Alternatives to Blood Transfusion in Transfusion Medicine

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SECOND EDITION

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PART 1

History and Development of Transfusion Medicine
CHAPTER 1
From Blood Transfusion to Transfusion Medicine

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Attempts at using blood transfusion for the treatment of bleeding and anemia were made centuries ago mostly with disastrous effects, and although James Blandell (1818) is granted with the first successful transfusion, it was only during the twentieth century that blood transfusion came of age. The first half of the century was the era of pioneers and ingenious, hardworking individuals who made major breakthroughs. The second half saw the organization of large institutions charged with developing methods of procurement of safe and effective blood products. During this time, developments occurred in quick succession in a variety of fields like immunology, biochemistry, microbiology, genetics, molecular biology, and biotechnology, all impacting on transfusion and leading to today’s complex therapeutic intervention and the new specialization of transfusion medicine.

“The history of blood transfusion is marked by numerous bright pages but also some dark moments” as pointed out by Douglas Starr.

The surgical phase

Blood transfusion was introduced by surgeons, as theirs was the main need of finding a method of transferring blood from donor to patient. Alexis Carrel became famous for accomplishing a transfusion through suturing of vessels of the donor to those of the patient, in this case, the father to his baby daughter.

The technique underwent numerous modifications with the use of cannulae and tubes but remained difficult and cumbersome, so as to be used only infrequently. By the end of the first decade of the twentieth century, surgeons were performing some 20 transfusions a year at Mount Sinai hospital, New York.

New York had become home to a number of prominent physicians and scientists like Carrel, Landsteiner, Lindemann (the first full time specialist in transfusion, who introduced the multiple syringe method of transfusion), and others.

Direct donor–patient transfusions performed by surgeons continued to be practiced for decades and even as late as the early 1940s, though as described by Douglas Starr, “nobody liked transfusion as it existed, not the patient or the donor not even the doctors, who spent more time performing the transfusion, than the operation they were using it for.” In addition to being cumbersome, transfusions were resulting in severe reactions in more than 30% of instances.

The laboratory phase

By the end of the first decade, Landsteiner’s discovery of ABO blood groups dating to 1900 began to enter the transfusion field through the efforts,
to a large extent, of Ottenberg, who was also the first to use compatibility testing before transfusion; he was thus able to reduce the posttransfusion accidents concluding that “accidents can be absolutely excluded by careful preliminary tests.”

The next problem to be addressed was clotting of the blood which necessitated either suturing of donor to patient vessels or very rapid removal and reinjection of the blood, which presented technical difficulties.

The syringe technique introduced by Lindemann eliminated the need for suturing blood vessels, as he inserted needles into the veins of donor and patient, and withdrew and reinjected blood with syringes; nevertheless, the method required quick action and clotting was not always prevented. So the next hero proved to be Lewisohn who introduced sodium citrate as the anticoagulant, publishing his method in 1915.

Surgeons, however, were apparently reluctant to accept the simplified procedure offered by anticoagulation (namely the collection of blood in a vessel containing sodium citrate); they wanted to maintain transfusion as “a complicated and lucrative operation.”

Donor recruitment

Despite the use of anticoagulants, blood could not be stored for any length of time, hence the need for proximity of donor and patient. Compatible donors had to be recruited by the doctor, either from the patient’s family or the environment, so the donor supply was difficult and unreliable. In London, donor recruitment techniques were developed similar to those used to this day; donors were tested for ABO group and called by telephone when needed. Through the efforts of Percy Oliver, 2500 nonremunerated donors were made available to London hospitals by 1930. Oliver’s example was followed in other countries as well.

Meantime in Russia, Dr Alexander Bogdanov in 1926 established the “Central Institute of Hematology” where research in transfusion was carried out; experimenting with transfusion on himself, he eventually died of a massive intravascular hemolysis. In 1930, cadaver blood for transfusion was used for the first time in Russia by Dr Serge Yudin.

Blood banking

It was in Russia that the idea of storing blood was originated by Dr Yudin, leading to the institution of blood banks. Blood storage facilities spread throughout the country and blood was being stored for weeks resulting in a high percentage of reactions. Blood bank establishments were followed in Europe and the United States. In 1937, Bernard Fantus in Chicago established what was initially called Blood Preservation Laboratory changing the name later to Blood Bank as it operated with deposits and withdrawals of blood! This, in my opinion, unfortunate name, lingers until today throughout the world, giving false messages to potential donors.

Eventually with the improvement of storage vessels, anticoagulants, and preservatives, longer storage periods became possible, and in the 1940s, blood collection and transfusion stopped being a surgical enterprise and came into the hands of blood bankers. The year 1940 also marks the separation of plasma from whole blood. With regard to the volume of blood to be collected, based on experiments carried out in the 1930s and 1940s, it was decided that it should not exceed 13% of the donor’s estimated blood volume; the 70 mL/kg rule may not be very accurate as pointed out by Frank Boulton, but has prevailed ever since as has the addition of 120 mL of anticoagulant to each blood unit.

World wars

The need for blood transfusion skyrocketed during World War II leading to a series of developments; glass bottles for blood collection, acid citrate dextrose developed by Patrick Mollison for blood anticoagulation, and separation and fractionation of plasma by Cohn with the production of albumin. Dried plasma and albumin were used as volume
expander on the battlefields during World War II. “By the end of 1943, the military had received more than two and a half million packages of dried plasma and nearly 125,000 ampoules of albumin” as mentioned by Starr.

In parallel with these developments, blood group serology was progressing thus increasing the safety of transfusion. The Coombs test introduced in 1945 for pretransfusion testing reduced significantly the risk of immune hemolysis of transfused RBCs. New methods of antibody detection led to the recognition of blood group systems, an endeavor that continues until today.

**Blood collection—blood centers versus hospital blood banks**

Blood collection from volunteers was relatively easy during the war but became increasingly difficult after the end of the war. Some countries like France and England managed to proceed to the development of National Blood Transfusion Centers and adopt the idea that blood should be voluntarily given without payment to donors. They developed networks of smaller and larger blood banks for collection and distribution of blood to hospitals.

In other countries such as Switzerland and Canada, it was the Red Cross that assumed the responsibility to recruit volunteer donors and supply blood products. In the United States, the American Association of Blood Banks formed in 1947 emphasized individual responsibility for blood procurement, asking patients to replace transfused units or else reimburse the blood bank; in contrast, the Red Cross supported community responsibility.

In many countries, a multitude of small blood banks collecting blood from paid blood donors prevailed in the 1950s and 1960s. By the late 1960s, it became apparent that most deaths by transfusion worldwide were because of viruses, bacteria, or parasites in the blood, and that the incidence was higher from paid donor blood leading to pressures to eliminate paid blood donation. In some instances, this led to substitution of paid donors by friends and relatives of patients, the so-called “replacement donors.” Replacement donors are safer than paid but not as safe as truly volunteer donors.

Even until today, very few countries have achieved 100% collections from truly volunteer donors.

**Blood components: hemapheresis**

Progress in the technology of blood collection allowed the separation of whole blood into cellular components and plasma, making it possible to cover the transfusion needs of more than one patient with one unit of blood. The terms “component therapy” or “blood economy” were coined by Edwin Cohn. In developed countries, whole blood transfusion is a rarity nowadays as each unit is separated into red cells, plasma, and platelets.

Plasmapheresis, a term coined in 1914 by John Jacob Abel, described the removal of plasma while returning the cells to the donor. It was initially conceived as treatment to remove toxic substances from blood but evolved into a component production technique to provide plasma for transfusion and also for fractionation. Initially, it was carried out manually but it expanded, as automation became available in the 1960s. Blood cell separators made the procedure faster, safer, and yielding a better product. The need for albumin, gamma globulins, and coagulation factors encouraged the expansion of the fractionation industry with numerous companies becoming active throughout the world.

Therapeutic plasmapheresis or rather plasma exchange has contributed significantly in the treatment of hematologic, autoimmune, and metabolic diseases by the removal of antibodies of immune complexes, monoclonal proteins, or cholesterol.

Selective removal of cells, platelets, granulocytes, erythrocytes, and hemopoietic progenitor cells with discontinuous or continuous cell separators are carried out today in blood banks around the world. Platelet apheresis available since the 1970s is gaining ground, replacing gradually the recovery of random platelets for transfusion. Peripheral blood stem cell collection is also replacing bone marrow harvesting for bone marrow transplantation. Red cell
apheresis is the most recent development with advantages to both donors and patients, but is limited to larger donors.

**Blood safety**

The 1970s were marked by progress in the safety of blood through the introduction of screening for hepatitis B virus, which reduced the incidence of posttransfusion hepatitis (PTH), followed by documentation of residual PTH, and the identification of hepatitis C, for which testing was developed in the early 1990s. Unfortunately, the 1980s were marked by the AIDS epidemic, which caused a tremendous amount of grief to both patients and blood providers.

Pathogens continued to emerge calling for constant vigilance; West Nile virus and Chikungunya are the most recent invaders of the blood supply, but such epidemics are quickly brought under control nowadays.

Transfusion risks are not limited to infectious agents; alloimmunization and transfusion reactions, platelet refractoriness due to HLA and antiplatelet-specific antibodies, immunosuppression, transfusion-associated graft versus host disease, and TRALI (transfusion-related acute lung injury) have all received attention in the last 20 years, and measures to prevent them are continuously being studied.

Since a number of risks are attributed to the leukocytes in blood units, leukodepletion, or reduction of leukocytes in blood units by filtration, was introduced some 20 years ago and has proven to be effective in reducing febrile reactions, platelet refractoriness, cytomegalovirus transmission, red cell alloimmunization, and transfusion-induced immunosuppression.

The latest weapon in enhancing the safety of blood products is the inactivation of pathogens.

Solvent detergent treatment of plasma disrupts lipid-enveloped viruses and has been used in pooled plasma since the 1990s, whereas methylene blue, a photoactive virucidal agent, can be added to single units as it has proven to be safe especially since it is being removed before transfusion. Inactivation of pathogens in cellular components is proving more difficult although for platelets, psoralen and UVA light activation are proving feasible and effective. Although screening for viruses will continue, treatment of blood components could be added to reduce the risk of pathogens that we cannot test for.

Information technology (IT) is also adding to the safety of blood transfusion; electronic medical records, electronic blood donor records, computer crossmatch, and virtual blood inventories are beginning to change the way transfusion medicine is practiced.

**Alternatives to allogeneic transfusion**

The realization that blood can never become 100% safe gave impetus to the development of transfusion alternatives.

**Autologous transfusion**
- Autologous transfusion, initially by predeposit autologous blood collection before surgery took off mainly in the 1980s after the AIDS epidemic; its advantages (safety, economy of allogeneic blood) were soon counteracted by disadvantages, mainly cost, and its practice is now limited to selective indications.
- Intraoperative hemodilution, the removal of two units immediately preoperatively replacing the volume with crystalloid, proved feasible and had the advantage of decreasing the loss of red cells during surgery but concerns over cardiac ischemia have limited its application to experienced centers.
- Intraoperative red cell salvage particularly with automated centrifugation and washing machines introduced in the late 1980s, is gaining ground. The method is safe but is suitable mainly for major procedures with significant predicted blood loss such as cardiovascular, vascular, and orthopedic operations.
- Postoperative red cell salvage, namely blood collected from drains in the first 6 hours following surgery and reinfused without manipulation, is simple and is adopted mainly by orthopedic
teams, but concerns regarding reinfusion of activated plasma proteins and wound debris remain.

**Pharmacologic alternatives**

Hemopoietic growth factors became available in the 1990s as a result of progress in recombinant technology.

Erythropoietin was the first one to be used in renal disease resulting in drastic decrease in transfusions for these patients. The indications for rhEPO have expanded reducing the need for transfusion in hematologic disease and cancer patients as well as in the anemia of chronic disease and of prematurity.

Colony stimulating factors (CSFs), granulocyte G-CSF, and granulocyte-macrophage GM-CSF for chemotherapy-induced neutropenia, chronic, and neonatal neutropenia are widely used and have resulted in decreased mortality from infection.

The use of thrombopoietin for the treatment of thrombocytopenia has been under investigation for the past 10 years but has not yet had an impact in reducing platelet transfusions.

**Hemostatic agents**

Almost 50% of blood units are transfused during surgical procedures, so, if perioperative blood loss could be reduced, transfusions would also be reduced.

Antifibrinolytic agents like tranexamic acid, epsilon-aminocaproic acid, and aprotinin have all been used in the last 20 years and have resulted in significant decreases in the need for transfusions, mainly in cardiovascular surgery; unfortunately, aprotinin was recently implicated in thrombosis and myocardial infarction and has been removed from circulation.

**Fibrin sealants**

Topical agents made of fibrinogen and thrombin or platelet gel applied on surgical surfaces to accelerate hemostasis have been developed in the last 10 years and are used mainly in cardiovascular and orthopedic surgery.

**Red cell substitutes**

The greatest hope for reducing the need for transfusions was the development of red cell substitutes; perfluorocarbons and hemoglobin-based oxygen carriers have been the subject of intense investigation for more than 20 years but safety problems are still limiting them to clinical studies.

**Hemovigilance quality systems**

Systematic surveillance of adverse transfusion effects begun in the 1990s; France was the first country to implement such a system in 1993, followed by the United Kingdom in 1996. Today, most European countries have a hemovigilance system, although it is not obligatory in all of them. In addition to disease transmission and reactions, these systems document errors occurring in the entire transfusion chain; by far, the most frequent adverse events were those resulting from errors in the transfusion process leading to the transfusion of ABO incompatible blood. Implementation of hemovigilance has led to establishment of new guidelines for a number of procedures.

In the last 15–20 years, emphasis was given to the application of quality systems principles; good manufacturing practices (GMPs) and quality management systems have been implemented in blood centers, leading to better standardization of blood products and reduction of errors and accidents.

**Transfusion medicine**

Blood transfusion started out as a relatively simple replacement therapy for bleeding or anemic subjects. The last 20 years, however, have seen a tremendous progress in the development of a number of blood products and in their safety; at the same time, emphasis was placed on the proper indications for transfusion and on the choice of available specialized blood products to cover the needs of patients. Hemotherapy acquired a complexity that necessitated specialized knowledge, and studies began to show the deficiencies in such knowledge of clinicians in making transfusion
decisions. The effectiveness of transfusion came under scrutiny, while the risks remained significant. Blood bank personnel used to dealing with normal subjects such as the blood donors, with the emergence of therapeutic apheresis and stem cell collection for transplantation, have to deal now with patients; clinical laboratory training is not sufficient any more. These developments created the need for a new medical discipline, namely transfusion medicine. Transfusion specialists trained in laboratory medicine, pharmaceutical production, clinical medicine, epidemiological aspects, stem cell transplantation, legal, ethical, and administrative aspects could bridge the gap between the blood bank and the clinicians, be it internists, anesthesiologists, or surgeons. Clinician education and audits of transfusion practice are the tools by which transfusion specialists are aiming at improving the use of blood products.

In 1989, Dr Sacket coined the term evidence-based medicine (EBM), defined as the integration of the best research evidence with the best clinical expertise for good clinical decision making.

Transfusion medicine had to follow the principles and research methodologies that support EBM in order to develop transfusion guidelines based on such evidence, by performing Randomized Controlled Trials (RCTs). As per the McCarthy et al.’s study, 1000 RCTs on transfusion and apheresis and 70 meta-analyses were published by 2006.

Borzini et al. in an article published 10 years ago pointed out that “transfusion medicine had become a self-sufficient autonomous discipline." He went on to say that in order for TM to be “a stand alone discipline," self-recognition of such autonomy was necessary but not recognition by other disciplines!

I would argue that the latter recognition is important but unfortunately 10 years later the specialty of TM is still not widely recognized. Mueller and Seifried questioned recently why European directives, recognizing professional qualifications of European doctors, do not include TM, blood transfusion, or immunohematology at all, although TM is recognized as a specialty by a number of EU member states.

Efforts to this end should continue in order to attract young doctors to the specialty of TM and secure not only the safety and economy of blood but most importantly the continued research in the particular field.

Further reading

PART 2

Allogeneic Blood Usage—Risks and Benefits
CHAPTER 2
Allogeneic Blood Components

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Donor selection and testing

Blood in Europe and America is collected from nonremunerated volunteer donors who undergo donor selection procedures designed to protect the health of both donor and recipient. A health questionnaire aims to identify any underlying illness in the donors which may put their health at risk when making a donation and identifies any factors (such as foreign travel or promiscuous sexual behavior) which may indicate an increased risk of carrying a potentially transfusion-transmissible infection. All donations are tested for mandatory microbiological markers (hepatitis B and C, HIV, syphilis, and HTLV; see the chapter by Kitchen and Barbara [1] in this volume) and ABO and Rh blood groups. A proportion of donations also undergo testing for other viruses (e.g., CMV) and additional typing, such as extended blood grouping and human leukocyte antigen (HLA) typing, for patients with specific requirements.

Whole-blood collection, storage, and processing

European and American guidelines recommend that the volume of whole blood collected is between 450 and 500 mL ± 10 % [2–4]. Blood is collected into an anticoagulant composed of citrate, phosphate, and dextrose designed to prevent blood from clotting and maintain cellular function during storage. Adenine may also be added to the anticoagulant to improve the quality of red cells during storage if other solutions are not added during later processing steps. It is generally accepted that there are very few clinical indications for transfusion of whole blood, and the vast majority of blood is therefore processed into its basic components: red cells, platelets, and plasma. This is achieved by centrifugation of whole blood in the primary collection pack, followed by manual or automated extraction of the components into satellite packs.

The initial storage temperature of whole blood determines which components can be produced from it (Figure 2.1). Because platelet function rapidly deteriorates at 4°C, whole blood must be processed on the day of blood collection or stored overnight at 22°C for platelet production. However, for the production of red cells, whole blood can be stored at 4°C for 48–72 hours prior to separation. Plasma is generally separated from whole blood on the day of collection or from blood that has been stored at 22°C for up to 24 hours, as these methods have been shown to preserve plasma quality. In the United States, “liquid plasma” (which has not been frozen) and thawed plasma are also available for use when transfusion of labile clotting factors (e.g., factors V and VIII) is not required. The storage temperature, media, and shelf life of blood components is tailored to each type of component, so that there is preservation of component quality while affording the maximal usable shelf life.
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Collection of blood components by apheresis

Apheresis, from a Greek word meaning “to take away,” is an alternative to producing blood components from whole-blood donations by selectively collecting one or more components directly from donors and returning the rest to the circulation. Automated apheresis can be used to collect platelets, plasma, red cells, or granulocytes, and more specialized products, such as stem cells. The main emphasis in the past has been the collection of platelets and plasma components, with red cells being returned to the donor. The size and complexity of the equipment, as well as welfare of the donor, has previously necessitated this activity to take place in static clinics. However, smaller portable machines are now available that can be used on mobile sessions to collect red cells, platelets, and plasma. The main advantage of apheresis collections are that more than one dose of platelets or red cells can be collected from one donor per donation, thus reducing patient exposure to multiple donors. In addition, the hematocrit and hemoglobin content of red cells is much more consistent than those produced from whole-blood donations, which vary considerably because of the variation in hematocrit of whole blood in different donors.

Leukocyte depletion

Many countries have implemented universal leukocyte depletion (LD) of blood components, whereas in others leukocyte-depleted components may be issued for selected patient groups only. In the UK, a perceived benefit in terms of reduction in the risk of variant Creutzfeldt-Jakob disease (vCJD) transmission was a major contributory factor in the decision to introduce universal LD in 1998. Other benefits of LD, such as the potential for reduced immune complications and transfusion transmission of some cell-associated viruses (e.g., CMV), were considered more important by other countries.

Although in the past LD was performed at the bedside, the preference is now, because of quality reasons, for LD to be performed prior to component storage, usually within 48 hours of donation. For whole-blood donations, this is achieved by filtration, whereas an LD step by centrifugation/elutriation is integral to some apheresis technologies. Most whole-blood LD filters remove $\geq 2$ logs of platelets in addition to $\geq 4$ logs leukocytes. Therefore, only fresh-frozen plasma (FFP) and red cells can be produced from whole blood that has been leukocyte depleted. To produce platelet concentrates, each component (red cells, plasma, or platelets) must be filtered after their separation from whole blood. However, a second generation of whole-blood filters is becoming available that permit platelets to pass through the filter, although these are not yet in widespread use. LD results in a 10–15% loss of volume of whole blood or processed component but has minimal adverse effects on the quality of blood components.

The specification for leukocyte-depleted blood components varies between countries (Table 2.1), but all reflect the current capability of LD systems.
Chapter 2

Table 2.1 Specifications for leukocyte-depleted blood components.

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>Council of Europe/European directive</th>
<th>AABB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of residual leukocytes</td>
<td>&lt;5 × 10⁶/U</td>
<td>&lt;1 × 10⁶/U</td>
<td>5 × 10⁶/U for red cells and apheresis platelets &lt;8.3 × 10⁵/U for platelet-rich plasma platelets</td>
</tr>
<tr>
<td>Percentage of components in which this must be attained</td>
<td>99</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>Statistical confidence that this is attained</td>
<td>95%</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

Adapted from Cardigan and Williamson [5].

The fact that only a fraction of components are tested for residual leukocytes and that the limit of sensitivity of current counting methods is around 0.3 × 10⁶/U. Recent studies have demonstrated >3.8 log reduction in all leukocyte subtypes by whole-blood filtration and >3.1 log reduction by platelet filtration and one platelet-apheresis technology [6].

Despite advances in technology, LD systems occasionally fail. The risk that an LD system will result in blood components being issued that fail to meet the required specification for residual leukocytes is dependent upon a number of factors: the capability of the ID system, potential manufacturing defects in the LD filter or pack system, the proportion of components that are tested for residual leukocytes, and donor-related causes. An estimation of the likelihood of components is issued that exceed certain levels of residual leukocytes are illustrated (Table 2.2). Although most donor-related causes of filter failure are poorly understood, it is known that donors with sickle cell trait are more likely to either block LD filters or fail to leukocyte deplete; 100% of donations from such donors are therefore usually assessed for residual leukocytes [7].

Preparation and storage of red-cell components

Red cells are transfused to treat clinically significant anemia or blood loss. They are produced by removing the majority of plasma from whole blood by centrifugation (Figure 2.2). Red cells produced from blood where the buffy coat has been removed to make platelets will contain slightly lower volume and hemoglobin content because of loss of some red cells into the buffy coat (Table 2.3).

Table 2.2 Estimation of the residual risk of a leukocyte-depleted component being issued containing residual leukocytes above defined levels.

<table>
<thead>
<tr>
<th></th>
<th>&gt;1 × 10⁶/U</th>
<th>&gt;5 × 10⁵/U</th>
<th>&gt;100 × 10⁵/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis platelets</td>
<td>1:175</td>
<td>1:1352</td>
<td>1:6381</td>
</tr>
<tr>
<td>Pooled platelets</td>
<td>1:202</td>
<td>1:2028</td>
<td>&lt;1:22304</td>
</tr>
<tr>
<td>Red cells in additive</td>
<td>1:160</td>
<td>1:1522</td>
<td>1:7250</td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
<td>1:1072</td>
<td>1:18251</td>
<td>&lt;1:14783</td>
</tr>
</tbody>
</table>

Figures are taken from UK quality monitoring data for an 18-month period.

Residual risk = number of units issued/(number of units not tested/number of units tested) × number of units that have residual leukocytes above defined level.

Adapted from Cardigan and Williamson [5].
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**Figure 2.2** Production of platelet components from whole blood. WB, whole blood; LD, leukocyte depletion; PRP, platelet-rich plasma. Reproduced from Williamson and Cardigan [8], with permission.

**Table 2.3** Specification and typical values for volume and hemoglobin content for leukocyte-depleted red-cell components.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Volume (mL)</th>
<th>Hb content (g/unit)</th>
<th>Typical values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK EU AABB</td>
<td>UK EU AABB</td>
<td>Volume (mL) Hb (g/unit) Plasma volume (mL)</td>
</tr>
<tr>
<td>Red cell in additive solution, LD all methods</td>
<td>&gt;75%, 220–340 mL NS NS &gt;75%, &gt;40 g NS</td>
<td>284 ± 25 56 ± 7 17</td>
<td></td>
</tr>
<tr>
<td>Red cell in additive solution, LD, apheresis</td>
<td>&gt;75%, &gt;95%, &gt;128 mL red cells</td>
<td>&gt;75%, &gt;40 g &gt;95%, &gt;42.5</td>
<td></td>
</tr>
<tr>
<td>Red cells in plasma, LD for exchange</td>
<td>NS &gt;75%, &gt;40 g NS</td>
<td>321 ± 27 60 ± 6 116</td>
<td></td>
</tr>
<tr>
<td>Red cells in additive solution, LD buffy coat removed</td>
<td>As above</td>
<td>250 ± 19 49 ± 6 6</td>
<td></td>
</tr>
<tr>
<td>Red cells in additive solution, LD</td>
<td>As above</td>
<td>304 ± 17 58 ± 5 28</td>
<td></td>
</tr>
</tbody>
</table>

LD, leukocyte depletion; NS, not stated. Adapted from Cardigan and Williamson [5].
Red-cell components are stored at 4 ± 2°C for a maximum of 35–49 days in additive solution or 28–35 days in plasma. The shelf life depends upon the combination of anticoagulant, storage medium, blood pack, and whether any further processing steps are performed on the red-cell component (e.g., irradiation of the component).

For the vast majority of red-cell units processed, an additive solution containing adenine is added following separation to achieve a hematocrit of 50–70% and maintain red-cell quality during storage. The amount of residual plasma in a red-cell unit in additive solution is dependent on the hematocrit of the donor and how hard red cells have been centrifuged; it is between 5 and 30 mL. Red cells used for intrauterine transfusions (IUTs) and exchange or large-volume transfusion to neonates are normally stored or reconstituted in 100% plasma because of concerns over potential toxic effects of some of the constituents of additive solutions.

For patients with immunoglobulin A deficiency or severe allergic or anaphylactoid reactions to red cells, it may be necessary to remove >90% of plasma by washing and resuspending red cells in saline. Red cells from donors with rare phenotypes may be stored frozen for up to 30 years and are washed prior to transfusion to remove the cryoprotectant used to store them.

### Preparation and storage of platelet components

Platelets are transfused to patients who have an inherited or acquired deficiency of platelet number or platelet function [9]. There are two basic methods for producing platelets from whole-blood donations: the “buffy-coat” method favored in Europe or the platelet-rich plasma (PRP) method favored in North America (Figure 2.2). Specifications for platelet components are given in Table 2.4. In the PRP method, whole blood is separated into PRP and red cells following a “soft spin.” The PRP is then subjected to a “hard spin” to remove plasma and concentrate the platelets. In the buffy-coat method, whole blood is subjected to a “hard spin”

<table>
<thead>
<tr>
<th>Platelet processing method</th>
<th>Number of donors per dose</th>
<th>Specification</th>
<th>Volume (mL)*</th>
<th>Platelet content (× 10^9/platelet)</th>
<th>Typical values†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet-rich Plasma</td>
<td>5–10</td>
<td>40 mL per 60 × 10^9 platelets</td>
<td>Not specified</td>
<td>&gt;60</td>
<td>&gt;55†</td>
</tr>
<tr>
<td>Apheresis</td>
<td>1–2</td>
<td>Locally defined 40 mL per 60 × 10^9 platelets</td>
<td>Not specified</td>
<td>&gt;240§</td>
<td>&gt;240§</td>
</tr>
<tr>
<td>Buffy-coat-derived pooled</td>
<td>4–8</td>
<td>Locally defined 40 mL per 60 × 10^9 platelets</td>
<td>Not specified</td>
<td>&gt;60 per single unit equivalent</td>
<td>297 ± 38</td>
</tr>
</tbody>
</table>

*The volume is also partly dictated by a requirement to keep the pH of platelet components within specified limits during storage.
†Typical values are taken from national quality monitoring data from the English National Blood Service and are likely to vary between countries.
‡More that 90% of components must meet this criterion.
§More than 75% of components must meet this criterion.
Adapted from Cardigan and Williamson [5].
and separated into plasma, red cells, and a buffy coat that contains most of the platelets but also some leukocytes and red cells. Buffy coats from four to six donations are then pooled with a unit of plasma from one of the donations (or PAS, platelet additive solution), subjected to a “soft spin” and the PRP removed. The main difference between platelet concentrates collected by apheresis and PRP or buffy-coat platelets is that one or more adult therapeutic doses can be collected by apheresis from a single donor, which is not possible from one whole-blood donation.

For either buffy-coat-derived or apheresis platelets, the majority of plasma (70%) in the platelet concentrate can be replaced with an artificial PAS designed to maintain platelet function during storage. PAS differ in their composition; key elements are the use of acetate or glucose as a substrate for platelet metabolism, phosphate that buffers lactate production, citrate to prevent coagulation and lactate production and the inclusion of potassium and magnesium to improve platelet function during storage. Three different PAS are CE marked in Europe for platelet storage, and some European blood centers routinely produce and store platelets in PAS. Platelets are stored with agitation at 22 ± 2°C for up to 5 days, although in some countries this is extended to 7 days, provided platelets are screened for bacterial contamination. For some patients with severe anaphylactic reactions to platelets because of contaminating plasma proteins, platelets can be re-suspended in 100% additive solution. However, these “washed” platelets have a reduced shelf life of 24 hours because of the rapid deterioration of platelet quality in the complete absence of plasma, and a proportion of the platelets may be lost during the process.

**Preparation and storage of frozen-plasma components**

Plasma from whole-blood donations or apheresis is used to either prepare plasma components for clinical transfusion or fractionate to produce pure plasma proteins.

FFP is produced by rapidly freezing the plasma removed from a whole-blood donation or collected by apheresis. This is usually performed within 8 hours of donation to preserve the activity of coagulation factors V and VIII, which are relatively labile. However, FFP can be produced from whole blood that has been stored at 4°C or 22°C for 24 hours. FFP is now only used to replace congenital single coagulation factor deficiencies where purified factor concentrates are not available (factors V and XI). Most FFP is used to treat acquired multiple coagulation factor deficiencies, usually in a clinical setting of massive transfusion, liver disease or disseminated intravascular coagulation [10]. Specifications of frozen-plasma component are given in Table 2.5.

Cryoprecipitate is produced by slowly thawing FFP at 4°C. This causes the so-called cryoproteins to precipitate out: factor VIII, fibrinogen, von Willebrand factor (VWF), fibronectin, and factor XIII. By centrifuging and removing the supernatant plasma, the cryoprecipitate left is a rich source of these proteins in a small volume of plasma. Because of the widespread availability of purified or recombinant concentrates of factor VIII and VWF, cryoprecipitate is rarely used in the developed world to replace these factors and is mainly used in the treatment of hypo- or dysfibrinogenemia. Because of its high fibrinogen content, cryoprecipitate is also used as a starting material for the production of fibrin glue.

The supernatant plasma removed from cryoprecipitate (CDP, cryoprecipitate-depleted plasma) has been used as a replacement fluid for plasma-exchange treatment of patients with thrombotic thrombocytopenic purpura (TTP), as an alternative to FFP. There are theoretical advantages of using CDP as it contains lower levels of high-molecular-weight multimers of VWF, but this benefit has not been proven clinically. In the UK, however, solvent-detergent-treated FFP is now recommended for the treatment of TTP because it is subject to pathogen inactivation during its manufacture and carries a lower risk of transfusion-related acute lung injury (TRALI) because of plasma pooling, which dilutes down the donor antibodies.

Frozen-plasma components can be stored for up to 36 months depending on the storage temperature, which is usually below −30°C. Once thawed, FFP should be used immediately but can be stored for up to 24 hours at 4°C.