Safe and appropriate prescribing of intravenous fluids requires an understanding of fluid and electrolyte homeostasis, the physiological responses to injury and disease, and the properties of IV fluids.

Problems arising from inappropriate fluid therapy can increase morbidity and prolong hospital stays. In addition, research has shown that the quality of IV fluid prescribing and monitoring is inconsistent and, generally, is left to junior doctors, whose knowledge may be limited.1–3 Pharmacists should be prepared to advise on IV fluid prescriptions in the same way as for other medicines.

The basics

Within the body, water is distributed into intracellular and extracellular compartments. The extracellular compartment comprises both the interstitial and intravascular (plasma) compartments.

Water can move freely across the membranes that separate the compartments to maintain osmotic equilibrium. Osmotically active substances — predominantly albumin — bind water in the intravascular compartment and thereby ensure that the circulating blood volume is adequate.

Fluid and electrolyte levels in the body are kept relatively constant by several homeostatic mechanisms. Normally, fluid (ie, water) is gained from intake of food and drink, and a small amount is generated from carbohydrate metabolism. Fluid is lost via the urine, sweat and faeces, as well as through insensible losses from the lungs and skin. Typical fluid requirements for a healthy adult are around 30ml/kg/day (see Box 1, p275). However, because the kidneys can concentrate urine considerably, the minimum obligatory water intake is considered to be 1,600ml/day from any source, allowing for a urine output of 500ml.

In healthy individuals, volume homeostasis is regulated largely by antidiuretic hormone (ADH). Osmoreceptors in the hypothalamus and baroreceptors (located in the aorta, the great veins, right atrium and carotid artery) detect small decreases in osmolality and blood pressure, triggering the release of ADH. This elicits a sensation of thirst and reduces renal excretion of water. The renin-angiotensin system also plays a role and is activated by falling renal perfusion pressure. It is important to remember that normal homeostatic mechanisms may not work well after major injury or during episodes of severe illness.
**SUMMARY**

Intravenous fluid therapy is required when enteral intake is insufficient, to replace large fluid losses or when very rapid replacement is necessary. An accurate record of overall intake and output is required for appropriate IV fluid prescription.

IV solutions can be crystalloid (dispersing small molecules such as sodium chloride or glucose) or colloid (dispersing large organic molecules). Solutions with electrolyte compositions more closely matched with plasma are often called "balanced solutions" (eg, Hartmann's solution). Successful therapy may be indicated by improvement in a patient's clinical signs (eg, weight, urine output, capillary refill time), biochemistry and comfort. Serious complications can result from over-administration of fluids.

**Indications for IV fluids**

Where possible, fluids should be provided enterally, since parenteral fluid therapy exposes patients to risks such as fluid overload (by overriding physiological safeguards) and adverse effects associated with individual fluids. IV fluid therapy is required when enteral intake is insufficient (eg, when a patient is "nil by mouth" or has reduced absorption), to replace large fluid losses or when very rapid replacement is necessary.

Losses can occur from the gastrointestinal tract (due to fistulas, vomiting or diarrhoea) or the urinary tract (eg, diabetes insipidus), or be caused by blood loss from trauma or surgery. Febrile patients or those who are suffering from severe burns will have increased insensible losses.

Fluids can also accumulate into spaces that normally contain minimal fluid volumes (eg, the peritoneal or pleural cavities) during surgery or as a result of inflammatory conditions (eg, sepsis). This is caused by vasodilation and "leakage" of vascular epithelial walls and is sometimes referred to as "third spacing". Breakdown of normal compartment integrity can result in loss of circulating intravascular volume.

**Assessing fluid requirements**

A patient’s medical history will give an indication of his or her expected fluid status. A detailed diagnosis is vital to gain information on the likely composition of the fluid lost. Practitioners also need to be aware of any concurrent conditions that can alter fluid distribution or make patients more susceptible to adverse effects from fluid therapy.

**Identifying dehydration**

On physical examination, signs of dehydration include:

- Thirst
- Reduced skin turgor
- Dry mucus membranes
- Increased capillary refill time
- Altered level of consciousness

If a patient is suffering from intravascular volume depletion, then his or her heart rate will increase to improve cardiac output and raise blood pressure. Blood pressure only falls after the intravascular volume has dropped by 20–30%.

Urine becomes concentrated in cases of volume depletion — more severe cases result in a fall in urine output. Raised plasma urea (above 6mmol/L) and sodium levels (above 145mmol/L) can indicate dehydration, as can acidosis on a blood gas analysis.

Signs and symptoms need to be evaluated as a whole, since their specificity in isolation is limited. It should be borne in mind that co-existing conditions or drug treatments may alter results (eg, tachycardia may be suppressed by concurrent drug therapy). Information on assessing response to IV fluid therapy is set out in Box 2 (p279)

**Fluid balance**

An accurately recorded fluid balance, documenting overall intake and output, is required for appropriate IV fluid prescription. Losses via urine, drains, stoma or nasogastric aspirates should be documented. In addition, insensible losses via the respiratory tract and skin (adjusted for body temperature) should be estimated.

It is important to interpret all observations in the context of a patient’s clinical diagnosis — eg, an oedematous patient may show a positive fluid balance but still be intravascularly depleted, resulting in insufficient tissue perfusion and oxygenation. Further details are provided in the accompanying article (p285).

**Special considerations**

Some conditions require special consideration. Patients with major burns require copious amounts of IV fluids, calculated according to body weight and percentage of body surface area affected.

In traumatic brain injury, fluid volume is often adjusted according to mean arterial pressure in an attempt to maintain optimal cerebral perfusion pressure. A delicate balance has to be met between providing sufficient fluid to maintain organ perfusion and avoiding an increase in blood loss due to dilutional coagulopathy (see below) or a sudden increase in cardiac output.

Fluid administration has to be particularly carefully balanced in individuals with heart failure, renal impairment or apparent respiratory failure since these persons are at higher risk of fluid overload.

Compared with adults, children have a higher risk of electrolyte disturbances caused by fluid therapy, owing to their lower ability to compensate. Therefore, paediatric fluid prescriptions require special scrutiny and pharmacists unfamiliar with this patient group should not hesitate to seek advice from experienced colleagues.

**Types of fluid**

IV fluids are generally categorised according to their physical composition. The two main categories are:

- Crystalloids — solutions of small molecules in water (eg, sodium chloride [NaCl], glucose)

**Box 1: Approximate fluid balance (80kg male)**

<table>
<thead>
<tr>
<th>WATER INTAKE (ml)</th>
<th>WATER LOSS (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drink</td>
<td>1,500 Urine</td>
</tr>
<tr>
<td>Food</td>
<td>800 Faeces</td>
</tr>
<tr>
<td>Cellular respiration</td>
<td>300 Skin and lungs</td>
</tr>
</tbody>
</table>
Colloids — dispersions of large organic molecules (eg, gelatin, albumin, etherified starches, dextran) in a carrier solution.

In addition, individual fluids distribute into the various fluid compartments in different ways (see accompanying article, p285, for specific details). In general, colloids remain in the intravascular space where they bind water, owing to their exertion of oncotic pressure; crystalloids distribute more readily into other tissues.

Crystalloid solutions NaCl distributes into the whole extracellular space (ie, into both intravascular and interstitial spaces, although not in equal proportions).

NaCl 0.9%, also known as “normal saline”, is isotonic with respect to plasma and is commonly used for fluid therapy. Hypo- and hypertonic solutions of NaCl are also available, but their use is limited; hypotonic NaCl is used to treat hypernatraemia and hypertonic NaCl is sometimes used to correct hyponatremia (very strong solutions are used to manage aspects of head injury). Careful monitoring is required for these uses.

Glucose solutions distribute throughout the intravascular, interstitial and intracellular compartments (see accompanying article, p285). Glucose 5% solution has the same tonicity as plasma and is used for maintenance fluid therapy. The glucose itself is metabolised quickly and is, in effect, providing free water. Hypertonic solutions of glucose (10% or 50%) are used when glucose substitution is required (eg, to treat hypoglycaemia).

Despite having the same tonicity as plasma, both normal saline and glucose 5% have an electrolyte composition that is different from plasma. Fluid solutions with electrolyte compositions that are more closely matched with plasma are often called “balanced solutions”. For example, compound sodium lactate (“Hartmann’s solution” or “Ringer’s lactate solution”) contains potassium, calcium, magnesium, lactate and sodium chloride.

Colloid solutions The characteristics of colloid infusions depend mainly on their molecular size. Etherified starches are starch molecules that have been “etherified” with hydroxyethyl groups and a range of these is available. Etherified starches have relatively high molecular weights (tetrasacht 130,000 daltons; pentasacht 200,000 daltons; and hetasacht 450,000 daltons) and can provide volume expansion for 6–24 hours.
The duration of action depends on the molecular size of the starch (larger molecules tend to have a longer duration), the rate of degradation and the permeability of the vascular endothelium.

Modified fluid gelatin is derived from animal collagen and has a molecular weight of 30,000 daltons. Its effective half-life is about four hours, but its volume-restoring effect may be shorter in patients with capillary leakage.

Dextran solutions are synthetic polysaccharide colloids, classified according to average molecular weight. Dextran 70 is the only remaining UK-licensed preparation.

Albumin is a natural colloid, derived from whole blood. It is commercially available in isotonic (4.5–5% albumin) and hypertonic (20% albumin) solutions.

Traditionally, colloid infusions were only available dispersed in NaCl solutions, but in the past decade both etherified starches and gelatine in balanced carrier solution have been licensed in the UK.

Approaches
Deciding which fluid is appropriate for a given patient, and how much should be administered, will depend on the aim of treatment: to replace normal losses (i.e., maintenance therapy) or to correct existing fluid deficits (i.e., replacement).

Maintenance therapy For patients who require maintenance fluids (and who have healthy kidneys and no comorbidities that would affect fluid homeostasis), administering a glucose-based fluid and a second fluid to boost intravascular volume (usually a sodium-based fluid) is suitable. This will often be prescribed as a combination of NaCl 0.9% and glucose 5% infusions, or as “dextrose-saline” (generally glucose 4% and NaCl 0.18%). Usually, up to 3L will be administered over 24 hours. Dextrose-saline solution is not recommended for long-term maintenance because it does not provide the required daily amount of sodium, unless excess volume is administered.

In addition to providing water, maintenance fluids should also provide sodium and potassium. Calcium,
Fluid replacement or resuscitation

Deciding which fluids are appropriate for a patient requiring fluid replacement depends on the type of fluid that has been lost and the body compartments that require additional volume. A patient’s renal and cardiac function, acid-base balance, glucose levels and electrolyte levels also need to be considered.

Fluid resuscitation is required in situations where a patient is experiencing acute circulatory shock or intravascular volume depletion. The objective is to restore circulating blood volume and increase cardiac output, thereby restoring tissue perfusion and oxygen delivery.

Any sodium or colloid-based fluid can be used to restore intravascular volume. Fluids that distribute throughout total body water (eg, glucose) do not restore intravascular volume and can exacerbate interstitial oedema in patients who are suffering from inflammatory conditions (eg, sepsis).

Practitioners should remember that any fluid administered during the resuscitation phase (and its associated electrolyte load) will have to be cleared or redistributed by the body. This may take several days or weeks in a patient with impaired homeostasis.

If large volumes of fluid are required, a balanced crystalloid solution (eg, Hartmann’s solution) is preferred because of the complications associated with excessive NaCl load. The selection of colloids versus crystalloids and of saline versus balanced fluids is discussed in Box 3 and Box 4 (p282), respectively. Practical aspects of fluid replacement and resuscitation are discussed in the accompanying article (p285).

Complications

A range of complications can occur as a result of fluid therapy. Perhaps the most obvious complication is the administration of too much fluid. When this occurs, the heart can fail to pump the expanded circulatory volume effectively.

Over-distension of the left ventricle can cause heart failure and, consequently, pulmonary oedema. A patient with pulmonary oedema will be short of breath and have a cough, respiratory crackles on auscultation and reduced oxygen saturation. These clinical features are often accompanied by an increased heart rate, which must not be confused with tachycardia caused by hypovolaemia. Renal failure and pre-existing ventricular impairment can exacerbate the condition.

Abdominal compartment syndrome and acute respiratory distress syndrome are both known consequences of excessive fluid resuscitation and fluid overload. Particular care has to be taken when treating any

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**Box 3: Colloids vs crystalloids**

Colloids allow fast restoration of intravascular volume, but there has been much debate about their safety and superiority over crystalloids for fluid resuscitation.

A recently updated meta-analysis showed no difference in mortality between patients treated with colloids and those treated with crystalloids for fluid resuscitation. In the original Cochrane review, there was particular controversy regarding albumin infusions. Subsequently, the SAFE study compared albumin 4% and NaCl 0.9% for fluid resuscitation in intensive care and demonstrated no difference in outcomes. In addition, colloid infusions are significantly more expensive than crystalloid infusions. In the UK, the use of albumin is now restricted to conditions in which the synthesis of clotting factors is reduced (eg, severe hepatic failure).

The lower overall volume load associated with colloids is often pointed out as an advantage of their use. For replenishing intravascular volume, 3L of a crystalloid solution is assumed, generally, to be equivalent to 1L of colloid solution. However, the SAFE study reported a ratio of 1.4L of normal saline to 1L of albumin. Gelatin has a similar molecular size to albumin so the difference in administered volume is unlikely to be substantial.

It may be possible to use smaller volumes of solutions containing large starch molecules (eg, hetastarch) to replenish intravascular volume. In particular, for conditions where there is increased epithelial wall permeability (eg, sepsis, other inflammatory conditions, prolonged anaesthesia), starches may be more effective at reducing leakage into the interstitial space by increasing oncotic pressure. Evidence is needed about whether and how this translates into improved clinical outcomes.

Another Cochrane meta-analysis failed to show any difference in outcome between different types of colloids. However, a wide variety of studies was included and further research is required. Each colloid has its own adverse effect profile, which should be taken into account when making choices for individual patients.

Current evidence suggests that certain types of etherified starches are associated with increased morbidity. Although this may not be transferable to all starch infusions, serious consideration should be given before treating patients with large amounts of any etherified starch.

It is worth noting that another factor complicating the colloid versus crystalloid debate is that there are doubts around the integrity of some of the research — publications from one particular researcher were retracted by 16 peer-reviewed journals after it emerged that ethical approval had not been sought and data had potentially been falsified. This cast doubt on the results of meta-analyses in which the researcher’s data had been included.
Box 4: Saline vs balanced fluids

High-volume administration of sodium chloride-based IV fluids, and the resulting load of sodium and chloride ions, can cause marked biochemical disturbances and hyperchloraemic acidosis.

For patients with underlying tendencies towards acidosis (eg, those with carbon dioxide retention secondary to respiratory failure, or those with increased lactate levels following surgery), compensation mechanisms can easily be overwhelmed, resulting in severe metabolic acidosis. Therefore, many clinicians prefer the use of a balanced crystalloid or colloid solution when large volumes are required (such as in major trauma surgery), and for patients with impaired compensatory mechanisms (eg, the critically ill).

Recently updated consensus guidelines advise on the use of a balanced infusion for maintenance therapy in all surgical patients.9

Despite this, it is not clear if the use of balanced fluids translates into meaningful benefits in clinical outcomes. Additionally, the anions contained in these balanced fluids (lactate, malate) could be associated with their own risks if administered in excess.10

Biochemical abnormalities

Biochemical abnormalities occur frequently in patients receiving IV fluids and reflect the response to the fluid administered. In particular, infusions of NaCl 0.9% can result in over-provision of sodium and chloride and cause hyperchloraemic acidosis (see Box 4). It is worth noting that there are risks associated with rapid correction of both hypo- and hypernatraemia, but these are outside the scope of this article.

Allergic reactions

Allergic reactions, although rare, can be associated with synthetic colloids such as etherified starches, gelatin and dextran.

Haemodilution

Administering IV fluids in large volumes will inevitably lead to haemodilution and a fall in haemoglobin levels. This usually corrects itself within a few days as the extra fluid is cleared by the kidneys. However, blood transfusion may be required depending on a patient’s condition and local transfusion criteria.

Dilutional coagulopathy

Dilutional coagulopathy is an effect of high-volume fluid administration. In addition, some colloid infusions impair components of the clotting cascade (eg, dextran solutions are known to be antithrombotic).

The higher molecular weight etherified starches (eg, hetastarch, pentastarch) have been associated with increased bleeding, this is probably of less clinical consequence with colloids of smaller molecular size.

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Renal impairment Recently, it has been suggested that starch solutions have the potential to cause renal impairment. A possible explanation for this is hyperoncotic acute renal failure. If these products are given with insufficient water, the oncotic pressure of plasma is raised to the point where it effectively opposes filtration pressure in the kidneys, thereby impairing normal glomerular filtration. To avoid this, starch infusions should be accompanied or followed by a crystalloid infusion of the same volume.

References