Crystalloids, colloids, blood products and blood substitutes

Christopher Naisbitt
KFA Mos
Roop Kishen

Learning objectives

After reading this article, you should be able to:

- describe the physiology of the body's fluid compartments
- recognize the effects of the commonly used non-blood fluids
- list the advantages and disadvantages of non-blood fluid therapy
- explain the methodology of blood collection and storage
- summarize current and prospective methods utilized to reduce the risks of donor blood transfusion

Abstract

Understanding the physiology of fluid distribution in the human body is fundamental to good clinical practice in anaesthesia and intensive care. Intravenous fluid therapies have a range of clinical and metabolic consequences and they should be context and patient specific. Inadequate or excessive fluid treatment is harmful to patients. There are numerous trials, both historical and current, investigating best practice in fluid therapy. New paradigms and guidelines are being published, and it is important for clinicians to keep up to date with current practice. There is a continued drive to improve the safety of donor blood and prevent transfusion errors. Knowledge of how blood products are collected, separated and stored is essential to prevent harm to patients through transfusions. The development of blood substitutes is progressing, with NHS trials involving stem cell originated red cells having begun.

Keywords Blood; blood substitutes; coagulation; colloid; crystalloid; goal-directed fluid therapy; plasma; platelets

Royal College of Anaesthetists CPD Matrix: 1A01, 1A02, 1E04, 2A05

Physiology

Total body water accounts for 60% of body weight; however, this varies with age, adiposity and gender. For a healthy adult male weighing 70 kg, this amounts to 42 litres of water (Figure 1).

The intracellular compartment contains 28 litres and the extracellular compartment holds the remaining 14 litres. This extracellular compartment is further subdivided into the interstitial and transcellular spaces (comprising 9.5 litres and 1 litre, respectively), and the plasma (comprising 3.5 litres) (Figure 2).

Starling forces and the Gibbs–Donnan equation help determine water distribution by osmosis across the capillary bed's semipermeable membrane. Starling forces explain the balance of oncotic and hydrostatic pressures in the capillary bed and Gibbs–Donnan describes the demand for electrical neutrality across a semi-permeable membrane.

We can describe fluids (or solutions) in terms of osmolality (osmoles of solute per kilogram of solvent [Osm/kg]), and tonicity (effective osmolality; equal to the sum of the concentrations of the solutes which have the capacity to exert an osmotic pressure gradient across the membrane). Fluids in relation to plasma are hypotonic (fewer solutes), isotonic (same amount of solutes) or hypertonic (greater amount of solutes). Traditional physiology indicated that a solution containing small, rapidly and easily metabolized molecules would quickly re-distribute as free water. Whereas one containing large, difficult to metabolize molecules will remain in the intravascular space for longer.

However, this long-held view has recently been challenged as the endothelial glycocalyx layer is becoming increasingly recognized as responsible for fluid movement across the capillary membrane. This is a complex luminal layer of glycoproteins and proteoglycans that lies between blood and the vessel wall. This membrane can become 'leaky' during insults such as sepsis, resulting in peripheral oedema. It provides a degree of mechanical protection (e.g. from shear stress), and houses vascular protective enzymes such as superoxide dismutase. The integrity of this layer is essential in maintaining fluid homeostasis.[1]

Crystalloids

Crystalloids contain low-molecular-weight solutes dissolved in water. Conventionally, we considered those with slowly metabolized molecules would remain in the circulation longer. The subsequent rise in oncotic pressure would draw water out of the intracellular space and into the intravascular space increasing the intravascular volume further. This would be sustained until the ions re-distribute into the intracellular space; a process dependent on the permeability of the cell membrane and activity of the ATPase pumps. The end result was believed to be a temporary expansion of the intravascular volume. However, ultimately a redistribution of free water into all compartments occurs and the respective volumes are reset to their original values. Small sugar solutions were considered to undergo this process rapidly, leaving behind free water to be re-distributed. This occurred as a result of the small molecular sugars being rapidly metabolized, and the solvent not being electronically bound to the solute (such as in electrolyte solutions). However, this theory is being modified in light of the identification of the endothelial glycocalyx layer.

Christopher Naisbitt *FRCA is an ICU Registrar at Royal North Shore Hospital, and a Lecturer at Griffith University, Queensland, Australia. Conflicts of interest: none declared.*

KFA Mos *is a final year PICU Trainee. Conflicts of interest: none declared.*

Roop Kishen *FRCA is a retired Consultant Intensivist and Anaesthetist at Salford Royal Foundation Trust, UK. Conflicts of interest: none declared.*

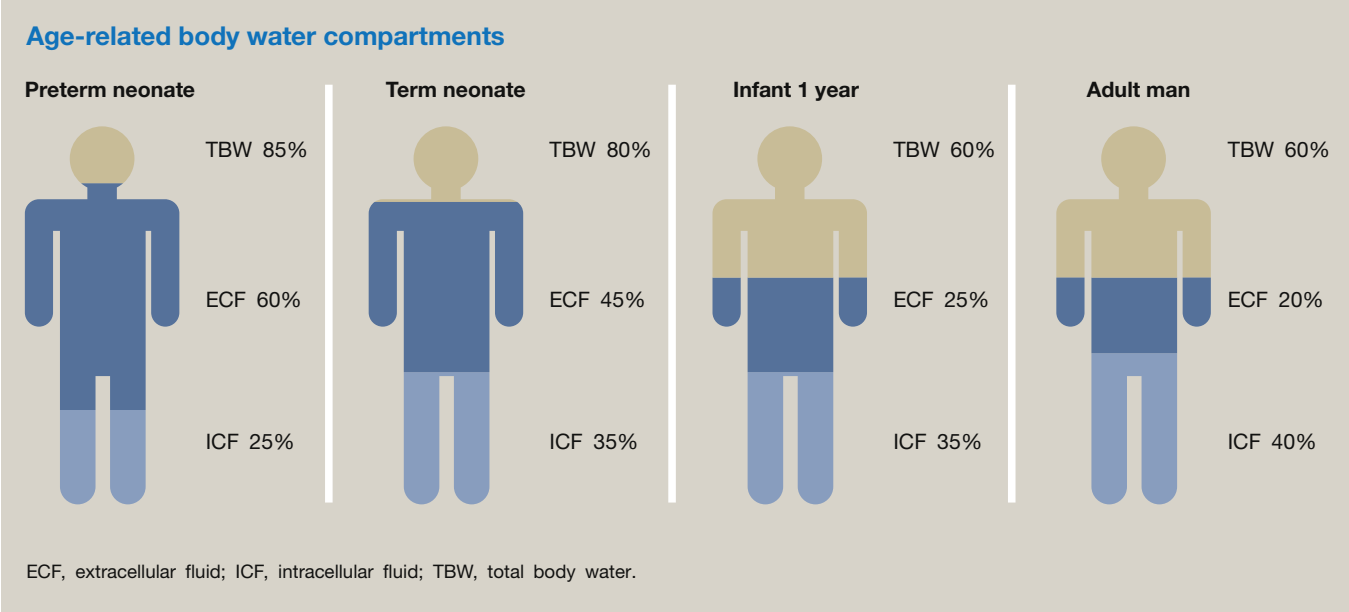

Figure 1

Salt solutions

Most salt solutions are isotonic and isosmotic and can further be divided into non-balanced and balanced solutions. There is also a recognized role for hypertonic solutions.

0.9% Sodium chloride solution is an isotonic and isosmotic solution when compared to plasma. However, the solution contains a far higher chloride concentration compared to that of plasma (Table 1), which has led to criticism of its use. The concern is that an infusion of large volumes will lead to a hyperchloraemic metabolic acidosis (HCMA). The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) recommends the use of balanced salt solutions over 0.9% sodium chloride when crystalloid resuscitation and replacement is indicated in surgical patients.[2] They quote the risk of HCMA as the reason for this with level 1b evidence.

The mechanism behind the resultant HCMA is best understood using Stewart's approach to acid–base balance.[3] This approach relies on the theory that electrical neutrality must always be maintained and therefore the addition of an anion needs to be balanced by the production of cations.

Stewart proposed that three independent variables influence plasma pH: carbon dioxide, strong ion difference (SID) and the

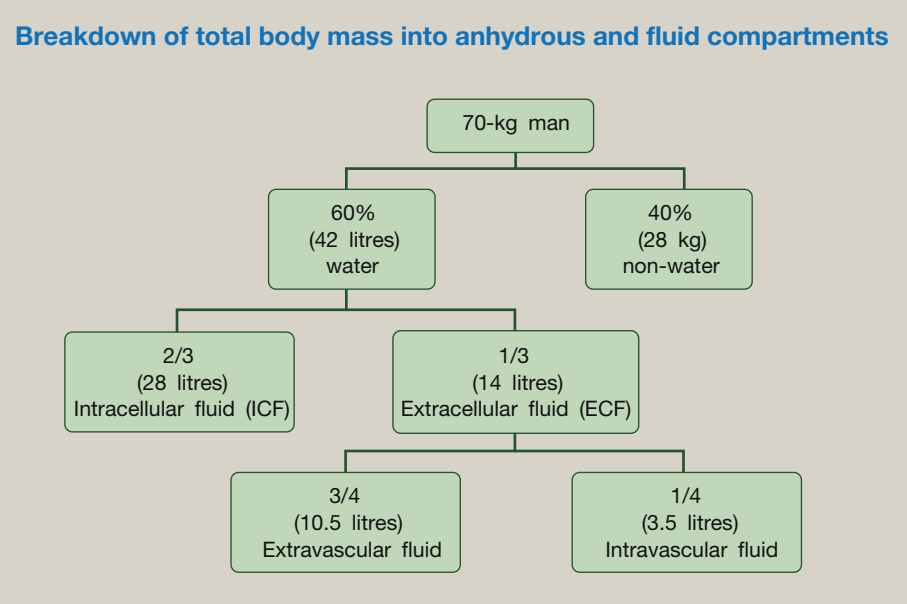

Figure 2

Electrolyte content of crystalloids versus plasma

Type of fluid	Sodium (mmol/l)	Chloride (mmol/l)	Potassium (mmol/l)	Calcium (mmol/l)	Others	Osmolality (mOsmol/kg)	pH
Plasma	135–145	98–105	3.5–5.0	2.2–2.6		280–300	7.35–7.45
5% Dextrose	–	–	–	–	D-glucose 50 g/litre	278	4
10% Dextrose	–	–	–	–	D-glucose 100 g/litre	278	4
0.9% Saline	154	154	–	–	–	308	5
1.8% Saline	308	308	–	–	–	616	
0.18% Saline/4% dextrose	30	30	–	–	D-glucose 40 g/litre	283	4.5
Compound sodium lactate (Hartmann's)	131	111	5	2	Lactate 29 mmol/litre	278	5

Table 1

sum total of weak acids (A_{TOT} – which is almost entirely due to albumin). Most infusions of intravenous fluid do not change carbon dioxide in significant quantity, and it can be considered stable. The SID can be calculated as:

$$SID = (Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + \text{lactate}).$$

The SID narrows (or decreases) due to increase in anions relative to cations or decrease in cations relative to anions, whereas SID widens (or increases) when the opposite occurs. Narrowing of SID requires addition of a cation to restore electric neutrality; this is accomplished by release of H^+ by disassociation of water. If A_{TOT} is diluted (e.g. by a large infusion of crystalloid) a metabolic alkalosis occurs. If there is an increase in A_{TOT} (e.g. albumin infusion) a metabolic acidosis occurs. Therefore, when SID narrows or A_{TOT} increases – metabolic acidosis will be present and when SID widens or A_{TOT} decreases – metabolic alkalosis occurs.

When saline solutions are infused an increase in chloride levels leads to a decrease in strong ion difference that needs to be balanced in order to restore electrical neutrality. In order to restore the electrical balance, water is hydrolysed. This releases OH^-, which is buffered by haemoglobin and cellular buffers, and H^+ (a cation), resulting in the observed metabolic acidosis.

One randomized, controlled, double-blind study in healthy volunteers of 2-litre infusions of 0.9% saline versus Plasma-Lyte® 148 identified a decrease in renal blood flow and cortical perfusion in the 0.9% saline group.[4]

Hypertonic sodium chloride solution: Sodium chloride solutions with concentrations greater than 0.9% are available as 1.8%, 3% and 30%. When administered intravenously at these concentrations, saline expands the circulating volume by drawing water from the extravascular space. This is a direct result from its high tonicity. These solutions can be beneficial in the management of raised intracranial pressure. They are also used in the correction of hyponatraemia. However, their use in preference to balanced crystalloids for resuscitation has not been proven.[5]

When being administered caution must be exercised. The higher concentrations are irritant to smaller vessels and large-bore intravenous access, often via a central line, may be required. In correcting hyponatraemia, the duration and severity of hyponatraemia must be taken into account. In some patients care must be taken to not cause a rapid rise in plasma sodium concentration that can lead to disruption of osmotic gradients across the blood brain barrier and potentially result in osmotic demyelination syndrome.

Balanced salt solutions: The most commonly used balanced solutions are Hartmann's solution (compound sodium lactate solution), Plasma-Lyte® and lactated Ringer's solution. The electrolyte composition of these solutions closely resembles that of plasma.

Lactate has been added to these solutions in order to reduce the effective chloride concentration. The lactate acts as an anion substitute for chloride and maintains the solutions' electroneutrality. Benefits from this include a reduction in the incidence of HCMA, which forms the foundation of GIFTASUP's recommendation discussed earlier.

These solutions have a buffering capacity through the metabolism of lactate in the liver. Gluconeogenesis removes lactate from the solution leaving sodium behind which directly influences SID (an increased SID will increase plasma pH). Oxidation metabolizes a proportion of lactate to bicarbonate also providing some buffering capacity. Previously these solutions were not recommended for use in patients with diabetes mellitus due to the lactate entering gluconeogenesis, but there is little evidence of any clinical harm from their use in this patient cohort.[6] Balanced crystalloid resuscitation in patients with diabetic ketoacidosis, has been associated with more rapid correction of base deficit when compared to 0.9% saline.[7]

Sugar solutions

Sugar solutions utilize the D-isomer of glucose (dextrose) as the solute and water as the solvent. They are formulated in standard concentrations, with the most commonly used clinically being 5% and 10% solutions.

On intravenous administration dextrose is rapidly metabolized leaving behind free water that redistributes across the body's compartments. This short plasma half-life and inability to maintain an oncotic pressure leaves sugar solutions little role as resuscitation fluids and plasma expanders.

Sugar solutions do however have an important role as maintenance fluids, helping fulfil the body's free water requirement. They are used as part of the management of hypernatraemia caused by water depletion.

Their use is more common in the paediatric setting where dextrose is often combined with a saline solution, and some gastrointestinal surgeons have used them to attempt to improve gastrointestinal function.

Maintenance IV fluids are widely used in the paediatric cohort. Historically guidelines have been mainly opinion based with weak evidence to support them. Thus there has been little consensus and high variability in administered fluid composition, with a significant role for hypotonic IV fluids. Undoubtedly there is a place for IV fluid administration, especially when enteral administration is not an option. However, increasing awareness of the possible side effects of rapidly administered IV fluid and potential harm makes conscious and purposeful use an essential requirement.

Worldwide there have been a significant amount of critical events with hyponatraemia and neurological impairment due to hypotonic IV fluid administration. Locally the NPSA has reported four such deaths.[8]

At the end of 2018 the American Academy of Pediatrics published a novel clinical practice guideline using an evidence-based approach to IV fluid administration in paediatrics. The AAP recommends (level A, strong) that patients 28 days to 18 years of age requiring maintenance IV fluid should receive isotonic solutions with appropriate KCL and dextrose. This significantly reduces the risk of hyponatraemia.[9]

Accumulating evidence in the last decade (the 2011 FEAST trial[10,11] being the landmark study) has shown the harmful effects of rapid and large fluid bolus administration in shocked infants and children. Maintenance fluid only conferred a statistically relevant survival benefit over a bolus with albumin or normal saline. In 2016 the WHO updated their guidelines to a more conservative approach to fluid resuscitation in shock to 10–20 ml/kg of isotonic crystalloid fluids over 30–60 minutes followed only by one further infusion of 10 ml/kg over 30 minutes if the child is still in shock. This is a considerable change from the previously well known 2013 WHO guidelines. That algorithm included the rapid infusion of 20 ml/kg of Ringer's lactate or normal saline up to 60 ml/kg prior to consideration of vasopressors and/or inotropes.[12]

Proposed mechanisms of harm include worsening acidosis (hyperchloraemic), release of natriuretic peptides due to atrial stretch, disruption of the glycocalyx and loss of the physiological mechanisms maintaining a maximally compensated shock state.[10,11]

Colloids

Colloids rely on a suspension of synthetic molecules of a large enough molecular weight to exert an oncotic pressure across the capillary basement membrane. In clinical practice gelatins, starches or dextrans are suspended in a salt solution (0.9% sodium chloride), or as balanced colloid solutions.

Gelatins

Gelatins use polypeptide molecules derived primarily from bovine collagen. They undergo modification in one of two ways:

- hydroxylation and succinylation, as in Gelofusine, Isoplex and Volplex
- degradation and modification with nitrogen as in Haemaccel.

Gelatins have a mean molecular weight of about 35 kDa. It was thought that their higher molecular weight enabled them to stay in circulation longer and thus cause greater plasma volume expansion than crystalloids. As previously mentioned, this long-held view is being challenged with insights into the endothelial glycocalyx layer.

In conjunction with other colloidal plasma expanders, gelatins can cause mild urticarial reactions. Severe anaphylactic reactions have a reported incidence of 1:6000–1:13,000 units administered.

Dextrans

Dextran is formed from lactic acid-producing bacteria, most commonly *Leuconostoc mesenteroides*. It is a high-molecular-weight branched polysaccharide and preparations average between 40 kDa and 70 kDa, commonly suspended in 0.9% or 7.5% saline.

In clinical practice, dextran has been used for its colloidal, anticoagulant and hypoviscosity effects on the plasma. As with the gelatins, they have been used to expand intravascular volume. Dextran mediates its anticoagulant effects by reducing platelet and erythrocyte aggregation. It also reduces levels of von-Willebrand factor further decreasing platelet aggregation. Furthermore dextran acts as a plasminogen activator providing thrombolytic properties. These anticoagulant and antithrombotic effects reduce clot production and sustainability and dextran's oncotic effects reduce plasma haematocrit and thus viscosity. The combination of these two effects achieves an improvement in blood flow.

Dextran use has, however, been linked to direct nephrotoxicity causing acute kidney injury (AKI). There is also a recognized incidence of anaphylaxis and it has been shown to interfere with blood cross-matching.

RescueFlow™, 6% dextran 70 and 7.5% saline, has been promoted in the management of acute hypovolaemia associated with trauma and in the management of raised intracranial pressure (ICP). There are no strong data to promote its use over mannitol or hypertonic saline in the management of raised ICP, both of which do not have the side effect profile of dextran.

Starches

Hydroxyethyl starches (HES) are synthetic polymers of glucose derived from the breakdown of amyloidpeptin by amylase. There are multiple preparations that can be differentiated by three characteristics, which influence the length of time taken to metabolize the starch molecules and hence a solution's effect on plasma expansion.

Molecular weight: Within a given solution starch molecules vary in weight. A solution is therefore defined by its average molecular weight and can be subdivided as low- (70–130 kDa), medium- (200–260 kDa) and high-molecular-weight (>450 kDa) groups. After intravenous administration the molecules are metabolized and at a molecular weight of less than 50 kDa the molecules can be excreted in the urine.

Degree of substitution: Within a starch solution there is a mixture of glucose polymers with hydroxyl group substitutions and those without. The ratio of the two within a solution is called the substitution ratio (SR). A fluid with a higher SR takes longer to metabolize and increases the duration of plasma expansion.

C2/C6 ratio: The hydroxyl group substitutions occur at the C2, C3 and C6 positions of the glucose polymer. Substitution at C2 increases the time taken to metabolize the molecule compared to C6 substitution. Hence a high C2/C6 ratio (>8) has an increased duration of plasma expansion.

The initial starches contained high molecular weight (e.g. 480) and high SR (0.6), written as 480/0.6. These solutions were shown to provide a plasma expansion of up to 24 hours. However, concerns arose over the development of coagulopathies secondary to a reduction in factor VIII and von-Willebrand factor, as well as increased incidence of AKI. Production was switched to medium starch solutions (200/0.5) but not only did these demonstrate the same problems, they also showed a trend towards increased mortality.[13] On this basis most physicians switched to low-molecular-weight starches (130/0.4).

Two large trials have demonstrated direct harm from their infusion when compared to crystalloid administration. The Scandinavian Starch for Severe Sepsis/Septic shock trial demonstrated an increased incidence of AKI, mortality and requirement for dialysis in patients with severe sepsis who received low-molecular-weight starch. More recently the Australian and New Zealand Intensive Care Society Clinical Trial Group demonstrated no mortality difference at 90 days but increased need for dialysis with starch administration. The United States Food and Drug Administration has issued a black box warning against their use in critically ill patients due to increased mortality, severe renal injury and risk of bleeding. The European Medicines Agency suspended their marketing in the EU in 2018. Reports of unethical conduct in some of the earlier research evaluating HES, which emphasized safety of starch solutions, has led to re-traction of these studies.

Albumin

Albumin is a purified single polypeptide derived from pooled donor plasma. It has an average molecular weight of 65–69 kDa. It comes in isotonic (4 or 5%) and concentrated (20 or 25%) formulations, and being purified it can therefore be considered free from the risk of transmitting infection.

It is a constituent of normal plasma, and its infusion has been advocated on the basis that it increases plasma oncotic pressure, hence increasing plasma volume as well as preventing oedema in the critically ill. However, the relationship between the oncotic pressure and albumin levels in the critically ill is complex and not as simple as shown in laboratory animal studies.[14] In 1998, the Cochrane Injuries Group Albumin Reviewers recommended the cessation of albumin administration to critically ill patients after a meta-analysis demonstrated an absolute increased risk of death of 6%.

The Saline versus Albumin Fluid Evaluation study investigators (SAFE) demonstrated no difference in outcome or harm between 4% albumin and normal saline within critical care. Subgroup analysis showed a possible exception in the management of trauma patients with head injuries, where albumin may increase harm.[15] Two further recent studies have also added strength to this argument. Firstly, the Albumin Italian Outcome Sepsis (ALBIOS) study; albumin replacement in addition to crystalloids in patients with severe sepsis (or septic shock) was compared to crystalloids alone. There was no improvement in the rate of survival at 28 and 90 days. Secondly, Early Albumin Resuscitation during Septic Shock (EARSS) identified similar outcomes between saline and albumin.

Blood products

In 1901, Karl Landsteiner discovered the most wellknown of the grouping systems, the ABO groups. Prior to this, blood transfusions, which date back to the 17th century, were associated with mortality in the region of 50%. Since the development of the ABO system, identification of rhesus status and antigen recognition have further driven down complication rates.

New challenges surrounding blood safety have developed with the need to avoid bacterial, viral and prion disease transmission. White cells, recognized as pathogens, have been reduced in donated blood in order to reduce graft versus host disease and transfusion-related lung injury (TRALI). The UK monitors transfusion adverse advents through the independent advisory group: Serious Hazards of Transfusion (SHOT). Data from 2016 continue to demonstrate that one of the most frequent adverse events is the transfusion of the incorrect blood component. This emphasizes the importance of delivering the right product to the right patient at the right time.

NHS Blood and Transplant service (NHSBT) are responsible for the collection and distribution of blood products in the UK. Whole blood is collected and currently separated into red cells, platelets and plasma (Figure 3).

Whole blood

Whole blood has been used less since the 1980s because of an increased demand for specialist clotting factors. It is still used in developing countries and in the military.

In theory, whole blood has a shelf life of about 35 days, but blood can confer a lot of benefits if transfused fresh (under 5 days). Fresh blood is rich in clotting factors, has near normal physiological oxygen carrying capabilities and acts as an efficient volume expander; however, it is impractical to store and can rarely be used within this time frame. With time, there is a reduction of levels of 2,3-diphosphoglycerate, factors V and VII, and impaired platelet function.

The collection bags contain citrate (which acts as an anticoagulant by binding calcium), phosphate, dextrose and adenine to support cell metabolism (CPDA).

Packed red cells

The collected blood (suspended in CPDA) is leucodepleted by passing it through a negatively charged filter after which the plasma is removed. In the UK, the remaining red blood cells are re-suspended in a saline, adenine, glucose and mannitol (SAGM) solution. Each bag has a shelf life of 35 days.

Packed red cells (PRC) sometimes undergo further screening to prevent the transmission of cytomegalovirus (CMV) to at-risk

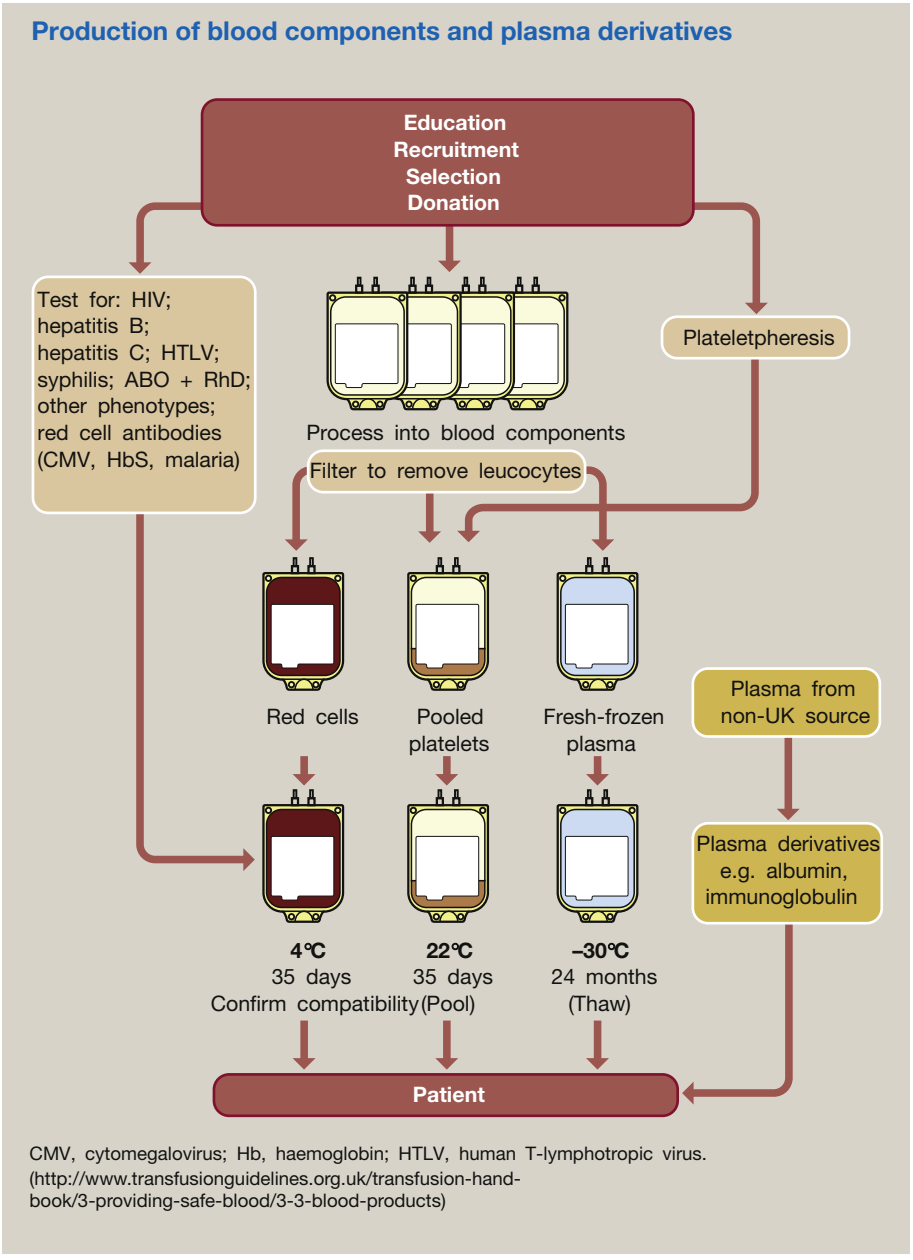

Figure 3

groups, such as allogeneic stem cell transplant patients or the CMV-negative parturient. PRC can also undergo gamma irradiation to ensure complete leucodepletion, this is particularly important for patients suffering with an immunodeficiency syndrome or haematological malignancy.

PRC are stored between 2°C and 6°C and are transfused through a 170–200 μm filter after being warmed. After removal from stored temperature they should be transfused within 4 hours.

Platelets

Platelets are derived in two forms. Random donor platelet concentrate (RDP) is comprised of units of blood from several donors being pooled. Alternatively a single donor can be used and the amount required achieved through plateletpheresis. This process isolates the platelets immediately from the donated blood before returning the remaining products back to the donor.

Platelets are suspended in plasma and are therefore ABO and Rhesus typed. As the volume of plasma is small, the need for ABO matching in the clinical setting is desirable rather than essential. However, Rhesus status must be considered, especially in rhesus negative women of childbearing age.

Platelets are stored at 22°C and are continually agitated to prevent clumping. Shelf life is only 5 days due to the risk of bacterial growth.

Plasma

Plasma is removed almost immediately from whole blood after donation. It can be frozen and delivered as fresh frozen plasma (FFP) or further processed into its constituents:

- cryoprecipitate
- human albumin solution
- human immunoglobulin
- specific clotting factors.

FFP: Although traditionally derived from a single donor, FFP can also be obtained from pooled plasma after undergoing solvent/detergent treatment (SDFFP). Each 150-ml bag is rich in clotting factors and stored at −20°C to −30°C and can be kept like this for 2 years. It is ABO matched and once thawed needs to be used within 4 hours. As with all blood products it carries an infection risk and paediatric donations should be sourced from bovine spongiform encephalopathy free areas, namely the USA. The usual dose is 10−15 ml/kg.

Cryoprecipitate: As FFP thaws the high-molecular-weight molecules precipitate first, which are separated to form cryoprecipitate. This concentrated solution is rich in factor VIII, fibrinogen and von-Willebrand factor. It is stored at −30°C for up to 12 months in aliquots of 40−50 ml. A normal dose is two pools of five single units (10 units), which should increase plasma fibrinogen levels by roughly 1 g/litre. ABO compatibility is desired.

Specific clotting factors: Individual clotting factors can now be produced through recombinant processes that negate the concern of viral transmission.

Red cell substitutes

Red cell substitutes have been in serious development for over 30 years. Some products are involved in ongoing clinical trials but none are commercially available in Europe or the USA. NHS trials of stem cell originated red cells have begun.

The ideal blood substitute should have little antigenicity, be unable to transmit infection, be readily available, have a long half-life and be stable if stored at room temperature. Furthermore, its oxygen-carrying ability should at least match that of human blood.

First-generation development focused around the use of perfluorocarbons. Initial results demonstrated a marked increase in oxygen-carrying capacity independent of body temperature and pH; however, storage and safety issues meant most trials were ceased prior to completion.

Since 1940, stroma-free haemoglobin has been under investigation. This cell-free haemoglobin is developed from bovine or recombinant sources. Its advantages over red blood cells include withstanding sterilization and a potential shelf life of up to 2 years at room temperature. Several products reached phase III trials but due to side effect profiles, namely myocardial events, none have been approved. New-generation products are attempting to address these issues.

There remains continued interest in haemoglobin-based oxygen carriers (HBOC), and it has been used in Jehovah's witness patients. One product showing promise is the polymerized bovine haemoglobin marketed as Hemopure. It is currently available in South Africa and the USA. A comparative study of HBOC versus allogeneic red blood cell transfusions in non-cardiac surgical patients found that up to 7 units of HBOC infused over 6 days resulted in RBC transfusion avoidance in 43% of patients.[16] Hemopure can be stored at room temperature, has a prolonged half-life compared to native haemoglobin and demonstrates high oxygen delivery capacity.

In Europe and the USA, MP4OX (oxygenated polyethylene glycol-modified haemoglobin) is in ongoing clinical trials. Its chemical structure allows it to dissociate from oxygen only in tissue areas of low oxygen concentration, thus delivering oxygen to the tissues with the highest requirement. It is being developed as an ischaemic rescue therapy to perfuse and oxygenate tissues at risk during haemorrhagic shock.

Increased attention is being placed on blood 'farming'. This technique produces human red blood cells from cells extracted from umbilical cords. The technique can in theory produce a universal donor group blood. Researchers envisage the technique being available at the point-of-need in the next 5−10 years.

A note on fluid infusion in early goal-directed therapy (EGDT)

Early goal-directed therapy (EGDT) uses patient monitoring to guide administration of fluids, vasopressors and inotropes in the critically ill, both perioperatively and in critical care, especially in sepsis. Initially, a protocol-led assessment of cardiovascular performance is made using central venous pressure and oxygen saturation monitoring as well as peripherally applied haemodynamic monitors such as LiDCO. Subsequently, an intervention is made, for example a fluid bolus to increase CVP or venous oxygen saturation. Initial studies identified more favourable outcomes when employing EGDT.[17]

There has recently been a shift from protocol-led early goal-directed fluid therapy. EGDT was evaluated in two large multicentre randomized controlled trials, the Australasian Resuscitation In Sepsis Evaluation (ARISE),[18] and Protocolized Care for Early Septic Shock (ProCESS) in the United States.[19] ARISE examined EGDT in critically ill patients in early septic shock presenting to the emergency department, and its use did not reduce all-cause mortality at 90 days. The ProCESS study, in patients with severe sepsis or septic shock, also showed no improvement in outcomes. These outcomes included 60-day in-hospital mortality, 90-day mortality, 1-year mortality, and the requirement for organ support.

In the UK, the Protocolised Management in Sepsis (ProMISe) trial, concluded that haemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome.[20]

Outcomes following surgery have also been evaluated in high-risk gastrointestinal surgical patients undergoing major surgery (OPTIMISE trial). This was a large trial of a perioperative, cardiac output-guided GDT; no difference in outcome was found between the GDT group and the usual care group.[21]

Therefore after more than 15 years of EGDT, a number of large randomized controlled trials have demonstrated a lack of benefit with this type of protocolized management. This may support the assumption that the care of the critically ill patient has improved over the last decade. Evidence is also accumulating that excess fluid is harmful and has a negative effect on survival. Clinicians should therefore take extreme care when infusing fluid in the critically ill. ◆

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