shelf-life is the risk of growth of bacteria that enter the pack from the donor's skin at the time of collection. Platelets in plasma are a good culture medium for many bacteria and growth is promoted by storage outside a refrigerator. Routine culture of untransfused platelet packs after 5 days storage shows that up to 1 in 2,000 may contain bacteria, although the frequency of clinical reactions is much lower. Although most of the bacteria are relatively harmless skin germs from the donor arm, much more dangerous bacteria occasionally grow and fatal reactions have been estimated at around

1 in every 25-80,000 platelet transfusions. UK SHOT reports from 1996-2009 have documented 33 bacterial transmissions by platelets, with 8 fatalities. All UK blood services have taken major measures to reduce this risk in recent years, including new, research based arm-cleaning protocols for donors, diversion of the first 20-30ml of each donation (most likely to contain germs) to use in blood testing and the routine culture of samples from all platelet packs during their shelf-life. New technologies to "sterilise" platelets using light-activated chemicals are also in development, but not yet suitable for routine clinical use.

Because of their high plasma content, platelet transfusions cause allergic reactions more often than red cells and may also, rarely, cause the serious complication of transfusion-related acute lung injury (TRALI).

Clinical guidelines

The scientific evidence base for the use of platelet transfusions is generally weak and, until recent years, few good clinical trials have been performed to guide clinical practice in terms of when?, how often? and how much? Current guidelines are, therefore, largely based on expert opinion. Audits[2] show that most transfusions are given "prophylactically" to non-bleeding patients with low platelet counts, with the intention of preventing rather than treating bleeding. Following recent studies suggesting that a policy of only giving platelet transfusions to patients with minor signs of bleeding, whatever the platelet count, is just as safe and exposes the patient to many fewer transfusions a large randomised trial has been set up involving hospitals in England, Scotland and Australia and should complete in late 2011.

Current consensus guidelines for platelet transfusion[13] can be summarised as follows (the normal platelet count is 150-400x10^9/l):

- Low platelets due to bone marrow failure or cancer chemotherapy – transfuse if count less than 10x10^9/l
- Low platelets due to major trauma and/or massive transfusion – transfuse if count less than 75x10^9/l

- Surgical procedures in patients with low platelet counts
  - $50x10^9$/ is safe if clotting tests are otherwise normal ($100x10^9$/l recommended for brain surgery or high velocity injuries)

5.4 Fresh Frozen Plasma (FFP)

FFP is stored at -30°C and has to be thawed in the hospital Blood Bank immediately before it is used. Each pack contains around 200ml and the recommended dose is between 15 and 20ml/kg patient body weight (at least 4 units of FFP in an average sized adult). Alternatives to UK single donor FFP include commercially available FFP prepared from pooled donations (mainly US donors) and treated by the *solvent detergent* technology to kill most viruses (Octaplas™) and single donor plasma units imported from US donors and treated with methylene blue and light exposure to kill viruses (recommended by the UK Department of Health for children under 16 years of age as a vCJD risk reduction measure).

Safety issues

FFP and platelets are the blood components most often associated with severe allergic reactions[1]. The 2009 SHOT Report estimates the incidence of allergic reactions to FFP to be 10.4/100,000 units transfused, compared to 20.3/100,000 for platelets and 2.4/100,000 for red cells. However, the incidence of very severe or life-threatening (anaphylactic) allergic reactions is significantly higher for FFP.

Transfusion-associated acute lung injury (TRALI) was recognised as a significant, and sometimes fatal, transfusion hazard from the mid-1990s. It is caused by antibodies in the donor plasma that react with the patient's white blood cells and damage the lungs. These antibodies are usually found in female donors who have had pregnancies. SHOT data[1] suggests that the risk of TRALI is around 1 in every 6800 units of female donor FFP issued, compared to virtually zero risk for male donor FFP (and 1 in 88,000 for platelets). Following a SHOT recommendation in 2003 to source all FFP from male donors, the UK blood services have now achieved this and there has

been a significant fall in the number of cases of TRALI related to FFP – an example of effective *haemovigilance*.

Clinical guidelines

The scientific evidence base for the use of FFP is limited and guidelines, once again, are largely based on expert opinion. The 2004 British Committee for Standards in Haematology (BCSH) Guideline[3] can be summarised as follows:

Consensus indications for FFP:

- Bleeding due to multiple clotting factor deficiencies, such as massive haemorrhage and intensive care patients with abnormal clotting
- Inherited clotting factor deficiencies where no factor concentrate exists (eg Factor V deficiency)
- Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)

There is wide variation in the clinical use of FFP, both in the UK and worldwide, largely based on traditional practice. The recent English National Comparative Audit[5] showed that around 40% is used in non-bleeding patients because of abnormal clotting tests, 14% was used to reverse the anticoagulant drug warfarin (for which a specific antidote exists and FFP is no longer recommended in the UK) and 40% of patients were given a dose below the recommended range. Most specialists in Transfusion Medicine believe there is substantial scope to reduce current use without impairing patient care.

6. Alternatives to blood component transfusion

6.1 Red cells

For some patients undergoing planned surgery likely to need transfusion support, it was customary to offer the chance to have units of their own blood removed and stored in the 5 weeks before the operation (*pre-deposit autologous transfusion* or "PAD"). PAD is now rarely performed in the UK as it was originally designed to reduce the risk of viral infections such as Hepatitis C and HIV that are now so rare as to make the process both

clinically and cost-ineffective. Furthermore, PAD does not protect patients against the most common serious hazard of transfusion – receiving blood intended for another patient because of misidentification. Indeed, PAD may increase overall risk as patients who have pre-deposited blood tend to be more anaemic and at higher risk of receiving a transfusion.

New and effective technologies to reduce exposure to donor red cells in surgery include *intraoperative cell salvage* (ICS), where blood spilt during the operation is automatically washed and retransfused using a special machine. ICS is quickly becoming routinely available for many types of major surgery and in the treatment of massive bleeding in UK hospitals and its use can be life-saving in emergency situations. ICS is also acceptable to many patients who otherwise refuse blood transfusion on religious grounds.

"Artificial blood" using haemoglobin solutions or other chemicals capable of carrying oxygen has not entered clinical practice, despite many trials over three decades. Most of these agents have proved to be ineffective or dangerous and it is unlikely there will be progress in the near future. There is promising work on growing red cells in the laboratory from human stem cells, but the technical problems are great and clinical use is still probably many years away.

6.2 Platelets

Attempts to produce artificial platelets have failed, so far, to progress from the laboratory to clinical trials despite some encouraging results in animal experiments.

6.3 Plasma and clotting factors

Many experts in blood clotting believe that, over the next few years, there will be a move away from using FFP to more targeted therapy with manufactured blood products like *Prothrombin Complex* and *fibrinogen concentrate* that contain predictable amounts of specific clotting factors and have been treated to kill viruses. Some single blood clotting factors, such as Factor VIII for

haemophilia, are now made by recombinant DNA technology, rather than from donor blood.

7. Recording blood transfusions and seeking patient consent

7.1 Recording of blood transfusions

7.1.1 It has long been recognised, and reflected in national guidelines, that good documentation of the clinical transfusion process increases patient safety and may improve the quality of decision making. This has been raised to a new level by the Blood Safety and Quality Regulations (SI 2005 No. 50), translation of the European Blood Directive into UK law, which requires blood component storage and "cold chain" records to be stored for 15 years and positive evidence of the transfusion of every unit to be stored for 30 years. The latter requirement is intended to ensure the "traceability" of all blood components from donor to recipient in the event of transfusion-transmitted infection.

7.1.2 In terms of recording the transfusion process in the patient medical record, the "*Notes on Transfusion*" issued to UK hospitals by the Department of Health and Social Security in 1973 already state clearly that "*A record of every transfusion should be made in the patient's case notes* ...", emphasising that "... *the main reason for accurate recording is the protection of the patient*". They underline the need to retain the *serial numbers* of all blood units transfused so that, in the case of "... *suspected post-transfusion serum hepatitis* ..." donors could be traced and any other implicated components withdrawn. The only proven viral cause of post-transfusion hepatitis at that time was what we now know as hepatitis B. The *Notes* go on to recommend that notes are kept of the patient's pulse rate, blood pressure and temperature before and during the transfusion and any reactions that occur. Laboratory records should include the "... *clinical condition necessitating transfusion* ...". The 1984 update of these *Notes* has almost identical requirements for record keeping, with the exception of a requirement to retain laboratory records for not less than 7 years. The 1st edition of the UK Transfusion Services *Handbook of Transfusion Medicine* (1989)[14] simply

states that: "*Details of all blood components infused (including the donation numbers) must be entered into the patient's case record together with the compatibility report provided by the transfusion laboratory*". It strongly advises readers (clinical staff) to be familiar with their institution's policies and procedures for safe blood transfusion.

7.1.3 The British Committee on Standards in Haematology (a subcommittee of the British Society for Haematology) produced its first guidelines for *The administration of blood and blood components and the management of transfused patients* in 1999[15]. These state that good documentation is essential for investigation of adverse effects and to allow audits of the clinical indication for transfusion. A key recommendation is that the medical notes should contain a "*permanent record of the transfusion of blood and blood components* ..." including the blood transfusion compatibility report form (with donation ID numbers), sheets used for the prescription of blood and the record of nursing observations during the transfusion. There should also be "... *an entry in the case notes, describing the indication for the use of blood or blood components, the date, the number and type used, whether or not it achieved the desired effect and the occurrence and management of any adverse effects*". Laboratory records should be kept for 11 years (based on Product Liability legislation).

7.1.4 The BCSH *Guideline on the administration of blood components* was revised in 2009[16]. These give much more detailed recommendations for documentation of the transfusion process, in the laboratory and clinical records, taking into account the requirements of the Blood Safety and Quality Regulations (2005). It recommends that all organisations where blood transfusions take place should have local policies or guidelines, including the requirements for documentation and that staff members are trained and competency assessed for their role in the process. There are recommendations for minimum documentation of transfusion episodes in the clinical record. These should include the clinical indication for transfusion, the date the decision to transfuse was made and relevant discussion with the patient or those with parental responsibility (*vide infra*), exactly what should be

transfused, and when, and any special blood component requirements. The clinical record should also contain records of transfusion prescription, administration, post-transfusion observations, adverse events and whether or not the transfusion achieved the desired effect. This guideline recommends the use of specifically designed transfusion care pathways or combined transfusion prescription and monitoring charts that should form a permanent part of the patient clinical record.

7.1.5 Despite these recommendations, audits show continuing incomplete compliance with documentation of transfusions. Although many hospitals now use dedicated transfusion charts to capture and store key data, the reason for transfusion and its outcome are often not recorded. For example, the English National Comparative Audit (NCA) of the use of FFP (2009) found no reason for transfusion recorded in 28% of case notes. The NCA Bedside Transfusion Re-audit of 2009[17] found that no pre-transfusion clinical observations were recorded in 10% of records and post-transfusion observations were missing in 35%. Similarly, the NCA of Red Cell Transfusion in Neonates and Children (2010)[18] found clear records of the outcome of transfusion in only 18% of case notes.

7.1.6 In summary, the requirement for adequate documentation of transfusions in the case notes and laboratory records has been well-recognised and included in national recommendations since the 1970s. The basic information to be recorded has changed little over this time. There is no doubt that the quality of record keeping in the laboratory and the "traceability" of blood donations has improved to very high levels in recent years by application of the Blood Safety and Quality Regulations (2005) and regular inspection of hospital transfusion laboratories by the Medicines and Healthcare Products Regulatory Authority (MHRA). Whilst clinical record keeping has undoubtedly also improved, there is still evidence of variable compliance.

7.2 Patient Information and consent for transfusion

7.2.1 The questions of consent for blood transfusion and the provision of information for patients have achieved a higher profile in recent years in line with a general recognition of the importance of involving patients in choice about their medical treatment. The "*Notes on Transfusion*" issued to UK hospitals by the Department of Health and Social Security in 1973 and 1984 make no mention of patient information or consent. Similarly, these issues are not specifically addressed in the 1st edition of the UK Blood Services *Handbook of Transfusion Medicine* published in 1989.

7.2.2 Consent for transfusion

Specific written consent for blood transfusion, and the discussion of possible alternatives to donor transfusion, became a legal requirement in several countries and US States following the HIV epidemic in the 1980s. At present, there is no legal requirement to seek separate consent for blood component transfusion in the UK, although the legal basis for this was recently questioned by Farrell and Brazier[19]. Transfusion related to surgical procedures has generally been regarded as just a part of the general process of seeking consent for the operation. The 1999 BCSH guideline on administration of blood components[15] stated that *signed* consent for transfusion is not required. This is reiterated in the 2009 revision of this guideline[16] but it is noted that local institutional policies may require written consent. The 2009 guideline concludes that: "*Informed consent, either verbal or written, should be obtained (wherever possible) and documented in the patient's clinical notes*". The issues around consent for transfusion (and the information provided to patients) have recently been the subject of a large stakeholder consultation exercise carried out by the UK government's Advisory Committee on the Safety of Blood Tissue and Organs (SaBTO) in 2010[20]. The consultation process revealed a wide variety of opinion, especially on the question of whether formal written consent for transfusion should be required. Opinion among those responding to the consultation was more or less equally divided, although the main surgical specialist societies and Royal Colleges felt that separate written consent for blood transfusion is unnecessary (in contrast to some patient groups). There was general

agreement that better information for patients is important. The policy recommendations from the SaBTO consultation are awaited.

7.2.3 Patient information

During the mid to late 1990s, there was increasing awareness of the need to improve information for patients. A survey by Murphy et al in 1997[21] showed that only 31% of patients were given *any* information before transfusion and 20% of those who were informed would have liked more information, especially about risks of transfusion. The provision of better information to patients (and the parents of children) needing blood component transfusion was a key component of the *Better Blood Transfusion* initiatives promoted by the UK Chief Medical Officers in Health Services Circulars published in 1998, 2002 and 2007[8]. This agenda has been promoted by the appointment of Transfusion Practitioners and Hospital Transfusion Teams in most hospitals across the UK in the last decade. The UK Transfusion Services started to produce patient information leaflets for distribution to hospitals during the 1990s and there is now a wide selection of quality assured material, both national and local, available in all UK countries. The 1999 BCSH guideline[15] recommends the provision of patient information leaflets. In the 2009 BCSH guideline[16] there is recognition that patients vary in how much information they wish to receive, and the need for clinical judgement, but "*... the presumption must be that the patient wishes to be well informed about the significant risks and benefits of the proposed transfusion and any proposed alternatives*". However, audits continue to show that provision of information to patients, and documentation of the information given, is highly variable (highlighted in the SaBTO consultation exercise[20]). A very recent survey of 342 adult patients carried out in a typical UK District General Hospital[22] found that 13% of patients were unaware they had had a transfusion (very important information, as they would be excluded from being blood donors in the future). Fifty-nine % of patients remembered being given some information about transfusion but only 15% of these received a leaflet although these were readily available in the hospital. Of those receiving information, 70% remembered being told about the potential benefits of transfusion but only 23% remembered information about risks or possible harmful effects. Overall,

only 57% of patients surveyed felt they had been sufficiently informed about the transfusion process.

7.3 *Conclusion*

Informed consent for blood component transfusion does not appear to have been a major issue for clinicians in the 1970s although there was increasing awareness following the emergence of HIV in the 1980s. In the UK, consent for transfusion has not been formalised and, in the surgical setting, has been regarded as part of the normal process of obtaining consent for the overall procedure. The benefit of separate consent for transfusion, especially signed consent, remains controversial and there is a lack of good research evidence to inform best practice. There is more general agreement that patients should be provided with better information about transfusion, its risks, benefits and alternatives, ideally with access to objective, quality assured written material. The information provided and the patients consent, verbal or written, should be clearly documented in the patient record. Audits show that current practice in terms of providing access to information and recording consent often falls below that recommended in national guidelines.

Dr Derek R Norfolk
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