Fluid replacement

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Appropriate fluid replacement is an essential component of trauma patient resuscitation. Once haemorrhage is controlled, the restoration of normovolaemia is a priority. In the presence of uncontrolled haemorrhage, aggressive fluid resuscitation may be harmful. The crystalloid-colloid debate continues, but existing clinical practice is more likely to reflect local biases and dogma rather than evidence-based medicine. Colloids vary substantially in their pharmacology and pharmacokinetics and the experimental findings based on one colloid cannot be extrapolated reliably to another In the initial stages of trauma patient resuscitation, the precise fluid used is probably not important, as long as an appropriate volume is given. Later, when the microcirculation is relatively leaky, there may be some advantages to colloids such as hydroxyethyl starch. Hypertonic saline solutions may have some benefit in patients with head injuries. A number of haemoglobin solutions are under development but one of the most promising of these has been withdrawn recently. It is highly likely that at least one of these solutions will eventually become routine therapy for trauma patient resuscitation. In the mean time, contrary to traditional teaching, recent data suggest that a restrictive strategy of red cell transfusion may improve outcome in some critically ill patients.

After ensuring an adequate airway, oxygenation and ventilation, the focus for resuscitation of the severely injured patient switches to stopping haemorrhage and restoring the circulation. Appropriate and effective fluid replacement will reverse haemorrhagic shock and restore perfusion to vital organs. Although restoration of an adequate intravascular volume is of paramount importance and short-term anaemia is usually well tolerated, consideration must also be given to the need for red cells. In the presence of an adequate cardiac output and oxygenation, the lactic acidosis associated with haemorrhagic shock should resolve. Clinical considerations at this stage include which fluid to infuse and how much to give. Differences in clinical practice are more likely to reflect the availability of fluids locally, along with the prevailing dogma, rather than evidence-based medicine.

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British Medical Bulletin 1999, 55 (No 4) 821–843

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Physiology

The total body water comprises about 42 l in a 70 kg man and is distributed across three fluid spaces (Fig. 1). Intracellular fluid (about 28 l in a 70 kg man) is separated from extracellular fluid (ECF) by a cell membrane which is highly permeable to water but not to most electrolytes. The intracellular volume is maintained by the membrane sodium-potassium pump, which moves sodium out of the cell (carrying water with it) in exchange for potassium. Thus, there are significant differences in the electrolytic composition of intracellular and extracellular fluid (Table 1). The capillary membrane separates the two main extracellular fluid compartments: the interstitial fluid (about 11 l in a 70 kg man) and the plasma (about 3 l). The pores of the capillary membrane are highly permeable to almost all solutes in the extracellular fluid except the proteins. Thus, the ionic composition of plasma and interstitial fluid are similar but the former contains a higher concentration of protein.

The total osmolarity of each of the three fluid compartments is approximately 280 mOsm/l. The osmotic pressure of a solution is related directly to the number of osmotically active particles it contains. Thus, about 80% of the total osmolarity of interstitial fluid and plasma is due to sodium and chloride ions. An isotonic solution (*e.g.* 0.9% sodium chloride) will have an osmolarity of approximately 280 mOsm/l and cells placed in it will neither shrink or swell. A cell placed in a hypotonic solution (< 280 mOsm/l) will swell and those placed in a hypertonic solution (> 280 mOsm/l) will shrink. An isotonic saline solution given intravenously will distribute quickly across most of the extracellular fluid space. Although capillary pores are highly permeable to sodium and chloride, the cell membrane behaves as if it were impermeable to these ions, thus keeping the saline solution out of the intracellular space.

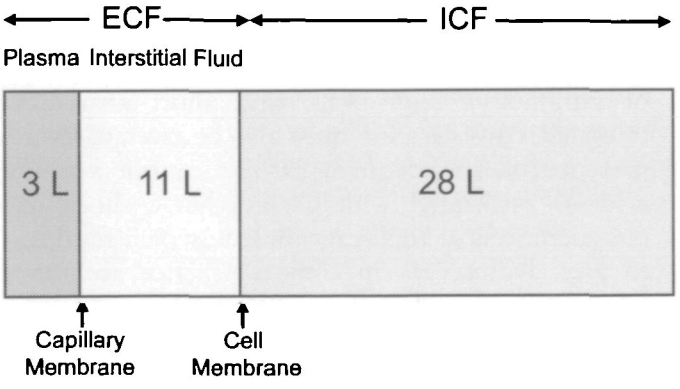

Fig. 1 Body fluid compartments in a 70 kg adult male. ECF = extracellular fluid; ICF = intracellular fluid.

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Table 1 Osmolar substances in extracellular and intracellular fluids

	Plasma (mOsm/l H_2O)	Interstitial (mOsm/l H_2O)	Intracellular (mOsm/l H_2O)
Na^+	142	139	14
K^+	4 2	4 0	140
Ca^{2+}	1 3	1 2	0
Mg^{2+}	0 8	0 7	20
Cl^-	108	108	4
$HCO3^-$	24	28 3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^-	0 5	0 5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0 2	0 2	9
Lactate	1 2	1 2	1 5
Adenosine triphosphate			5
Hexose monophosphate			3 7
Glucose	5 6	5 6	
Protein	1 2	0 2	
Urea	4	4	4
Others	4 8	3 9	10
Total mOsm/l	301 8	300 8	301 2
Corrected osmolar activity (mOsm/l)	282 0	281 0	281 0
Total osmotic pressure at 37°C (mmHg)	5443	5423	5423

Because plasma and interstitial proteins do not readily penetrate the pores of the capillary membrane, they are responsible for the osmotic pressure at the capillary membrane (oncotic pressure). In health, albumin accounts for 80% of the total plasma oncotic pressure of 28 mmHg. The relatively low number of proteins in comparison with other particles results in only a small contribution to the total osmotic pressure at the cell membrane. The osmotic pressure generated by crystalloidal particles is approximately 5400 mmHg (Table 1)[1]. Starling has described the factors determining fluid movement through the capillary membrane (Fig. 2). The forces tending to move fluid outwards are the mean capillary pressure

$$Q_f = K_f ([P_{cap} - P_{int}] - \sigma [\pi_{cap} - \pi_{int}])$$

(17.3 -3 0) (28 0 8.0)

Fig. 2 Starling equilibrium for capillary exchange. Q_f = fluid flux; K_f = membrane filtration coefficient (permeability to water), P = hydrostatic pressure in mmHg, σ = membrane reflection coefficient (permeability to protein), π = colloid osmotic pressure in mmHg; cap = capillary; int = interstitial.

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(17.3 mmHg), a negative interstitial fluid pressure (3.0 mmHg), and the interstitial fluid colloid osmotic pressure (8.0 mmHg). The plasma oncotic pressure tends to move fluid inward. The reflection coefficient (σ) provides an indication of the extent to which the microvascular membrane is a barrier to protein. This coefficient varies from tissue to tissue, ranging from 1.0 for the cerebral vasculature to 0.2 for the hepatic microvasculature. Under normal conditions, there is a net outward force of 0.3 mmHg which, in the presence of a normal filtration coefficient (K_f, flow of fluid across the microvascular membrane per unit time per unit pressure per 100 g of tissue), results in a net rate of fluid filtration in the entire body of 2 ml/min. This fluid is carried away by the lymphatic system and is returned to the blood. Higher capillary pressures will substantially increase the rate of fluid filtration, but the lymphatic system can cope with 20-fold increases in flow. In inflammatory conditions, the capillary pores may be considerably larger and the reflection coefficient will be low. The increased loss of protein molecules through these 'leaky' capillaries may make it difficult to extrapolate fluid therapy data derived from healthy subjects to those with inflammatory disorders [*e.g.* the systemic inflammatory response syndrome (SIRS) associated with multiple injuries].

Pharmacology

Crystalloids

A crystalloid is a solution of small non-ionic or ionic particles. The contents of a number of commonly used crystalloids are listed in Table 2. Most crystalloid intravenous fluids are isotonic with plasma. They do not contain larger, oncotic particles and will, therefore, pass freely across the microvascular membrane. Their precise distribution will be determined by their sodium concentration. Solutions containing approximately isotonic concentrations of sodium (*e.g.* 0.9% saline, Hartmann's solution) will distribute rapidly across most of the extracellular space. The volume kinetics of crystalloids is very complicated and differs between normovolaemic and hypovolaemic subjects. Simplistically, about three-quarters of an intravenous infusion of this solution will pass into the interstitial space and one-quarter will remain initially in the intravascular space. Thus, 1500–2000 ml fluid is needed to replace an acute blood loss of 450 ml during 1 h, depending on how fast normal blood volumes are reached[2]. Crystalloids containing less than isotonic concentrations of sodium will be increasingly distributed to the intracellular space. Dextrose 5% is distributed throughout the total body water and is ineffective for replacing intravascular fluid loss.

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Table 2 Physicochemical properties of common crystalloids

Crystalloid	Osmolality (mosmol/kg)	pH	Na^+ (mmol/l)	K^+ (mmol/l)	HCO_3^- (mmol/l)	Cl^- (mmol/l)	Ca^{2+} (mmol/l)
0 9% Saline	300	5 0	150	0	0	150	0
Hartmann's	280	6 5	131	5 0	29*	111	2
PlamaLyte B	299	5 5	140	5 0	50	98	0
5% Dextrose	278	4 0	0	0	0	0	0
4% Dextrose in 0 18% saline	286	4 5	31	0	0	31	0
7 5% Saline	2400		1250			1250	

*HCO_3^- is provided as lactate

Hypertonic saline

Hypertonic solutions of saline continue to be investigated as resuscitation fluids. The highly hypertonic 7.5% sodium chloride has an osmolality of 2400 mOsm/l and produces a transient increase in intravascular volume of many times the volume infused[3]. This may be an advantage where storage volume and or weight is limited (*e.g.* prehospital). The effects of hypertonic saline on the cardiovascular system are not confined to volume expansion; heart rate and contractility is increased and peripheral vascular resistance is reduced. The intravascular persistence of hypertonic saline can be extended by mixing it with a colloid. The commonest of these hypertonic-hyperoncotic solutions is hypertonic saline dextran (HSD, typically NaCl 7.5% and dextran-70 6%).

Colloids

A colloid is a fluid containing particles that are large enough to exert an oncotic pressure across the microvascular membrane. In comparison with crystalloids, they have greater intravascular persistence. The duration of intravascular persistence depends on molecular size, shape and ionic charge. A negatively charged substance (*e.g.* albumin) tends to be repelled by the negatively charged endothelial glycocalyx. Albumin is the only colloid containing particle of uniform molecular weight (monodisperse). The other colloids are polymers and contain particles with a wide range of molecular weights. This makes the weight average molecular weight (MW_w) an unreliable indicator of likely intravascular persistence. The number average molecular weight (MW_n) takes into account the distribution of molecular weights and is a better indicator of intravascular persistence. Molecular weight distribution curves (Fig. 3) will provide the best indicator of intravascular effect for a colloid[4]. Albumin, dextran and blood are naturally occurring colloids. Semi-synthetic colloids include modified gelatins, hydroxyethyl starch and

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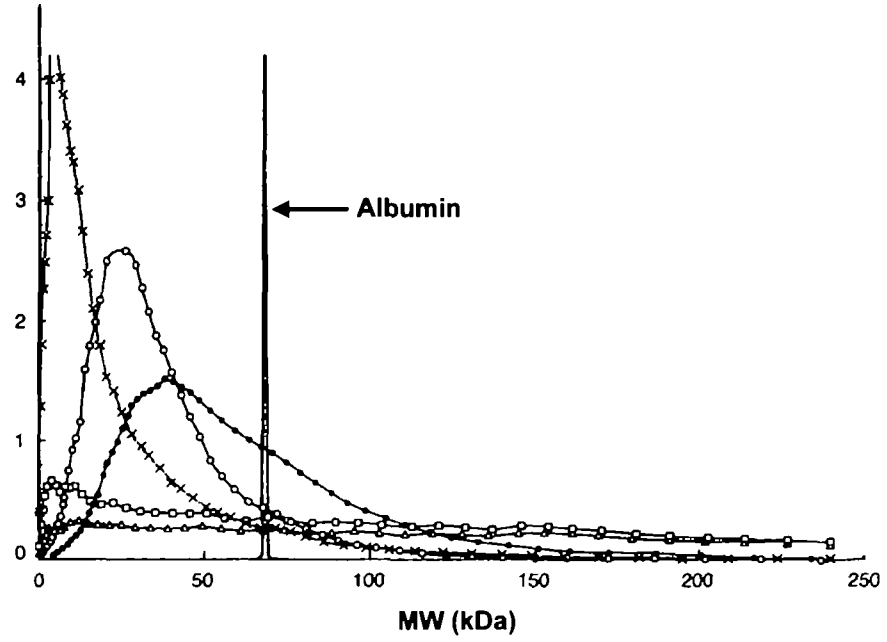

Fig. 3 Molecular weight distribution of different colloids. Urea-linked gelatin (crosses); Dextran-40 (open circles); Dextran-70 (filled circles); hydroxyethyl starch 200/0.5 (open squares); hydroxyethyl starch 400/0.7 (open triangles). Adapted from Arfors and Buckley[4]

Table 3 Physicochemical properties of colloids

Colloid	MW_w (kDa)	MW_n (kDa)	pH	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	Ca^{2+} (mmol/l)
4 5% Albumin	70	70	7 4	150	2	120	0
Haemaccel	35	24 5	7 4	145	5 1	145	6 2
Gelofusine	35	22 6	7 4	154	0 4	154	0 4
Dextran 70 in saline	70	39	3 5–7 0	150	0	50	0
Hydroxyethyl starch (450/0 7)	450	70	5 5	154	0	154	0
Hydroxyethyl starch (200/0 5)	200	60	5 0	154	0	154	0

haemoglobin solutions. An appropriate choice of colloid will take into account cost, intravascular half-life, and side effects, such as coagulopathy and anaphylactoid reactions. The molecular weights and ionic composition of various colloids are shown in Table 3.

Gelatin solutions

Gelatin polypeptides are derived from bovine collagen[5]. Chemical modification lowers the gel melting point and produces a sufficient molecular size for intravascular retention. Urea-bridged gelatin (*e.g.* Haemaccel, MW_n 24.5 kDa) is derived from cattle bone and is prepared by cross-linking polypeptide chains of 12–15 kDa. Succinylated gelatin (*e.g.*, Gelofusine, MW_n 22.6 kDa) is produced by the thermal degradation of calf skin collagen to produce 23 kDa polypeptides. The addition of succinic acid anhydride induces a conformational change, which

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Table 4 Incidence of anaphylactoid reactions caused by colloid solutions

Colloid	Infusions	Anaphylactoid reactions	Incidence (%)
Haemaccel	6151	9 (3)	0 146
Gelofusine	6028	4 (1)	0 066
Hydroxyethyl starch	16405	14 (1)	0 085
Dextran 70	34621	24 (6)	0 069
Albumin	60048	7 (2)	0 011

Figures in brackets represent the number of severe, life-threatening reactions Adapted from Ring and Messmer[6]

increases molecular size. Approximately 80% of the molecules in urea-bridged gelatin are smaller than 20 kDa and are rapidly excreted through the kidneys (Fig. 3). Thus, the intravascular persistence of gelatin solution is relatively low (2–3 h) with urea-bridged gelatin being less than succinylated gelatin.

It is very difficult to estimate the incidence of anaphylactoid reactions to the various colloids with any reliability. Traditional estimates are based on relatively old data from Ring and Messmer (Table 4)[6]. On the basis of this study, the highest incidence of anaphylactoid reactions (0.146%) occurred with Haemaccel. Presumably influenced by these data, the US Food and Drug Administration (FDA) withdrew gelatin solutions in 1978. The subsequent lack of availability of an inexpensive colloid in the US is possibly a significant factor in the transatlantic crystalloid-colloid debate (see below). After modifying the way Haemaccel was prepared, the incidence of anaphylactoid reactions had apparently fallen. However, more recent data from a large French study suggest that gelatins remain the most likely colloid to induce an anaphylactoid reaction (Table 5)[7]. Gelatins are generally considered to have little effect on clotting. However, there is some *in vitro* evidence that gelatin may reduce the quality of clot formation[8]. The clinical implications of this observation have yet to be determined. In comparison with the rest of Europe and the world, gelatin solution usage in the UK is remarkably high (Table 6).

Table 5. Incidence of anaphylactoid reactions caused by colloid solutions. Data from Laxenaire *et al.*[7]

Colloid	Infusions	Anaphylactoid reactions	Incidence (%)
Gelatins	9424	32	0 345
Hydroxyethyl starch	5231	3	0 058
Dextrans	1861	5	0 273
Albumin	3073	3	0 099
Total	19593	43	0.219

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Table 6 World colloid consumption 1994

Colloid	World market million units (%)	European market million units (%)	UK market million units (%)
Albumin	14 9 (31 4%)	4 5 (26 9%)	0 343 (20%)
Gelatin	9 3 (19 6%)	4 5 (26 6%)	1 00 (68%)
Dextran	14 4 (31 4%)	2 3 (12 5%)	0 045 (3%)
Starch	6 4 (13 5%)	5 6 (33%)	0 15 (10%)
Others	2 33 (4 9%)	0	0

Data from Mr David Coorey, Fresenius Kabi, personnel communication

Dextrans

Modern dextrans are produced by the action of the enzyme dextran sucrase during the growth of the bacteria *Leuconostoc mesenteroides* on a sucrose medium. The resulting polysaccharide is hydrolysed to produce dextrans of various molecular weights. Currently available dextran solutions are 6% dextran 70 and 10% dextran 40. Both dextran 40 and dextran 70 are available in 0.9% saline and in 5% dextrose solutions. Dextran 40 is hyperoncotic and will initially expand the intravascular volume by more than that infused. However, dextran 40 is more rapidly excreted than dextran 70. Approximately 70% of dextran is excreted through the kidneys and the remainder is broken down by endogenous dextranase. Dextran reduces blood viscosity, reduces platelet adhesiveness, and enhances fibrinolysis. These properties make dextran useful for prophylaxis against thromboembolism, however, doses above 1.5 g/kg body weight will increase bleeding. Dextran 40 has been associated with renal failure, particularly in the presence of hypovolaemia and pre-existing renal dysfunction. Roleaux formation and interference with blood cross-matching was a feature of the very high molecular weight dextrans which were first used in the 1940s[9]. Modern dextran solutions do not interfere with the cross-matching of blood[9]. Dextrans can cause mild anaphylactoid reactions. The more severe anaphylactic reactions are relatively uncommon and are cause by naturally occurring dextran reactive antibodies (DRAs) of IgG class. These reactions are caused by immune complex (type III) anaphylaxis. The reactive sites of the antibodies can be blocked by giving an injection of 20 ml of dextran 1 (monovalent hapten dextran). This prevents the formation of immune complexes when an infusion of dextran 40 or 70 is given and has dramatically reduced the incidence of serious reactions to dextran[9]. Although dextran is used relatively rarely in the UK, on a global basis it remains one of the most frequently used colloids (Table 6).

Hydroxyethyl starch

Hydroxyethyl starch (HES) solutions are synthetic polymers derived from amylopectin. They are broken down by amylase. Substitution of

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Table 7 A classification of hydroxyethyl starch solutions

Concentration	High	10%
	Low	6%
Weight average MW	High	450–480 kDa
	Medium	200 kDa
	Low	70 kDa
Degree of substitution	High	0 62–0 7
	Low	0 45–0 58
C2/C6 ratio	High	> 8
	Low	< 8

Modified from Treib *et al*[10]

hydroxyethyl groups into the D-glucose units will increase the resistance to degradation by amylase and will extend the intravascular persistence. A high degree of substitution (*e.g.* 0.7 or 7 hydroxyethyl groups for every 10 glucose units) and a high C2/C6 ratio (relative proportion of substitutions at the C2 and C6 positions on the glucose ring) will maximise the intravascular half-life. On this basis, HES solutions can be divided into high, medium, and low molecular weights (Table 7)[10]. Intravascular persistence will depend on the molecular weight, the substitution ratio, and the C2/C6 ratio. Polymers with a molecular weight less than about 60 kDa are eliminated rapidly by glomerular filtration. Larger polymers are broken down by amylase and then eliminated by the kidneys. Some of the HES is extravasated into the interstitial space where a proportion is taken up by the reticulo-endothelial system. High molecular weight HES (*e.g.* 450/0.7) has a prolonged intravascular persistence with 38% of the initial dose remaining in the intravascular space for 24 h. Accumulation of the higher molecular weight HES in the reticulo-endothelial system causes some theoretical concerns but other than possibly causing pruritis[11] has yet to be associated with significant clinical problems. A randomised, controlled study comparing medium molecular weight starch with lactated Ringer's solution showed no difference in the incidence of pruritis[12].

High molecular weight HES reduces factor VIII and von Willebrand factor and will cause a coagulopathy[10]. For these reasons, the maximum dose of high molecular weight HES is restricted to approximately 20 ml/kg/day and it can not be recommended for trauma patient resuscitation. Medium molecular weight starch (*e.g.* 200/0.5) has significantly less effect on coagulation but the precise impact a given HES solution has depends also on the degree of substitution and C2/C6 ratio. Those with low substitution ratios (*e.g.* 200/0.5) have a lesser effect on bleeding except in very high dose[13]. On a rather empirical basis, the maximum daily volume of HES 200/0.5 is restricted to 33 ml/kg/day. This solution

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will have an intravascular persistence of around 4–6 h. Low molecular weight HES may have minimal effect on coagulation[14].

Animal studies suggest that fractionated HES solutions producing a molecular range of 100–1000 kDa (*e.g.* Pentafraction HES-Pz) may be capable of plugging leaky capillaries in inflammatory states[15–18]. Hydroxyethyl starch encourages the restoration of macrophage function after haemorrhagic shock[19]. A recent study of trauma and sepsis patients showed that 10% HES (200/0.5) resulted in significantly better systemic haemodynamics and splanchnic perfusion than volume replacement with 20% human albumin[20]. Although the incidence of significant anaphylactoid reactions associated with HES appears to be low[6,7], a number of anaphylactic reactions have been reported[21].

Albumin

Human albumin is a single polypeptide with a molecular weight of 65–69 kDa and a strong negative charge of minus 17[22]. It has transport functions, free radical scavenging and anticoagulant properties, and may have a role in preserving microvascular integrity. In health, it contributes about 80% of oncotic pressure but in critically ill patients serum albumin concentration correlates poorly with colloid oncotic pressure[23]. It is relatively expensive and its use in critically ill patients does not improve outcome[24]. As a result of the manufacturing process, human albumin solution is generally considered to be free from any risk of transmitting infection. However, a single bottle of albumin represents exposure to many thousands of donors and, in the UK, there is a concern about the theoretical risk of transmission of the prion causing new variant Creutzfeldt-Jakob disease. As a result, all human albumin solution in the UK is now sourced from the US.

Haemoglobin solutions

At the moment, blood is the only fluid in routine clinical use that has significant oxygen carrying capability. While this property makes it indispensable during resuscitation of haemorrhagic shock, it is expensive, in short supply, antigenic, requires cross-matching, has a limited shelf-life, requires a storage facility and carries a risk of disease transmission. Homologous blood transfusion is immunosuppressive and may independently increase the risk of infection after trauma[25]. Having overcome a number of problems related to toxic stroma, short intravascular half-life, and high colloid osmotic pressure, a number of haemoglobin solutions are now at advanced stages of development[26,27]. Free haemoglobin causes severe renal injury. Polymerisation of the haemoglobin overcomes this problem and improves intravascular persistence. There are three main

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Table 8 Haemoglobin-based red cell substitutes

Company	Product	Type	Comments
Baxter	Diaspirin cross-linked (HemAssist)	Human	Development ceased
Northfield	Glutaraldehyde polymerised (PolyHeme)	Human	Phase III trials
Hemosol	O-raffinose polymerised (Hemolink)	Human	
Biopure	Glutaraldehyde polymerised (Hemopure)	Bovine	Phase III trials
Somatogen	Recombinantly cross-linked (Optro)	Recombinant	Acquired by Baxter

sources for the haemoglobin solutions currently under development: bovine blood, out-of-date human blood (5–13% of blood donated in the US is discarded), and recombinant haemoglobin (Table 8). The products currently under investigation do not require cross-matching, have similar oxygen dissociation curves to blood, and are apparently free from risk of transmitting viral or bacterial infections. They have an intravascular half-life of about 24 h. Diaspirin cross-linked haemoglobin [DCLHb (HemAssist, Baxter)] and bovine haemoglobin solution (Hemopure, Biopure) have a significant vasopressor effect which is thought to result from scavenging endothelial nitric oxide[27].

Objectives for fluid replacement in trauma patients

Severe hypovolaemia is associated with cardiovascular decompensation, reduced cellular perfusion and oxygen delivery, and the development of profound lactic acidosis[28]. If oxygen delivery is not restored quickly, cell membrane pumps fail and cellular function will not recover even if adequate oxygen delivery is restored. Depending on the number of cells sustaining irreversible damage, organ failure or death may ensue. The rationale behind fluid replacement in the trauma patient is to minimise the number of irreversibly damaged cells by restoring adequate tissue perfusion and oxygen delivery as rapidly as possible. While both intravascular volume and oxygen carrying capacity must be addressed, the former takes priority, because acute anaemia is better tolerated than hypovolaemia. Factors to be considered when addressing fluid replacement for the trauma patient are when to give fluid, which fluid to give, and how much fluid to give.

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When to give fluid

It might seem logical to start rapid fluid infusion as soon as possible after trauma so that adequate perfusion is restored as quickly as possible. This implies starting fluid replacement at the scene. However, attempts to replace fluid may delay the patient's arrival in hospital and, under some circumstances, increasing the patient's blood pressure before control of haemorrhage may be detrimental.

Permissive hypotension

Animal studies from the 1950s and 1960s utilised controlled haemorrhage models (*e.g.* Wiggers' model) in which bleeding was stopped before fluid resuscitation started. It was these experiments that defined the goal of rapid restoration of normal blood pressure in haemorrhagic shock. However, these early models do not accurately reproduce the dynamics and pathophysiology of fluid resuscitation in the presence of ongoing haemorrhage. More recently, animal studies of uncontrolled haemorrhage have demonstrated that aggressive fluid resuscitation will increase blood pressure but will also reverse vasoconstriction, dislodge early thrombus, increase blood loss, cause a dilutional coagulopathy, and reduce oxygen delivery causing a metabolic acidosis[29,30]. In these animal studies, allowing the blood pressure to stay low until control of haemorrhage was achieved (permissive hypotension) improved survival.

The animal research was taken to a clinical setting by Bickell and co-workers[31]. In a prospective, controlled study, patients with penetrating torso injury and a prehospital systolic blood pressure of $\leq$ 90 mmHg received either standard intravenous fluid therapy or were cannulated but received no fluid until arrival in the operating theatre. Of 289 patients receiving delayed fluid resuscitation, 203 (70%) survived to discharge from hospital, compared with 193 of the 309 patients (62%) who received immediate fluid resuscitation ($P = 0.04$). Methodological flaws in the study have led some clinicians to disagree with the authors' conclusions[32]. Furthermore, the study was conducted under very specific circumstances. All patients were injured within the city limits of Houston, only those with penetrating injuries to the torso were included, the mean age of the patients was only 31 years, and prehospital times were extremely rapid (mean interval between call and arrival at the trauma centre was 30 min). The findings of this study should not be extrapolated to include patients with blunt trauma, elderly patients with chronic illness, those with head injuries, or to other emergency medical services (EMS) where prehospital time may not be as short[33].

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Prehospital fluid therapy

The practice of prehospital fluid therapy for trauma patients is being challenged. In theory, the early restoration of adequate tissue perfusion should reduce the incidence of multiple organ failure. However, attempts to cannulate the patient and give fluids at the scene will delay the delivery of definitive care in hospital[34]. A recent UK study has shown that intravenous cannulation contributed to the increase of 12 min in the mean scene time which was associated with paramedic interventions[35]. On the other hand, cannulation *en route* does not add extra time and may be as successful as when attempted at the scene[36]. In the UK study, 68% of those trauma patients given fluid before arrival at hospital received less than 500 ml[35]. Prehospital studies from the US have also shown that ineffective volumes of fluid are given to trauma patients[37,38]. There are at least two circumstances where minimal or no prehospital fluid resuscitation is likely to be extremely detrimental: patients with head injury, and those where prehospital times are prolonged. Hypotension will dramatically increase the morbidity and mortality following severe head injury, therefore, attempts must be made to maintain an adequate cerebral perfusion as soon as possible[39]. In a patient with even slightly raised intracranial pressure, this implies the need for a mean arterial pressure (MAP) of at least 90 mmHg[33]. Trauma patients who remain hypotensive for prolonged periods are likely to sustain significant ischaemic injury. The bowel is particularly vulnerable to hypovolaemia and bowel ischaemia may fuel sepsis and multiple organ failure.

Despite any theoretical benefit of prehospital fluid replacement, the concerns surrounding increasing scene time and the data emerging from models of uncontrolled haemorrhage are now impacting on prehospital practice. The Joint Royal Colleges Ambulance Service Liaison Committee (JCALC) have suggested guidelines which restrict the indications for cannulation by paramedics (Table 9) and there is already a tendency to limit fluid resuscitation at the scene[37].

Table 9 JCALC guidelines for cannulation

• Entrapment for > 20 min
• Transit time to hospital > 20 min
• If possible, attempt cannulation *en route*, not at scene
• Critically injured patients should be moved quickly to the most appropriate hospital without cannulation or infusion
• A maximum of two attempts in one arm is permitted, provided the other arm is available

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Assessment of hypovolaemia

The advanced trauma life support (ATLS) classification of haemorrhage is now well established and is taught to doctors throughout the world[40]. Unfortunately, the physiological responses (heart rate, blood pressure, skin perfusion, respiratory rate, urine output, conscious state) to haemorrhage are not as consistent as is commonly believed. Heart rate may be as poor as systolic pressure as a warning of hypovolaemia. Two recent studies have shown no significant increase in heart rate in volunteers undergoing haemorrhage of 20–30% of their circulating volume[41,42]. Alterations in venous tone can make interpretation of central venous pressure very difficult. After a short time, oliguria and the development of a lactic acidosis will confirm suspicions of hypovolaemia but they will not give an immediate indication of the patient's volume status. The response (ideally central venous pressure) to a fluid challenge remains the simplest way of acutely assessing a patient's volume status.

Which fluid for volume replacement?

Whilst there is some debate about when fluid replacement should start, there is universal agreement that once haemorrhage has been controlled, fluid resuscitation is important. At this stage, all would agree that intravascular volume should be restored as quickly as possible in an effort to restore an adequate cardiac output and reverse tissue ischaemia. The main controversy surrounds which fluid or fluids are the most appropriate for achieving these goals and whether the specific choice of fluid has any impact on morbidity or mortality.

Crystalloids versus colloids

The colloid-crystalloid controversy is at least 50-years-old[43]. The principal reason for the controversy is the total lack of quality data to support the choice of either crystalloid or colloid. There are no prospective randomised controlled trials with adequate power to detect a difference in survival as the primary end point. There is little doubt that, in comparison with colloid, larger volumes of crystalloid are required to restore intravascular volume. There is also generalised agreement that colloids, but not crystalloids, can cause anaphylactoid reactions. Beyond these two facts, however, there would appear to be very little agreement. The results of individual studies, particularly those

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in which the volume of extravascular lung water (EVLW) is an end point, tend to reflect the biases of the principal investigators. The crystalloid protagonists argue that following severe trauma, the interstitial fluid volume, as well as the intravascular space, is depleted[44]. They suggest that it is appropriate to restore volume to both spaces by using a crystalloid and present evidence that pulmonary function is not adversely effected by crystalloid resuscitation[45]. The ability of the lymphatics to increase their flow rate by up to 20 times[1] presumably explains why, in most cases, the additional fluid given during crystalloid resuscitation does not cause pulmonary oedema. Others claim that in comparison with crystalloid resuscitation, colloids will increase EVLW and worsen pulmonary function after severe trauma[46]. Their rationale for these findings is that in the presence of leaky capillaries (which occurs with SIRS following severe trauma), colloids will pass into the interstitium and will tend to increase interstitial water and oedema. Those preferring to use colloids tend to focus on the concept of targeting the intravascular space specifically[43] and defend this philosophy with studies which show that, in comparison with crystalloids, colloids reduce the incidence of pulmonary oedema[47,48].

Inevitably, the subject of fluid resuscitation has attracted a number of meta-analyses[49,50]. The most recent concluded that resuscitation with colloid solutions was associated with an absolute increase in the risk of mortality of 4%[50]. This systematic review has been criticised heavily and fails to help us decide which fluid resuscitation strategy we should use for critically ill patients. Another review from the same group, which also received considerable criticism, concluded that the use of albumin in critically ill patients resulted in six additional deaths for every 100 patients treated[51]. Unfortunately, the strength of the conclusions derived from these statistical manipulations can only be as good as the quality of the individual studies included in the analyses. The studies included were very different in their design and used patients of heterogeneous case mix, different resuscitation fluids, and with different resuscitation goals. The numbers of patients in the individual studies are small. There are so many variables impacting on outcome that to focus on fluid resuscitation alone would require hundreds of patients in any one study.

The popular approach to fluid resuscitation of the trauma patient in the UK is to use both crystalloid and colloid. After haemorrhage there will be some movement of interstitial fluid into the intravascular space[2] while intracellular volume remains unchanged[52]. The replacement of interstitial fluid as well as intravascular fluid would seem logical. In reality, it is far too simplistic to think that colloids will remain in the intravascular space, even in patients without capillary leak. Patients with severe injuries will quickly develop SIRS[53] and with it, a leaky microcirculation. A significant proportion of any colloid solution will

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enter the interstitial space, the precise quantity being determined by the range of molecular sizes, molecular charge and extent of capillary leak. The better intravascular retention of colloids in comparison with crystalloid may make it easier to interpret the results of a colloid fluid challenge.

Gelatin is the most popular colloid in the UK (Table 6) and is relatively inexpensive. The fact that it has not been available in the US for many years may partly explain the transatlantic differences in opinion in the crystalloid-colloid debate. Colloid resuscitation in the US has largely comprised the use of albumin and, more recently, HES. Both of these are significantly more expensive than gelatin.

Colloids versus colloids

One of the chief weaknesses of the systematic review by Schierhout and Roberts[50] was that it failed to take into account significant differences between one colloid and another. Indeed, the crystalloid-colloid debate has evolved into a colloid-colloid debate[54]. The wide-ranging pharmacological and pharmacodynamic properties of the colloids emphasise the significant differences between these fluids. The oncotic pressure exerted at the capillary membrane will depend not just on the specific colloid but also on the porosity of the capillary endothelium. Thus, on the basis of *in vitro* measurements of oncotic pressure only, it may be very difficult to predict what effect a specific colloid will have on the intravascular oncotic pressure of a severely injured patient. Whilst smaller molecular weight colloids (*e.g.* gelatins) may pass easily through leaky capillaries, colloids of larger molecular size (*e.g.* HES) will have better intravascular retention[55].

In patients without capillary leak, the gelatin solutions will exert a reasonable plasma oncotic pressure but, in comparison with other colloids, this effect is short lived (about 2 h). In the UK particularly, many clinicians seem happy to accept this short-term gain and will use liberal quantities of gelatin during initial resuscitation of the trauma patient. Later, when the patient with severe trauma will have a significant 'leaky capillary syndrome', the intravascular retention of gelatin is likely to be minimal. At this stage, any clinical benefit of gelatin over crystalloid is highly doubtful.

Intravascular retention of dextran and HES is significantly better than gelatin. However, the potential for dextran and HES to impair coagulation limits their use for very high volume resuscitation. This problem limits the maximum safe dose of dextran to about 1500 ml/70 kg body weight/day. Dextran is not used in the UK for trauma patient resuscitation. Medium and low molecular weight HES has less effect on coagulation than high molecular weight HES (450/0.7) but data sheet

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recommendations restrict its use to approximately 2 l/day in the average patient. In reality, these volumes are often exceeded without inducing a clinical problem. The medium molecular weight starches are being used increasing for trauma patient resuscitation. There is some evidence that HES 200/0.5 may improve microcirculatory perfusion, possibly by reducing endothelial swelling or by modifying leukocyte adhesion[20]. It may inhibit some components of acute inflammation[19] but as yet the potential impact of this on outcome remains unclear. Most of these theoretical advantages have been attributed to dextran as well[56].

Albumin is relatively expensive. Although recent claims that it increases mortality in critically ill patients are unproven[51], there is no clear indication for its use in adult trauma resuscitation. It is still used by many paediatricians, partly because HES is not licensed for use in children.

Hypertonic fluids

Hypertonic crystalloid solutions are attractive as they provide small volume resuscitation and rapid restoration of haemodynamics with laboratory evidence of improved microcirculatory haemodynamics[57]. In theory, there are some practical advantages for the prehospital use of hypertonic solutions. However, before haemorrhage is controlled, raising the blood pressure may not be an ideal goal, and the role of hypertonic solutions in trauma resuscitation has yet to be defined. A number of prehospital trials using small volumes of 7.5% saline or HSD have now been completed[58]. Many of these studies have shown a trend toward increased survival in those receiving HSD, but in none of these was the overall difference in survival statistically significant. In a subset of head-injured patients with a Glasgow Coma Scale score of 8 or less, survival to hospital discharge was higher in patients receiving hypertonic saline (with or without dextran 70) compared to those receiving Ringer's lactate[59]. Hypertonic solutions require further clinical investigation and, as yet, are not in common use.

Haemoglobin solutions

In comparison with blood, haemoglobin solution may provide oxygen delivery to ischaemic tissue; the acellular fluid may perfuse capillaries that are compressed by oedema that would prevent the passage of red cells, and haemoglobin polymer is able to filter from the circulation[27]. In a rat model of controlled haemorrhage, DCLHb was superior to crystalloid, albumin, and blood in gut resuscitation[60]. In a phase II randomised study of 44 trauma patients, up to 6 units of PolyHeme (human polymerised

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haemoglobin) was given to 21 patients without serious complications[61]. Unfortunately, a phase III in-hospital, clinical trial of the efficacy of DCLHb in haemorrhagic shock has been stopped after enrolment of the first 100 patients[27]. For reasons that are as yet unknown, the mortality of the study group was significantly higher than that of the control group. Although the long-term safety of massive transfusion with any of the haemoglobin solutions has yet to be demonstrated, it is highly likely that in the future at least one of these fluids will be a routine therapy for trauma patient resuscitation.

Goals of fluid replacement

Once haemorrhage control has been achieved, the goals of fluid resuscitation are to optimise oxygen delivery and improve micro-circulatory perfusion to facilitate the repair process. Patients with severe injuries have high oxygen requirements immediately, and will rapidly accumulate a significant oxygen debt, as indicated by high blood lactate levels and an increasing base deficit[28]. In the past, trauma patients were routinely exposed to very aggressive fluid resuscitation combined with high doses of inotropes in an attempt to achieve 'supranormal' goals for oxygen delivery (DO_2I) and consumption (VO_2I)[62]. There is little doubt that failure to achieve supranormal values of DO_2I and VO_2I is a strong predictor of multiple organ failure and death[63], while the standard haemodynamic measurements of MAP and CVP fail to differentiate between survivors and non-survivors[63]. However, despite the results of one study[64], very few intensivists are adopting this approach. Instead, DO_2I is elevated with appropriate fluid resuscitation (assessed by CVP or pulmonary artery occlusion pressure, urine output and peripheral perfusion), with or without moderate doses of inotrope, while tracking the base deficit and/or blood lactate. The use of gastric tonometry to monitor splanchnic perfusion may have some benefit in guiding trauma patient fluid resuscitation[65]. However, despite simplification of the technique with gas tonometry[66], gastrointestinal tonometry is still controversial and, as yet, is not commonly used.

Fluid warming

All intravenous fluids given to the injured patient should be warmed. A high capacity fluid warmer, such as the Level 1[67], will be required to cope with the rapid infusion rates used during trauma patient resuscitation. Hypothermia (core temperature less than 35°C) is a

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serious complication of severe trauma and haemorrhage and will independently increase acute mortality[68]. Hypothermia has a number of adverse effects[69]:

1 The oxyhaemoglobin dissociation curve is shifted to the left which impairs peripheral oxygen unloading.

2 Shivering will compound the lactic acidosis that accompanies hypovolaemia.

3 Hypothermia increases bleeding[70].

4 Hypothermia increases the risk of infection[71].

5 Hypothermia increases the risk of cardiac morbid events[72].

Transfusion and the acute trauma patient

Traditional teaching is that all patients require a haematocrit of 30% or a haemoglobin of 10 g/dl for optimal oxygen delivery. However, normovolaemic humans with good cardiopulmonary function will tolerate haemoglobin levels down to as low as 5 g/dl[73]. In critically ill patients less than 55 years of age, or with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of less than 20, mortality may be reduced if a restrictive transfusion strategy is adopted and haemoglobin levels are maintained at 7–9 g/dl instead of 10–12 g/dl[74]. These data have yet to be validated in trauma patients specifically. As long as normovolaemia is achieved, the reduction in viscosity results in a significant increase in cardiac output[75] and tends to improve tissue oxygenation. It may be difficult for the clinician to translate these data to the acutely injured patient. This is partly because a history of ischaemic heart disease or significant respiratory disease may not be available initially, but also because the haemoglobin concentration of a haemorrhaging patient undergoing resuscitation will be changing rapidly. Under these conditions the margin of safety is very small if the haemoglobin concentration is reduced as low as 6 or 7 g/dl, even if the patient is previously healthy. Until more data are available from studies on acute trauma patients, the haemoglobin concentration of the severely injured patient should probably be targeted at 8 g/dl. However, in the confirmed cardiovascularly fit trauma patient with only moderate injuries, a haemoglobin value as low as 6–7 g/dl may be acceptable.

Summary

In the presence of uncontrolled haemorrhage, aggressive fluid resuscitation may be harmful. Prehospital fluid replacement must not delay

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the patient's transfer to hospital. Once haemorrhage is controlled, restoration of normovolaemia is a priority. Initially, the precise fluid used is probably not important, as long as an appropriate volume is given. Anaemia is much better tolerated than hypovolaemia. The crystalloid-colloid debate continues but existing clinical practice is more likely to reflect local biases and dogma rather than evidence based medicine. Colloids vary substantially in their pharmacology and pharmacokinetics. The experimental findings from one colloid cannot be extrapolated reliably to another. In the presence of SIRS, when the microcirculation is 'leaky', there may be some advantages to high or medium weight colloids such as hydroxyethyl starch. At this stage, smaller molecular weight colloids such as gelatins offer little advantage over crystalloids. Hypertonic saline solutions may have some benefit in patients with head injuries. A recent study suggests that a restrictive strategy of red cell transfusion (targeting a haemoglobin concentration of 7–9 g/dl) improves outcome in young (< 55 years) critically ill patients. A number of haemoglobin solutions are under development but one of the most promising of these has been withdrawn recently. It is highly likely that at least one of these solutions will eventually become routine therapy for trauma patient resuscitation.

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