OXFORD TEXTBOOK OF NEUROCRITICAL CARE

Chapter 5 - Fluid management

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This chapter identifies and discusses the general issues surrounding the fluid management of critically ill patients. These are universal, regardless of whether or not there is significant brain or spinal cord pathology, and those issues related to specific neurological conditions are covered in the relevant chapters dealing with those subjects.

By way of introduction, a fluid is defined as a substance that continually deforms under an applied shear stress. This physical property lends itself to biological processes, in particular as the medium for convective and diffusive transport.

WATER HOMEOSTASIS

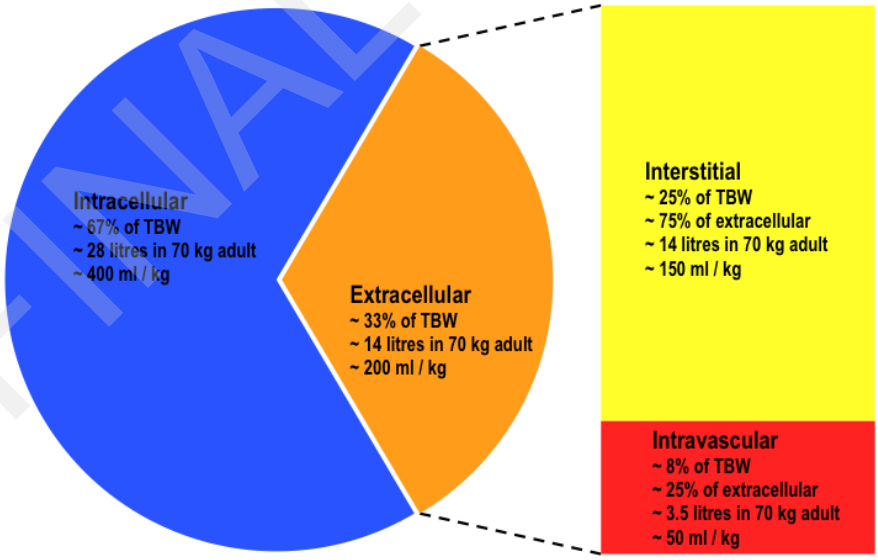
Water is the predominant and essential fluid in the human biology but its biophysical properties remain incompletely understood and the focus of much research (1-5).

Total body water

Healthy humans comprise approximately 60% water (~42 litres in a 70kg adult). With the exception of fat, which is 10% water, all tissues, including the brain (6), are 70%-80% water. Thus, the proportion of fat, which increases with age or in obesity, determines the percentage of body mass that is made up of water.

Water is distributed between two compartments - intracellular and extracellular. The latter is subdivided into the extravascular, or interstitial space, and the intravascular space (see Figure 1).

Figure 1: The distribution of water between body compartments



TBW = total body water

Brain water

The average intra cranial volume is ~1,700ml of which ~1,400ml is brain, ~150ml blood and ~150ml cerebrospinal fluid (CSF). The average adult human brain weighs ~1,350g, and comprises ~77% of water (70% of white matter is water and 80% of grey matter).

CSF is 99% water and formed at a fairly constant rate of 0.2-0.4ml per minute, or 400 – 600 ml/day per day. Production occurs via diffusion, filtration, pinocytosis and active transfer by the choroid plexus (~50%), with the remainder forming around cerebral vessels and along the ventricular walls. CSF is passively absorbed through the arachnoid villi into the venous sinuses, and also drains directly into lymphatic vessels. The rate of absorption is primarily dependent upon the CSF to venous hydrostatic pressure gradient. There is no feedback system between production and absorption of CSF and, if the latter is impaired, CSF accumulates leading to hydrocephalus. For a review of the different types of hydrocephalus and their management please refer to chapter 7, or the article by Bergsneider et al (7).

Homeostasis of total body water

Table 1 details the organs involved in the homeostasis of total body water. Water is lost as a consequence of thermoregulation (heat loss via evaporation of sweat), ventilation (expiration of 100% humidified gas), digestion and excretion. For a 70kg, healthy human adult in a temperate climate undertaking normal levels of activity and eating a standard (mixed) diet, the total daily water loss is in the order of 2,500ml. Approximately 300ml of water is produced as a metabolic by-product, leaving ~2,200ml to be replaced by enteral intake.

Assuming normal losses in the subject described above, physiological adaption to changing circumstances can accommodate reductions in intake to a minimum of ~1,000ml water per day. Reductions in intake beyond this threshold, and/or excessive losses of water with or without sodium or other osmolytes, results in progressive dehydration and initially reversible but negative effects on all organ systems. The brain, skeletal muscle and skin (heat loss) are the organs most affected initially, followed by cardiovascular decompensation. Both the rate of loss and cumulative deficit of water determine the point of irreversible organ injury. Acute deficits of >15% of total body water may be fatal.

Physiological adaptation to excess fluid intake is considerable and dependent not merely on the amount, but also the composition and rate of administration/ingestion. The limit of physiological renal excretion of ingested water is for a 70kg adult in the order of 600ml per hour beyond which water intoxication occurs.

Water passes freely between the body compartments through a variety of semi-permeable cellular membranes, extracellular matrices and intercellular junctions. The permeability of these barriers varies with tissue type and is affected by physiological and pathological processes. Water flux between compartments is principally passive and determined by hydrostatic and osmotic forces (8). However, active co-transport of water against these gradients (uphill) does occur and there is increasing evidence of the importance of this mechanism (9).

The critical intracellular and extracelullar osmolytes are potassium and sodium respectively. Maintenance of this compartmental gradient, via plasma membrane bound sodium/potassium adenosine triphosphatase (Na^+/K^+-ATPase), consumes around 20% of cellular energy expenditure. Exceptionally, this activity may account for 60-70% of energy expenditure in neurones, making them particularly vulnerable to sodium and water influx. The osmotic gradient between the extra- and intra- vascular compartments is the result of colloids, principally albumin. Thus any discussion of fluid management cannot be dissociated from issues affecting electrolytes and colloids.

The physiology of the intravascular compartment volume and composition

The intravascular space has a number of homeostatic mechanisms that maintain effective convective transportation despite significant changes in intravascular volume. The circulation is designed such that 60-70% of the circulating volume is contained within the venules and veins which act as a rapidly responsive reservoir to respond to both volume losses and gains.

Table 1: Daily water homeostasis for a 70kg, healthy human adult, in a temperate climate, undertaking normal levels of activity, eating a standard (mixed) diet

Tissue	Net contribution	Components / dependent upon	Physiological process
Skin	Loss ~250-500ml	• Ambient temperature and humidity • Heat production from activity Minimum ~100ml Maximum ~8,000ml	Thermoregulation - heat loss through evaporation
Respiratory tract	Loss ~500-750ml	• Temperature and humidity of inspired gas • Upper airway anatomy • Ratio of nasal to oral breathing • Minute ventilation • Core temperature	As part of the conditioning process of inspired gas, it is filtered, becomes heated to core body temperature and takes up water to become ~100% humidified.
Kidney	Loss ~1,500ml	• Cardiac output • Systemic blood pressure • Glomerular filtration rate • Renal tubular function • Plasma osmolarity Maximum concentration ~1,400mOsmol/l Minimum concentration ~50mOsmol/l Assuming a daily clearance of 700mOsmol this equates to urine volumes of ~500 to 14,000ml	Excretion and principal organ of water balance. Water retention (resorption) mediated by aldosterone (in response to systemic hypotension) and vasopressin (in response to plasma hyperosmolarity). Water loss mediated by the absence of the above hormones and enhanced by the natriuretic peptides (in response to cardiac stretch).
TOTAL	**~2,500ml**		
Gastrointestinal tract	Gain ~2,200ml	Intake • Water in food ~1,500ml • Water in beverages ~2,000ml Total ~3,500ml Output • Saliva ~1,500ml • Stomach ~1,500ml • Bilary system ~750ml • Pancreas ~1,500ml • Small bowel secretions ~1,500ml Total ~6,750ml Absorption • Small bowel ~9,000ml • Large bowel ~1,000ml but capacity to increase up to 4,500ml principally under the control of aldosterone (systemic hypotension) Total ~10,000 - 14,500ml Losses • Large bowel stool ~200ml	Volitional intake +/- stimulated thirst Digestion Absorption Excretion
Metabolic production of water	Gain ~300ml	• Basal metabolic rate • Level of activity	By-product of enzymatic conversion of fuels to energy
TOTAL	**~2,500ml**		

Volume changes in the intravascular space result in changes in venous, atrial, ventricular and arterial pressures, which are detected by baroreceptors. The changes in the firing rates of these receptors results in changes in the autonomic output to the various components of the cardiovascular system, and compensatory changes aimed at preserving cardiac output and perfusion pressure. Thus, fluid loss triggers venoconstriction, tachycardia, positive inotropy and arterial vasoconstriction. Failure of this vasocontrictor response is commonly seen in acute severe illnesses, such as the more severe forms of the systemic inflammatory response syndrome (SIRS). In addition to the cardiovascular compensatory responses, hormonally driven renal (and colonic) sodium and water retention, mediated by increased secretion of aldosterone (sodium and water, kidney and colon) and vasopressin (water, kidney) is triggered. By contrast, intravascular volume gains are initially absorbed by the reserve capacity of the compliant venous circulation. If isotonic volume gains continue, venous pressure and hence cardiac filling pressures rise resulting in increased cardiac output with a consequent dieresis. This is mediated by a combination of increased renal filtration and hormonally permitted (passive) renal sodium losses, generated to a greater extent by the absence of aldosterone and vasopressin than by the secretion of natriuretic peptides (derived from increased cardiac stretch). It should be noted that, from an evolutionary perspective, humans possess extensive, rapid (minutes) and effective physiological adaptations to limited water availability, moderate free water excess and a paucity of sodium. By contrast the response to sodium excess is very limited and slow, occurring over hours and days.

The volume of blood in the microcirculation is locally controlled within tissues by rapidly responsive changes in vessel calibre, in response to local oxygen tension, and carbon dioxide and other waste acid concentrations. Of note, the effectiveness and efficiency of microcirculatory convective transportation is principally determined by blood viscosity (10), which in turn is determined by the haematocrit and concentrations of plasma proteins.

The microcirculation has variable permeability, both in different tissues and in response to physiological and pathological processes, which allows a proportion of plasma to pass into the interstitial space. The driving force for this movement is the hydrostatic pressure gradient between the intravascular and interstitial spaces, but a number of factors limit the flow of water, solutes and macromolecules down this pressure gradient. The Starling principle of microvascular downstream resorption of interstitial fluid back into the vascular space because of the colloid osmotic pressure of whole blood has been repeatedly proven false and recently been replaced by the glycocalyx model of transvascular fluid exchange (11). The differences between the old and new theories are summarised in Table 2.

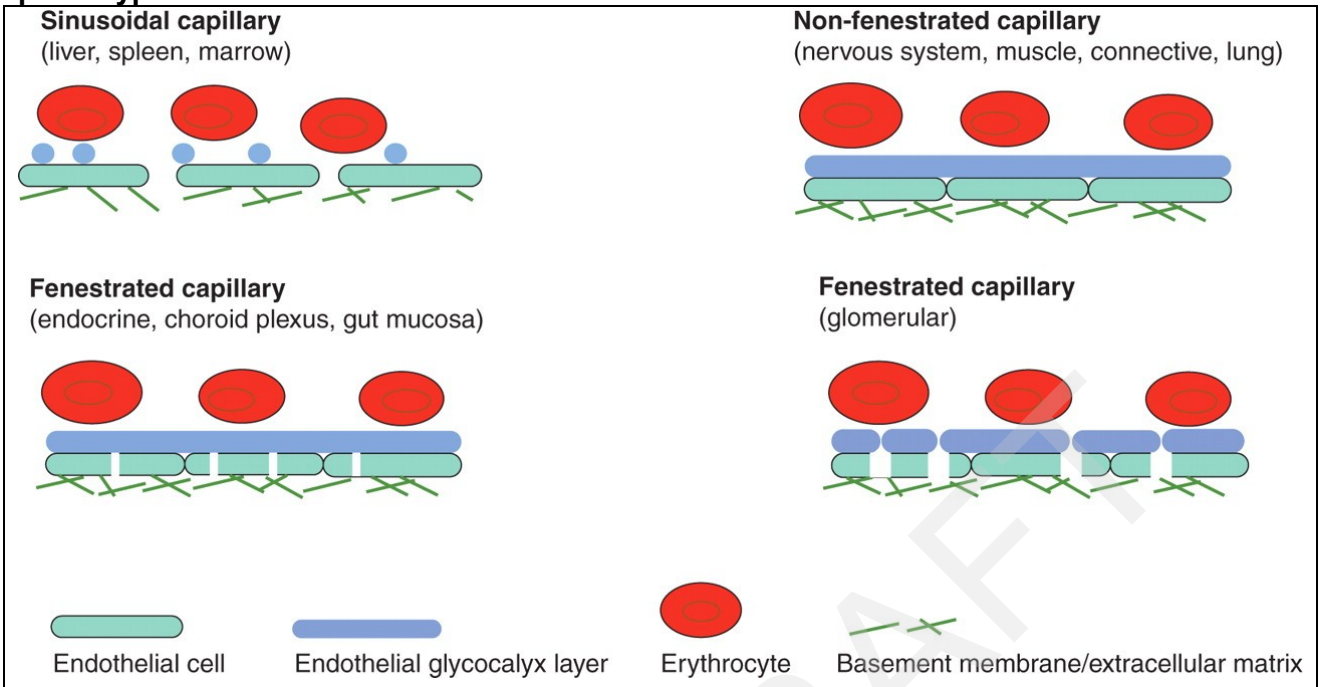
The glycocalyx model is based on the discovery of the endothelial glycocalyx layer (EGL), a web of membrane-bound glycoproteins and proteoglycans on the luminal side of the vascular endothelial cells. It is associated with various glycosaminoglycans, which contribute to the volume of the layer, and is the active interface between blood and the vessel wall and functions as a filter. The EGL varies in thickness from 0.2μm in capillaries to 8μm in larger vessels, and is semi-permeable with respect to anionic macromolecules such as albumin and other plasma proteins, whose size and structure determine their ability to penetrate the layer.

Four microvascular phenotypes have been described in different tissues (see Figure 2). Each exhibits specialist structural features affecting the EGL, the presence or absence of cellular fenestrations, variations in intercellular junctions and basement membranes. In health, the EGL acts to maintain the colloid osmotic pressure, which limits the hydrostatically driven filtration of plasma, such that net fluid movement only occurs when the hydrostatic pressure gradient exceeds the plasma colloid osmotic pressure. Understanding the physiology and pathophysiology of the EGL is thus essential to make a rational choice of intravenous fluid therapy (11).

Table 2: A comparison of the old and the new paradigms that govern net fluid movement between the microvascular and interstitial spaces. *Reproduced with permission from (11)*

Original Starling principle	**The glycocalyx model of transvascular fluid exchange**
Intravascular volume consists of plasma and cellular elements	Intravascular volume consists of glycocalyx volume, plasma volume, and red cell distribution volume
Capillaries separate plasma with high protein concentration from ISF with low protein concentration	Sinusoidal tissues (marrow, spleen, and liver) have discontinuous capillaries and their ISF is essentially part of the plasma volume Open fenestrated capillaries produce the renal glomerular filtrate Diaphragm fenestrated capillaries in specialized tissues can absorb ISF to plasma Continuous capillaries exhibit 'no absorption' The EGL is semi-permeable to anionic proteins and their concentration in the intercellular clefts below the glycocalyx is very low
The important Starling forces are the transendothelial pressure difference and the plasma–interstitial COP difference	The important Starling forces are the transendothelial pressure difference and the plasma–subglycocalyx COP difference. ISF COP is not a direct determinant of J_v
Fluid is filtered from the arterial end of capillaries and absorbed from the venous end. Small proportion returns to the circulation as lymph	J_v is much less than predicted by Starling's principle, and the major route for return to the circulation is as lymph
Raising plasma COP enhances absorption and shifts fluid from ISF to plasma	Raising plasma COP reduces J_v but does not cause absorption
At subnormal capillary pressure, net absorption increases plasma volume	At subnormal capillary pressure, J_v approaches zero. Auto transfusion is acute, transient, and limited to about 500 ml
At supranormal capillary pressure, net filtration increases ISF volume	At supranormal capillary pressure, when the COP difference is maximal, J_v is proportional to transendothelial pressure difference
Infused colloid solution is distributed through the plasma volume, and infused ISS through the extracellular volume	Infused colloid solution is initially distributed through the plasma volume, and infused ISS through the intravascular volume At supranormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure, and increases Jv At supranormal capillary pressure, infusion of ISS also raises capillary pressure, but it lowers COP and so increases Jv more than the same colloid solution volume At subnormal capillary pressure, infusion of colloid solution increases plasma volume and infusion of ISS increases intravascular volume, but Jv remains close to zero in both cases
Key: ISF = interstitial fluid; EGL = endothelial glycocalyx layer; COP = colloid osmotic pressure; J_v = the net fluid movement between the intravascular and interstitial spaces	

Figure 2: A cartoon illustrating the anatomical differences between four capillary phenotypes



Reproduced with permission from (11).

Plasma and interstitial fluid sodium concentration is regulated by vasopressin and aldosterone (see sections above and below). In health, plasma colloid osmotic pressure is principally determined by plasma albumin concentration. Albumin is exclusively synthesised by hepatocytes and immediately released into the circulation. The rate of production is dependent upon substrate availability, hormonal status (principally insulin) and, most importantly, the colloid osmotic pressure of the interstitial fluid around hepatocytes (12). Thus, any increase in plasma colloid osmotic pressure, from either an endogenous or exogenous source, results in decreased albumin production and a fall in plasma albumin concentration in order to maintain a normal colloid osmotic pressure. By contrast, a fall in plasma colloid osmotic pressure results in increased albumin production, a response that is inhibited by inflammatory cytokines (12, 13). In health, an albumin molecule lasts ~30 days. Around 10% of the body's albumin is catabolised daily, with increased catabolism occurring in response to protein and/or calorie deprivation, and acute systemic illness injury. The utility of monitoring plasma albumin concentration and the value of exogenous supplementation are discussed in the relevant sections below.

The physiology of the interstitial compartment volume and composition

The interstitial space is very plastic. In healthy tissues, the volume (water content) of this space is kept to a minimum to facilitate rapid diffusion between the convective transport of the intravascular space and the intracellular environment. This is achieved by drainage of interstitial fluid into the intravascular space via the lymphatic system, driven by gravity, skeletal muscle contraction and negative intrathoracic pressure/breathing. In response to injury or inflammation, effectors of the innate immune system, principally toll-like receptors and integrins, modulate the structure of the extracellular matrix resulting in an acute drop in compartment hydrostatic pressure sufficient to cause up to a 20-fold increase in transendothelial fluid flux, in addition to the compositional changes described below (11). Accumulation of excess fluid in the interstitial space is termed oedema, and originates principally from the vascular compartment. Not only does this limit diffusional transport but, as fluid accumulation continues, extravascular hydrostatic pressure exceeds venous and then microvascular pressure, resulting in tissue ischaemia.

Extracellular fluid osmolarity is tightly controlled, principally by hypothalamic osmoreceptors that regulate the secretion of vasopressin from the posterior pituitary. Increases in osmolarity of >1% stimulate thirst and the release of vasopressin, which, in turn, increases the permeability of the

renal collecting ducts to water. This results in increased water resorption from filtered plasma back into the circulation (14), thereby normalising plasma osmolarity. Decreases in osmolarity have the opposite effects. Acute and chronic changes in osmolarity that exceed the limits of this homeostatic process, or are a consequence of its failure, have profound effects on brain function and can lead to permanent injury and even death. The brain's physiological adaptation to osmotic challenges has been reviewed in detail by Verbalis (15).

The colloid osmotic pressure of interstitial fluid, like that of blood, is principally determined by albumin concentration. It is worth noting that in healthy subjects around 60% of total body albumin is in the interstitial space, although at only 40% of its concentration in plasma (12). However, this albumin pool is not static. 5% of the intravascular pool crosses into the interstitial space each hour with an equivalent amount returning to the circulation via the lymphatic system. In response to injury and inflammation there is a small, acute and transient efflux of albumin from the vascular to the interstitial space (16), although this is insufficient to explain the hypoalbuminaemia observed (17). Albumin has a circulation half-life of approximately 16 hours.

The physiology of the intracellular compartment volume and composition

Cells must actively manage their volume (water content) to avoid lethal injury. In association with the central role of plasma membrane bound Na^+/K^+-ATPase, the family of water channel proteins, the aquaporins (18), and the large variety of uphill co-transporters are pivotal in this regard (9). The complexity and regulation of cellular volume homeostasis remains incompletely understood but is an area of active research and rapid development (19). Much of this research has focused on brain tissue as these processes are central to acute and chronic brain pathologies. Cellular injury, regardless of pathology, frequently results in failure of water content homeostasis and results in an intracellular influx of water (20). As our understanding of this process evolves, it is hoped that effective therapies will emerge (21).

In contrast, adaptation to cellular dehydration, as a consequence of hyperosmolar extracellular milieu (global water losses), is a highly conserved, fundamental, stress response (22). Cells initially adapt to the osmotic efflux of water by active influx of inorganic solutes, in particular, potassium, sodium and chloride ions (23). However, these ions inhibit and/or become toxic to intracellular processes and cells start to synthesise heat shock proteins and accumulate non-toxic osmolytes, including neutral amino acids or their derivatives, polyols such as sorbitol and myo-inositol, and methylamines such as betaine. Although the precise detection and regulation of this process is not fully elucidated, the endoplasmic reticulum appears to play a key role by responding to cytoplasmic un- or mis-folded proteins that accumulate as a direct consequence of critical water loss (24). Acute pathologies that may result in acute cellular dehydration include gastrointestinal infections and hyperglycaemic, diabetic emergencies. The natural histories and responses to therapy of these conditions is testament to the effectiveness of the cellular dehydration response. Maladaptation or failure of this response may be a central driver in many chronic degenerative diseases (24).

ASSESSMENT AND MANAGEMENT OF FLUID STATUS

Fluid management is a fundamental component of the care of critically ill patients, but our ability to assess patients' needs for, and responses to, fluid therapy, and titrate it accordingly, remains surprisingly haphazard. Both inadequate and excessive fluid is harmful, and not infrequently adds a significant iatrogenic insult to the burden of the underlying disease process. Given the long history of fluid management, the gaps in our knowledge are both surprising and regrettable. Indeed, in an attempt to address these deficiencies, there has been a resurgence of both basic science and clinical trial data published on these topics in the last few years.

To mimic a patient's journey, we should first consider fluid resuscitation before discussing maintenance therapy and the active management of daily fluid balance.

Fluid resuscitation: cardiovascular optimisation versus iatrogenic injury

The primary role of the cardiovascular system is the convectional delivery of substrates (in particular oxygen) to within, and removal of wastes from, a diffusional distance of cells. There are

two related components to this delivery - flow and pressure - although the latter cannot be used as a reliable surrogate for the former. There are many methods used to assess the adequacy of single organ and global perfusion, all of which have limitations (25, 26). It is also important to remember that intravascular volume is but one of six physiological variables that determines cardiac output and perfusion pressure. The others are blood composition (viscosity and oxygen carrying capacity), heart rate and rhythm, myocardial contractility and relaxation, vascular tone, and microcirculatory variables (functional capillary density and flow rate). Hence cardiovascular optimisation requires at least consideration, if not direct measurement, of all six.

All patients who suffer an acute severe illness or trauma, or undergo major surgery, require cardiovascular monitoring and support. A major component of this is resuscitation and maintenance of an adequate intravascular volume using intravenous fluid and/or blood component products. Failure to provide such support results in tissue injury through hypoperfusion, the extent and duration of which adversely affect outcome (27). However, fluid therapy in excess of restoration of this adequate volume leads to significant tissue injury through oedema formation, affecting the lungs, kidneys, bowel, brain and soft tissues, and is responsible for delays in the return of normal organ function, organ failure, prolonged hospital stay and excess mortality.

The following questions are a useful guide to the amount and timing of fluid resuscitation, and will each be addressed in detail below.

1. How much of what fluid has been lost (and/or redistributed) over what time period?
2. What was the cause of the fluid loss, is it still on-going and what can be done to minimise further losses?
3. How compromised is the cardiovascular system or, more importantly, is there any evidence of one or more hypoperfused organs?
4. How much of what fluid should be administered and how quickly? By what means can the response to fluid therapy be judged?
5. Having established that a patient is no longer fluid responsive, how long should you wait before re-challenging the patient's physiology?

How much of what fluid has been lost (and/or redistributed) over what time period?

Clinical history, physical examination and routine blood tests (discussed below) should enable a reasonable estimation of fluid losses. The clinical signs of acute hypovolaemia are non-specific and may include sinus tachycardia, atrial fibrillation, normotension, hypotension, absent jugular venous pulsation, tachypnoea, normal mentation, altered mentation, poor peripheral perfusion, reduced skin turgor, and dry mucous membranes.

Historically, the gold standard physiological measure of intravascular volume status has been a static measure of central venous pressure (CVP), but this has repeatedly been shown to be no better than tossing a coin in predicting the stroke volume/cardiac output response to a bolus of intravenous fluid (28, 29). The same can also be said for the measurement of pulmonary artery occlusion pressure. There are a myriad of better static markers but all are derived from stroke volume/cardiac output monitors, and all demonstrate less reliability than clinical care demands. Dynamic measures, in which the percentage change in a measured variable in response to the respiratory cycle or a vascular manoeuvre is used to predict volume responsiveness, are significantly better than static markers, although also subject to limitations (28).

What was the cause of the fluid loss, is it still ongoing and what can be done to minimise further losses?

Initial fluid resuscitation should be guided by the working diagnosis of the degree of hypovolaemia and its cause. There are broadly three clinical scenarios that result in hypovolaemia - excess losses, most commonly renal or gastrointestinal (e.g. diabetic ketoacidosis, hyperosmolar hyperglycaemic state, norovirus infection), SIRS/sepsis (increased losses due to pyrexia and tachypnoea, reduced intake, vasodilatation, and fluid shifts out of the intravascular space), and haemorrhage (gastrointestinal tract, trauma, obstetric, ruptured aortic aneurysm, surgical).

Determining the likely aetiology is crucial because resuscitating patients following haemorrhage requires a significantly different approach to the hypovolaemia of water (+/- electrolyte) loss and SIRS/sepsis. There are substantial risks of significant iatrogenic secondary injury if aggressive fluid resuscitation is delivered before effective control of the source of bleeding is achieved. Such resuscitation may disrupt clots already formed, dilute the coagulation system and accentuate both hypothermia and acidosis, thereby precipitating further blood loss and worsening of any coagulopathy (30). In short, if haemorrhage is known or suspected to be the cause of hypovolaemia, don't delay haemostasis, especially to deliver fluid resuscitation. Do administer intravenous fluids, but use the minimum volume necessary to achieve clearly defined and measurable targets. The optimal choice of fluid in this setting is discussed below. By contrast, the rapid correction of hypovolaemia in the scenarios of excess fluid loss or SIRS/sepsis is strongly advocated.

How compromised is the cardiovascular system or, more importantly, is there any evidence of one or more hypoperfused organs?

Heart rate and blood pressure, except at extremes, are poor guides to cardiovascular adequacy. Normal mentation confirms adequate brain perfusion but altered mentation has multiple causes, only one of which is brain hypoperfusion. Poor peripheral perfusion can be chronic as well as acute and doesn't necessarily reflect vital organ perfusion. Good peripheral perfusion may also occur in distributive shock. Urine output is an unreliable marker of renal perfusion (31). A diagnosis of oliguria can only be made by hourly observations for 4-6 hours and is the physiological response to stress hormones (catecholamines, aldosterone and vasopressin) regardless of intravascular volume status and renal perfusion. Hence, the use of trend data of multiple variables, in particular stroke volume/cardiac output, arterial/central venous lactate and base deficit, central/mixed venous oxygen saturations, and central venous-to-arterial carbon dioxide difference, and their response to dynamic manoeuvres, is strongly recommended (25, 26, 32). Collectively these variables are surrogates for the ideal variables, namely the kinetics of global and organ specific oxygen supply-demand balance (27).

How much of what fluid should be administered and how quickly? By what means can the response to fluid therapy be judged?

For a hypovolaemic or shocked adult, 250ml aliquots, delivered as rapidly as possible (<5mins), of the most appropriate (least harmful) fluid should be used, and the response best assessed by continuous measurement of stroke volume/cardiac output. All available monitoring methods have their limitations and can only reliably detect changes ≥15%, though increases of ≥10% are often considered a positive response. Repeat boluses of fluid should be administered until the monitored response is <10-15%. Arterial/central venous lactate and base deficit, central/mixed venous oxygen saturations and central venous-to-arterial carbon dioxide difference after >15-30 minutes (the plasma half life of lactate is ~20 minutes) should be reassessed.

On the basis of the extent of change in all cardiovascular parameters, titration of vasoactive drugs should be considered. The value of targeting fluid and vasoactive drug therapy to an oxygen delivery index of 600ml/min/m^2 has biological plausibility but remains contentious (33), although it is certainly a reliable marker of prognosis. Adequately powered trials targeting this parameter in specific patient groups are currently underway and will hopefully clarify the utility of this target.

In the absence of invasive monitoring, the response to fluid boluses should be judged against changes in heart rate, blood pressure and mentation. This applies especially in the pre-hospital and acute admission setting. In the context of hypovolaemia secondary to haemorrhage, the commonly quoted and pragmatic advice is to aim for a palpable radial pulse, roughly equivalent to a systolic blood pressure of 80mmHg. However, in the presence of significant brain or spinal cord injury current consensus opinion suggests targeting a systolic blood pressure of 100-110mmHg.

Having established that a patient is no longer fluid responsive, how long should you wait before re-challenging the patient's physiology?

The answer to this question depends on the clinical circumstances. If fluid losses continue, if vasodilatation occurs and as fluid shifts between body compartments ensues, the trends in

cardiovascular parameters, in particular stroke volume/cardiac output, will decline. Given the limits of detectability, a >10-15% decrease should prompt the consideration of a further fluid bolus. A lack of response in this setting should trigger a systemic consideration of the cause of the hypovolaemia, and of the other five physiological variables that determine cardiac output.

Post resuscitation: doing the simple things well - daily fluid balance
The resuscitated patient will commonly have received water, sodium and chloride loading exceeding their needs. This is in part the consequence of fluid shifts from the intravascular to the interstitial space, but also the result of clinical (over) enthusiasm. As explained above, the physiological response to acute severe illness, injury, and major surgery, perhaps exacerbated by significant renal injury, is both the active retention of sodium and water and a limitation of the rate at which the kidneys can excrete excess fluid (31). Thus, although there is a theoretical minimum amount of water, sodium and potassium that a patient requires each day, this must take into account the cumulative picture and make allowances for any predictable further losses together with unavoidable gains, in particular from intravenous therapies.

Any calculated maintenance requirement is best delivered, along with nutritional support, via the enteral route. As a starting point, a euvolaemic patient with no excess fluid loading requires 25-35ml/kg of water, 1-1.5mmol/kg of sodium and 1mmol/kg of potassium each day. Beyond this, it would be ideal to measure all losses and gains (of water and sodium), thereby titrating the maintenance regime to the patient's requirements.

It is standard practice in critical care to record hourly fluid inputs, enteral and intravenous, and outputs, urinary, nasogastric, surgical drains etc. From these hourly measurements, a cumulative balance is calculated for a 24-hour period together with a daily reckoning of the cumulative balance since admission. Although estimates can be made of the additional unmeasured losses from the skin, the respiratory and gastrointestinal tracts (based on the data in Table 1), this is inconsistently performed and may not take account of such factors as the patient's temperature or the presence of external respiratory gas humidification. As a simple, although somewhat unreliable, method to confirm the cumulative fluid balance calculations, changes in the patient's daily weight should be measured, and some modern ICU beds have this facility in-built. Alternatively bed and patient weighing devices have been developed. Despite these simple technologies, concerns regarding the imprecision of this measurement results in it being rarely performed. Whether trend data of daily weight is sufficiently useful to guide setting of daily fluid balance targets remains uncertain, not least because there is a paucity of published data on the subject.

Daily clinical examination should attempt to estimate the degree of oedema, or perhaps more importantly any change in the degree of oedema, particularly in the dependant peripheries/soft tissues, lungs, gastrointestinal tract and brain. The extent and change in lung oedema can be inferred from trends in derived variables of the efficiency of oxygenation, such as oxygenation index, and standardised, dynamic lung compliance, but not reliably from plain chest x-ray series. Gastrointestinal oedema may result in ileus and/or intra-abdominal hypertension and trending regular, standardised measurements of intra-abdominal pressure may alert clinicians to the development of these complications of a positive cumulative fluid balance. In brain injured patients, trending measures of intracranial compliance, and correlation of these to local and/or global measures of the adequacy of brain perfusion, may influence decisions regarding the active management of cumulative fluid balance.

Additional insights into cumulative fluid balance can be gained from trends in routine haematological and plasma biochemical parameters, specifically, haematocrit, sodium, urea, creatinine and total protein, but not albumin. However, all are affected by multiple variables in addition to changes in intravascular and total body water. Haematocrit falls as a consequence of intravascular dilution and rises in response to intravascular water depletion. However, loss of red blood cells through bleeding and sampling, and shortened red cell lifespan and inhibition of red cell production by acute severe illness, confounds this relationship. Plasma sodium concentration is determined by multiple factors reflecting hydration and hormonal status, renal function, and sodium losses and gains. Unlike fluid balance, hourly/daily sodium balance is not routinely measured or

used to titrate daily administration. Critical care commonly results in significant sodium (and chloride) loading from intravenous drug therapies and other routine practices (34). A positive cumulative sodium balance is probably detrimental and should be minimised. An increase in the plasma urea to creatinine ratio is a marker of dehydration. Both are freely filtered by the kidney but only urea is passively reabsorbed. The degree of resorption is proportional to that of water and hence increased in dehydrated patients with good renal function. However, the same pattern of change is also seen following upper gastrointestinal haemorrhage, in hypercatabolic states and in urinary tract outflow obstruction.

Plasma total protein (TP) measurements can be used to estimate colloid osmotic pressure using the formula (35):

$$\text{Colloid osmotic pressure} = (2.1 \times TP) + (0.16 \times TP^2) + (0.009 \times TP^3)$$

This doesn't account for the effect of any administered synthetic colloids so measuring colloid osmotic pressure, using a relatively simple, quick and reliable laboratory technique, is preferred (36). However, given the controversies surrounding all colloid therapies the value of knowing the colloid osmotic pressure and its trends is arguably no longer likely to influence fluid therapy (11).

In summary, trend data and clinical acumen are required to interpret each of the relevant elements contributing to fluid status, and to reach a conclusion in setting daily fluid and electrolyte balance goals. This has to take account of essential therapies such as nutrition and intravenous medication, and may necessitate the use of diuretics (or renal replacement therapy) to control fluid volume. It is vital to review these goals regularly and, if necessary, revise them. Dynamic challenges with fluid boluses or fluid removal may also be helpful in determining both fluid status and optimal strategy.

RATIONAL CHOICE OF INTRAVENOUS FLUID THERAPY

Intravenous salt solutions (crystalloids) have been used since the 1830s. Sydney Ringer first described his physiological salt solution in the early 1880s, and Alexis Hartmann modified Ringer's recipe in the 1930s. Despite their work, 0.9% sodium chloride, misnamed 'normal' saline, went on to become, and remains, the most commonly administered intravenous fluid. Ernest Starling published his equation describing the effects of intravascular colloids in 1896. The first gelatin-based colloids were developed in 1915 and the first reported use of albumin infusions are ascribed to the American military in 1941. Yet, despite hundreds of clinical trials and countless meta-analyses, consensus statements and evidence based guidelines, the controversies and uncertainties surrounding the correct choice of intravenous fluid therapy remain. However, publication of the SAFE study in 2004 (37) and the subsequent large scale trials it spawned, the paradigm shift in trauma resuscitation accelerated by the conflicts in Iraq and Afghanistan (30), the evolution of the glycocalyx model of transvascular fluid exchange (11), and the retractions of publications, and inquiry into the work, of Joachim Boldt (38) have resulted in significant recent advances in fluid management after years of stagnation.

The questions that must answered, most especially in the context of a vulnerable brain, are:

- Are the more physiological ('balanced') solutions less harmful than unphysiological 0.9% sodium chloride?
- Do any of the colloids provide outcome benefits over crystalloids, or over each other?

Balanced solutions versus 0.9% sodium chloride

Table 3 details the composition, osmolarity and pH of commonly prescribed crystalloid solutions, using plasma as the reference solution. 0.9% sodium chloride is mildly hyperosmotic and contains 50% more chloride ions per litre than plasma and hence infusion of any significant volume results in a hyperchloraemic acidosis. Although the acidosis is rapidly buffered, the effects of hyperchloraemia are several and include impaired mental function, nausea, gastrointestinal dysfunction, renal vasoconstriction, hyperkalaemia, impaired coagulation and a pro-inflammatory response (39). What is less clear is whether these effects are clinically important.

Table 3: A comparison of plasma to commonly available intravenous crystalloid solutions

[Electrolyte] in mmol/l	*Plasma*	*0.9% NaCl*	*5% Dextrose*	*4% Dextrose 0.18% NaCl*	*Hartmann's*	*Ringer's*	*1.26% $NaHCO_3$*
Cations							
Na^+	135-145	154	0	30	131	130	150
K^+	3.5-5.2	0	0	0	5.0	4.0	0
Mg^{2+}	0.7-1.0	0	0	0	0	0	0
Ca^{2+}	2.2-2.6	0	0	0	2.0	2.5	0
Anions							
Cl^-	98-105	154	0	30	111	109	0
PO_4^{3-}	0.8-1.4	0	0	0	0	0	0
Lactate	0.5-2.0	0	0	0	29	28	0
HCO_3^-	18-24	0	0	0	0	0	150
Others	Significant	0	0	0	0	0	0
Osmolarity mOsm/l	275-295	308	252	262	275	273	300
pH @ 37ºC	7.35-7.45	5.0	4.0	4.0	6.5	6.5	8.6
Calories kcal/l			170	136			

Yunos and colleagues examined the renal effects of iatrogenic hyperchloraemia in a prospective, open-label, sequential period pilot study in 1,533 ICU patients (40). They found that a 30% mean reduction in chloride loading resulted in a 50% reduction in both the incidence of acute kidney injury (AKI) and the use of acute renal replacement therapy, but no difference in hospital mortality, hospital or ICU length of stay, or the need for renal replacement therapy after hospital discharge. Shaw and colleagues examined the effects of iatrogenic hyperchloraemia in an observational study of adult patients undergoing major open abdominal surgery, comparing the outcomes of 30,994 patients who received 0.9% sodium chloride with 926 patients who received a balanced crystalloid on the day of surgery (41). For the entire cohort, the in-hospital mortality was 5.6% in the saline group and 2.9% in the balanced crystalloid group (P<0.001). One or more major complications occurred in 33.7% of patients in the saline group and 23% in the balanced group (P<0.001). The authors performed a 3:1 propensity-matched comparison and confirmed that treatment with the balanced fluid was associated with fewer major complications (odds ratio 0.79; 95% confidence interval 0.66–0.97) and less resource utilization. In particular, patients receiving 0.9% sodium chloride had a 4.8 times greater use of dialysis (P<0.001) and a 40% higher incidence of major infection. The Cochrane group has undertaken a systematic review of trials comparing balanced solutions with 0.9% sodium chloride, and 13 randomised trials that together enrolled only 706 very heterogeneous patients were identified (42). Clinically important outcomes were only reported in a minority of the trials, with most being assessed on <300 patients, and no significant differences were detected. Although this systematic review is equivocal, it is based on inadequate data and the studies by Yunos et al and Shaw et al, though nonrandomised, do suggest that iatrogenic hyperchloraemia may cause significant harm and should be avoided. A large multicentre, randomised control trial, analogous to the SAFE study, is required to confirm this conclusion.

A largely uninvestigated option to limit chloride loading is the use of 1.26-1.4% sodium bicarbonate. The traditional role of intravenous bicarbonate has been the reversal of severe acidosis. Administration certainly achieves an increase in pH but has never been shown to positively affect outcome (43). This is perhaps unsurprising given that it can be argued that acidosis is never the cause of the problem, but merely a marker of the severity of illness or injury (39, 44, 45). Human cells are very resistant to extracellular acidosis and, analogous with dehydration, cellular adaptation to, and recovery from, it is a highly conserved fundamental stress response. However, sodium bicarbonate has never been shown to be harmful and is recommended in the management of rhabdomyolysis (46), the overdose of certain drugs (47), the

prevention of contrast induced renal injury (48), and is the basis of the replacement fluid in renal replacement therapies.

To date only two small studies, both in patients undergoing cardiac surgery, have compared routine sodium bicarbonate administration with 0.9% sodium chloride. In the first, a double blind, randomised control trial enrolling 100 patients at high risk of post-operative AKI, the groups were well matched and there was a significantly lower incidence of AKI in the bicarbonate group (49). In the second trial, a retrospective cohort analysis of all patients treated during two sequential time periods in a single centre was undertaken (50). 280 patients who received bicarbonate were compared with 304 historical controls who received 0.9% sodium chloride, and no difference was found between the two groups. As this second study has obvious methodological weaknesses, the only conclusion that can be drawn is that bicarbonate may benefit selected patients, probably those at high risk of AKI.

Sodium bicarbonate may yet prove to be an important addition to fluid management regimes. A logical next step would be to include bicarbonate therapy in a chloride restrictive fluid strategy, perhaps based on that employed in the Yunos study (40), and compare this to a standard, liberal chloride fluid strategy. From a neurointensive care perspective, 8.4% sodium bicarbonate has been shown to be as effective and as safe as 5% sodium chloride in the management of raised intracranial pressure following traumatic brain injury (TBI) (51).

Albumin, dextrans, starches and gelatins - colloids versus crystalloids

Talk of the colloid verses crystalloid debate is akin to a fruit verses vegetable debate. Whilst there is the obvious distinction of colloid osmotic pressure, there are as many differences between the various colloids, and crystalloids, as there are between fruit and vegetables. Table 4 sets out a summary and comparison of different colloid types. The discussion that follows has been dramatically simplified by the results of several recent landmark trials.

Albumin

There is an appealing logic to the argument that if any colloid is going to be beneficial it should be the predominant endogenous colloid, albumin. Importantly, albumin performs a myriad of vital molecular binding functions in addition to providing intravascular colloid osmotic pressure (12) and should therefore be considered a drug with distinct pharmacodynamic and kinetic properties. However, its binding properties make it vulnerable to chemical damage, in particular oxidation. Consequently, intravenous formulations exhibit a high degree of variability in binding potential (52), and this heterogeneity may be responsible for some of the inconsistency in clinical trial outcomes.

Hypoalbuminaemia is a near ubiquitous consequence of acute severe illness, although the precise mechanisms contributing to it development remain obscure (17). The consequences are also widely debated as are the safety, timing and efficacy of maintenance and replacement strategies, sometimes coupled with aggressive fluid restriction and active diuresis (53). The SAFE study (37) was the first large scale, pragmatic fluid trial of the current era of ICU trials and set a new standard for such studies. It put an end to the protracted and acrimonious debate about the safety of intravenous albumin that had resulted from a series of meta-analyses reaching diametrically opposing conclusions using the same flawed data. SAFE randomised 7,000 ICU patients, covering the whole spectrum of severity of illness and diagnoses, to receive either 4% albumin in 0.9% sodium chloride or 0.9% sodium chloride, as their resuscitation fluid during the first 28 days of their ICU admission. There were no statistically significant differences in 28 day mortality or in any of a myriad of secondary endpoints. In short, 4% albumin is safe but, in the doses given to a deliberately heterogeneous ICU patient population, of no benefit. Of note, patients in the albumin group received, on average, 40% less resuscitation fluid than those receiving 0.9% sodium chloride. Further, subgroup analysis on the basis of admission diagnosis suggested that there might be benefit in patients with severe sepsis and there was harm in those with TBI (54). Although there remains controversy in some quarters regarding this latter conclusion (55, 56), this subgroup analysis of the SAFE study represents the largest fluid trial in TBI to date. There is some evidence to support the early use of a bolus of 25% albumin following acute stroke (57) and subarachnoid

Table 4: A comparison of albumin solutions and synthetic colloid solutions

	Human albumin	Dextrans	Starches	Gelatins
Chemistry	Single polypeptide chain of 585 amino acids with a molecular weight of 69kDa Derived from donated, pooled human plasma	Highly branched polysaccharide with average molecular weights of 40-70kDa	Chemically modified hydrolysed amylopectin fragments with various mean molecular weights from 130-200kDa	Chemically modified hydrolysed collagen fragments with molecular weights of 5-50kDa
Metabolism and excretion	Lost into the GI tract and catabolised to amino acids in a variety of organs	Smaller molecules excreted unchanged in urine. Larger molecules hydrolysed (days)	Smaller molecules excreted unchanged in urine. Larger molecules hydolysed by amylase, excreated into bile or sequestrated in reticuloendothelial system	Excreted unchanged in urine
Common formulations	4-5% albumin in 0.9% sodium chloride 20-25% in hypotonic NaCl	10% solution with an average molecular weight of 40kDa in 0.9% sodium chloride 6% solution with an average molecular weight of 70kDa in 0.9% sodium chloride	6-10% solutions of varying composition, mostly 0.9% NaCl but some in balanced crystalloids	3-5% solutions of varying composition. Na 145-155mmol/l Cl 105-145 Some with K / Ca / Mg All pH 7.4
Claimed advantages	Physiological Myriad of therapeutic binding properties	Anticoagulation Enhance microvascular flow	Efficacy in expanding the intravascular volume thereby reducing cumulative volume required when compared to crystalloids and gelatins. Proven not to true (64, 76)	Least expensive colloid
Known problems	Cost Risk of transmission of blood borne pathogens	Anaphylaxis Anticoagulation RBC opsonisation and rouleaux formation - interferes with cross matching Acute kidney injury	Cost Anaphylaxis Unpredictable anticoagulation Acute kidney injury Accumulation in all tissues, especially skin causing pruritus	Anaphylaxis Unpredictable anticoagulation ? Acute kidney injury
Comments				Shortest intravascular half-life of all the colloids

haemorrhage (58), with further trials in progress. A number of trials of albumin in patients with severe sepsis are also underway (59).

In summary, albumin appears to be safe and may be efficacious in specific conditions. It should be avoided in patients with TBI, although a well designed randomised control trial in this group could be justified. If a clear therapeutic role emerges, a cost benefit analysis will be required.

Dextrans

The dextrans were developed in the 1950s and have all but been consigned to history, with a few geographical exceptions. Their purported utility in peripheral and microvascular surgery (60) has been superseded by better and safer fluid and antithrombotic strategies (61).

In the only recently published study of their use, a retrospective, historical, cohort analysis, of 332 patients with septic shock treated in a single institution (62), no benefit of dextrans over Ringer's solution could be demonstrated. Two additional findings of this study are noteworthy. Firstly, the doses of dextran were large and perhaps not surprisingly associated with a significantly higher incidence of major bleeding - 51/171 (30%) in the dextran cohort verses 31/161 (19%) in the Ringer's cohort. Second, there was no difference in the total volume of fluid required for resuscitation, demonstrating that the claimed volume sparing effect of dextrans appears to be false. The only other trials using dextrans in recent times have been in the pre-hospital resuscitation of shocked trauma patients and these will be addressed in the trauma resuscitation section below.

In summary, a resurgence of interest in the use of dextrans would appear both unlikely and unjustifiable.

Starches

Due in no small part to the marketing by the manufacturers of starches, their use worldwide has grown exponentially over the last decade (63). However, increasing concerns about their safety and efficacy, coupled with the retraction of a number of studies supporting their use, has led to two large-scale randomised control trials.

The first, known as the 6S study, randomised ICU patients with severe sepsis to receive either starch (6% 130/0.42 in Ringer's) or Ringer's for resuscitation (64). The primary outcome of the study was death or dependence on dialysis at 90 days. 1,211 patients were screened, 804 randomised and complete data sets are available for 798. There was no demonstrable volume sparing effect in the starch group, which had a 20% higher relative risk for receiving blood products. The primary outcome occurred in 51% of patients in the starch group but in only 43% in the Ringer's group (P=0.03). Kaplan-Meier survival curve analysis demonstrates separation between days 10 and 50. Renal replacement therapy was required in 22% of patients in the starch group verses 16% in the Ringer's group (P=0.04). In summary, the use of starch in this study conferred no benefits over Ringer's solution and was associated with a higher mortality and incidence of renal failure.

The second trial, the Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care (CHEST) study**,** randomised all ICU patients who required intravenous fluid resuscitation to receive either starch (6% 130/0.4 in 0.9% sodium chloride) or 0.9% sodium chloride (65). The primary and secondary outcomes of this study were death at 90 days and renal failure within 90 days respectively. 19,475 patients were screened, 8,863 were eligible, and 7,000 of these were randomised. There was no clinically significant volume sparing effect and no difference in death at any time point in the 90 days between the two fluid regimes. Nor was there a difference in days receiving mechanical ventilation, days receiving renal replacement therapy, or ICU and hospital length of stay. There were however significantly higher incidences of renal injury and pruritus in the starch group.

In summary, use of starches confers no demonstrable benefit over cystalloids and may cause significant harm, most especially in the sickest patients. In association with the very high comparative costs, these trials should result in the cessation of the use of starches.

Gelatins

As a consequence of non-medical factors (63), the use of gelatins has been geographically confined to Europe, and their use has yet to benefit from the spotlight of a clinical trial akin to SAFE. In the inadequate and largely outdated trials comparing gelatins to crystalloids and other colloids, they appear to offer no benefits, have a better safety profile than starches, but a worse one than crystalloids. Two systematic reviews are also worthy of note. An expert panel commissioned by the European Society of Intensive Care Medicine to review all of the data from published trials up to May 2011 concluded that synthetic colloids should not be used outside of clinical trials (66). The Cochrane group also independently reached the same conclusion (67).

Although they are the cheapest colloid gelatins are still significantly more expensive than crystalloids. In short, it is increasingly difficult to justify the continuing use of gelatins outside of a well-conducted clinical trial.

Resuscitation following major haemorrhage/haemorrhagic shock

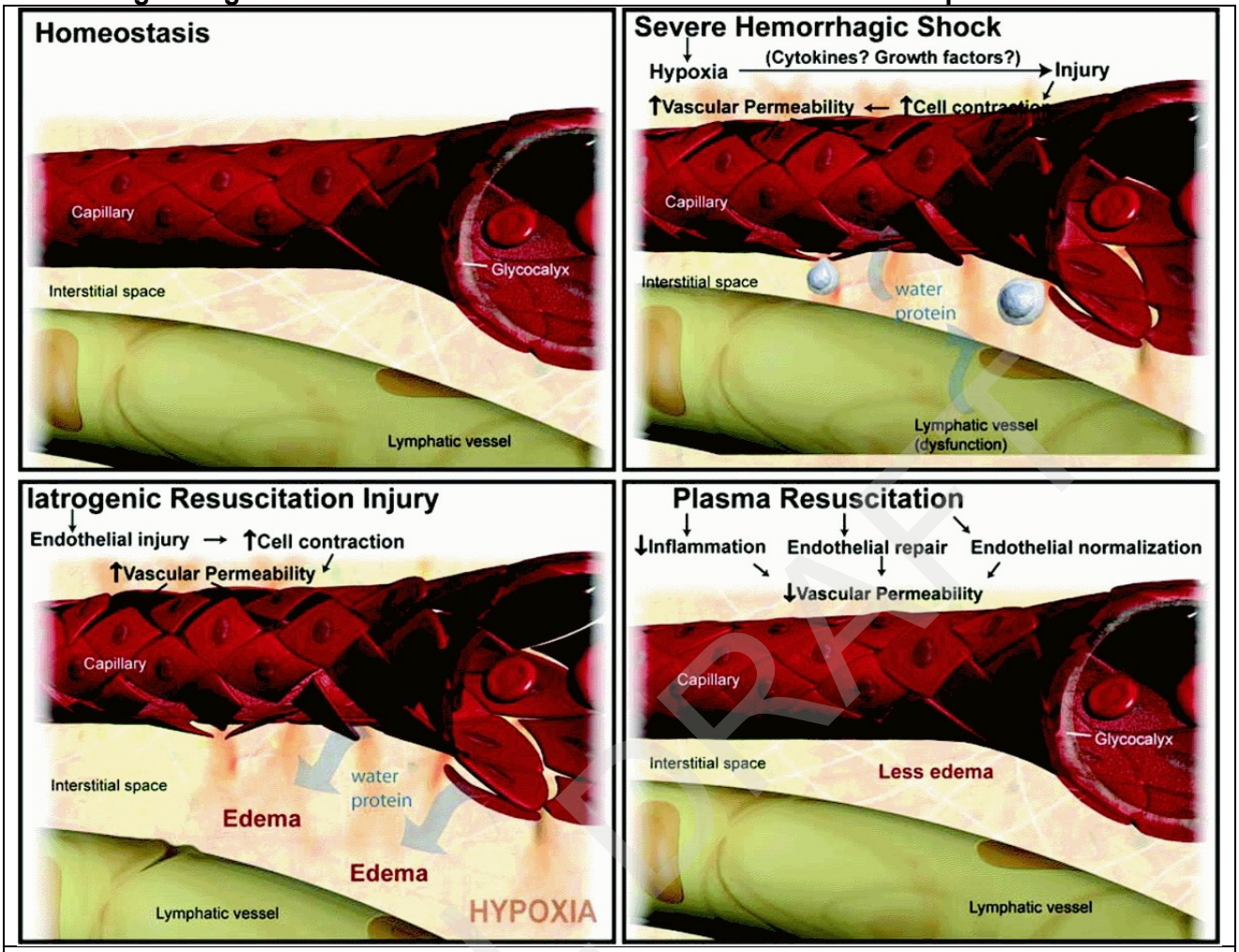
Regardless of the cause of haemorrhage, a large body of data, mostly from the trauma setting (both military and civilian) supports minimal, delayed, titrated and hypotensive fluid resuscitation until control of active bleeding and/or minimisation of the risk of re-bleeding has been achieved (30). These data also support the concept of minimising the volume of administered crystalloids/colloids, and, in their place, the early use of blood component products (uncross-matched if necessary) in a near physiological ratio. Initial resuscitation should use 1:1-2 packed red blood cells to fresh frozen plasma (FFP), supplied together in a ‘shock pack’ and administered simultaneously. The need for ongoing resuscitation beyond 2-4 units of red cells and FFP should include platelets, again in a physiological ratio (68). The volumes given should be titrated to pragmatic cardiovascular endpoints, haematocrit (target 0.30) and normalisation of thromboelastography parameters (69). This resuscitation paradigm encapsulates the early and simultaneous treatment of hypovolaemia, coagulopathy and endothelial dysfunction (70). A high dose of FFP is critical in correcting fibrinogen concentration, which is the first and most important factor deficiency in haemorrhagic coagulopathy (71-73). In addition to clotting factors, FFP contains hundreds of other proteins, including immunoglobulins and albumin, and, as such acts as a volume expander with physiological colloid osmotic pressures. Data from animal models also suggest that FFP, in contradistinction to synthetic colloids and Ringer's, has restorative effects on endothelial permeability and vascular stability (see Figure 3) (70).

However, a final word of caution regarding this approach is warranted. Transfused blood products have myriad negative effects as well as positive benefits (74) and they are also an expensive and limited resource. Thus titration to predefined cardiovascular and haemostatic endpoints, using the minimum of these resources should be applied.

So compelling is the evidence to support the approach described above that many pre-hospital services are now equipped with uncross-matched packed red blood cells and FFP to use for the resuscitation of haemorrhagic shock. However, this is neither a universal nor necessarily practical option, nor one proven to be beneficial. What then are the best, or least worst, alternatives?

There has been a longstanding enthusiasm for administering small volumes of hypertonic fluid for pre-hospital resuscitation of both haemorrhagic shock and/or presumed significant TBI. Both hypertonic and hyperoncotic (dextrans) fluids have been trialled but independent, systematic review of these options has found no evidence of benefit or harm when comparing these solutions to either the mildly hypertonic 0.9% sodium chloride or the mildly hypotonic Ringer’s/Hartmann’s solution (67, 75).The optimal strategy for resuscitating a patient with haemorrhagic shock and significant TBI remains a clinical paradox in which the risk of inducing further bleeding has to be weighted against the secondary brain injury associated with hypotension.

Figure 3
A working biological model of the mechanism of action of fresh frozen plasma



Haemorrhagic shock (HS) leads to a deviation of the vasculature from homeostasis. HS induces hypoxia, endothelial cell tight junction breakdown, inflammation, and leukocyte diapedesis. Fresh frozen plasma repairs and "normalizes" the vascular endothelium by restoring tight junctions, re-building the glycocalyx, and inhibiting inflammation and oedema, all detrimental processes that are exacerbated by iatrogenic injury with synthetic colloid and crystalloids. *Reproduced with permission from (70)*

Maintaining hydration NOT maintenance fluids

The anachronistic dogma of giving x mls/kg/hour of 'maintenance' intravenous crystalloid solutions to all critically ill patients should be consigned to history. There must be a clear rationale and a measurable target endpoint to all fluid prescriptions. The desired endpoint will dictate the rational fluid choice and route of administration for the particular circumstances of an individual patient. For example, a haemodynamically stable patient with a significant positive fluid balance following resuscitation may develop large nasogastric aspirates. However, if as a consequence of this loss the patient achieves their daily fluid balance target (whilst any electrolyte derangement is avoided), the losses should be considered therapeutic.

CONCLUSIONS

Fluid management is a core task in critical care. Historically, there have been diametrically opposing views regarding optimal fluid management but a much clearer understanding of the physiology and pathophysiology of water and electrolyte homeostasis and inter compartmental fluxes, together with the effects of the various components of administered fluids, has recently emerged. Fluid therapy should be titrated to an individual patient's needs and circumstances, avoiding fluids for which there is no evidence of benefit, at least some evidence of harm, as well as those with a cost that significantly exceeds a safer alternative.

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