16 FLUID, ELECTROLYTE AND METABOLIC MANAGEMENT

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16.1 Introduction

The medical management of the severely head-injured patient involves manipulations of the intracranial pressure (ICP), cerebral perfusion pressure (CPP), seizure control, fluid and electrolyte therapy and nutritional support. The goal of fluid management is homeostasis, i.e. to provide appropriate parenteral and/or enteral fluid to maintain intravascular volume, left ventricular filling pressure, cardiac output, blood pressure and ultimately oxygen delivery (\(\dot{D}O_2\)) to tissues, when normal physiological functions are often altered by surgical and traumatic stress and by anesthetic agents. A specific aim is to prevent secondary neuronal damage due to inadequate \(\dot{D}O_2\) to the brain; this requires adequate ventilation and oxygenation as well as cardiac output. The most obvious consequences of inappropriate fluid resuscitation are shock from insufficient volume replacement, and pulmonary edema from overhydration.

Glucose, lipids, protein, vitamins and essential trace elements are provided in order to retard the 'autocannibalism' of visceral protein for gluconeogenesis. Fluid planning must be individualized and take into account the patient's cardiac, renal, pulmonary, nutritional, functional and premorbid state.

Fluid and electrolyte abnormalities may result from the brain injury itself, e.g. diabetes insipidus, from therapy and from other injuries. The relationship between systemic abnormalities of water, electrolytes and acid–base metabolism and the brain can be approached from two vantage points:

- the effects of CNS lesions on renal function, water and electrolytes;
- the effects of metabolic abnormalities on the CNS.

16.2 Rationale of metabolic support

The outcome after a severe head injury is influenced by age, pre-accident health, the severity of the primary injury and any of six potentially preventable secondary insults: intracranial hematoma, raised ICP, seizures, meningitis, hypoxia and hypotension (Price, 1992). About 20% of patients with head injuries also suffer injury to other systems. The injured brain is highly vulnerable to hypoxia and ischemia, which may exacerbate neuronal damage by a number of mechanisms, including the release of excitotoxic neurotransmitters such as glutamate (Zwimpfer and Moulton, 1993). Extracranial injury that does not result in hypotension or hypoxia appears to have little influence on outcome (Jennett, Teasdale and Braakman, 1979). Hence preventing and aggressively treating hypotension and hypoxia are essential parts of the early management of all patients with head injury.

Approximately 50% of patients admitted to the hospital in a coma following head injury will require craniotomy (Butterworth and De Witt, 1989). Others who do not require craniotomy may require anesthesia and surgery for other major injuries. The anesthesia and surgery can both affect fluid and electrolyte status.

Intravenous therapy is an integral part of both the initial resuscitation phase and the later maintenance or supportive phase of management. The primary aim of resuscitation is to achieve satisfactory ventilation and restore intravascular volume, cardiac output and tissue perfusion, thereby preventing the sequelae of shock, acute renal and multiple organ failure and secondary neuronal damage. The secondary aim is correction of any underlying disorder. In adults prolonged hypotension is rarely due to head injury alone, unless the injury is massive and brain death is imminent, and concealed hemorrhage must be sought. In infants and young children, hypovolemic shock may result from blood loss in a large extradural hematoma, especially if there is additional bleeding under the scalp. Shoemaker has demonstrated that O\(_2\) transport variables (\(\dot{D}O_2\) and oxygen consumption – \(\dot{V}O_2\)) can reliably predict outcome in postoperative surgical patients. Conversely when these variables are manipulated in a controlled...
prospective manner, outcome can be improved (Shoemaker et al. 1982, 1988). The determinants of oxygen delivery are summarized in Figure 16.1. Fluid resuscitation augments preload, increases stroke output and total systemic flow, thereby increasing oxygen delivery. Care must be taken to avoid hemodilution, which may simultaneously reduce arterial oxygen content and prevent an increase in $\dot{D}O_2$ despite improvement in cardiac index. Oxygen saturation should be maintained at 90% or greater in accordance with the recommendation of the American College of Chest Physicians Consensus Conference on Mechanical Ventilation (Slutsky, 1993).

Following resuscitation, fluid therapy aims to maintain euvolemia, provide normal daily requirements and replace any continuing losses. It is usually combined with nutritional support.

Cerebral autoregulation determines the relationship between cerebral blood flow (CBF) and metabolic needs (metabolic coupling) and systemic hemodynamics (pressure autoregulation). When metabolic coupling is intact, cerebral oxygen delivery is determined by metabolic need and is unaffected by minor changes in blood pressure or viscosity. Both aspects of cerebral autoregulatory function may be impaired following traumatic brain injury, so that cerebral oxygen delivery is influenced by cerebral perfusion pressure (CPP) and blood viscosity (Shoemaker et al., 1988). Thus maintaining a normal CPP is a key aspect of the management of the head-injured patient.

Most severely injured patients develop only small changes in serum electrolyte concentrations, even though there are large fluid and electrolyte shifts between body compartments. Thus it is important to understand the physiological basis of the common electrolyte problems, the factors controlling electrolyte distribution and extracellular fluid volume and the distribution of administered fluids since the choice of intravenous fluids will influence brain metabolism and volume (Sutin, Ruskin and Kaufman, 1992). From this knowledge appropriate therapeutic strategies can be developed.

### 16.3 Basic principles

#### 16.3.1 FLUID DISTRIBUTION

The total body water content of humans is approximately 60% of body weight (Figure 16.2). Two-thirds is located in the intracellular and one-third in the extracellular compartment (Harrison, Darrow and Yannet, 1936). The extracellular compartment can be further subdivided into interstitial (protein-poor) and intravascular (protein-rich) compartments. Normally, 75% of the extracellular water is contained within the interstitium and 25% in the vasculature. There are marked differences in electrolyte content between intracellular and extracellular fluids: potassium is predominantly intracellular, and sodium and chloride extracellular (Gamble, Ross and Tisdall, 1923). The energy-consuming $\text{Na}^+$/-$\text{K}^+$ pump is

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**Figure 16.1** Systemic oxygen delivery – $\dot{D}O_2$ (ml/min) – is determined by the product of the oxygen content of the blood and total systemic blood flow. The major determinants of each component are pictured. $\text{Hb}$ = hemoglobin; $\% \text{SAT}$ = percentage saturation of $\text{Hb}$; $P_{\text{a}O_2}$ = partial pressure of oxygen in arterial blood; 0.0031 = solubility coefficient for oxygen in plasma.

**Figure 16.2** Distribution of body water in a 70 kg man (45.5 liters).
required to maintain these concentration gradients, which are sustained during sodium overload or depletion states. Distribution of water between the intracellular and extracellular compartments is determined by osmosis.

Extracellular fluid includes water ‘attached’ to bone and dense connective tissue, as well as free transcellular or ‘third-space’ fluid formed by secretions from epithelia and other membranes. Free transcellular fluid includes cerebrospinal fluid (CSF), urine, gastrointestinal and other secretory fluid, which may have strikingly different osmolalities from the two major body fluid compartments (Shoemaker, 1982). Although this third space may be greatly expanded in disease states such as ascites, pleural effusion, paralytic ileus or bowel obstruction, it is separated from other body fluid compartments by epithelium and therefore does not communicate freely with them. The third space can be thought of as ‘parasitic’ – it is generated at the expense of the other two compartments but is not available to ‘come to their rescue’ in states of hypovolemia. Since most forms of expansion of the extracellular fluid do not involve the third space fluids and the amount of water attached to bone and dense connective tissue is relatively fixed, the normal body water distribution can be simplified as shown in Figure 16.3.

Cell membranes are normally relatively impermeable to ions but freely permeable to water. Water, electrolytes and energy substrates continually move in and out of cells to maintain a dynamic steady-state relationship and major fluid and electrolyte shifts occurring with disease are often associated with only minimal serum concentration changes. For example, a decrease in extracellular sodium concentration and osmolarity following an infusion of 5% dextrose in water is followed by diffusion of water into the cells until the osmotic pressure between the two compartments is equal. Conversely, an increase in extracellular sodium concentration and osmolarity after infusion of hypertonic saline is followed by movement of water from the intracellular to the extracellular compartment. Infusion of an isotonic electrolyte solution does not alter the osmolarity of the extracellular compartment and therefore does not lead to shifts of water into or out from the intracellular compartment.

Water movement between the two components of the extravascular space is determined primarily by differences in protein concentration. Colloid osmotic pressure (COP) is the net osmotic pressure across the capillary membrane resulting from the impermeability of the endothelium to plasma proteins. Because physical confinement of protein molecules produces an osmotic imbalance, water moves from interstitial space into the bloodstream. Crystalloid molecules cannot establish a pressure gradient because they move freely across the capillary membrane.

Protein molecules are negatively charged and attract a small number of positive ions, preventing them from diffusing across the endothelium. These retained ions produce an additional osmotic pressure (called the Donnan equilibrium effect). Some 60% of normal COP is produced by protein molecules (75% by albumin, the rest mainly by globulins and fibrinogen); 40% is produced by the electrostatically held cations. However, if the plasma protein concentration rises, the influence of the Donnan equilibrium effect on COP increases disproportionately, producing a curvilinear relationship between total protein concentration and COP.

COP is measured by placing a protein solution on one side of a semipermeable membrane and a protein-free solution on the other side. Fluid moves through the membrane until a pressure is generated that prevents further osmosis. This pressure is defined as the COP (Morissette, 1977). Plasma COP in normal ambulatory patients is approximately 25 mmHg, in supine patients 22 mmHg and in an Intensive Care Unit patient 18–20 mmHg (Weil et al., 1974, 1981; Rackow, Fein and Leppo, 1977). Although protein is the primary determinant of osmotic pressure in peripheral tissues, it contributes very little to the total number of particles dissolved in plasma. Total plasma

Figure 16.3 Simplified distribution of body water in a 70 kg man. The forces that influence fluid distribution between the compartments are shown in italics.
osmolarity is normally 285 mosmol/kg, of which plasma protein accounts for less than 1 mosmol/kg.

Infusing an iso-oncotic solution such as 5% albumin in isotonic saline expands the intravascular space without producing a shift of water from other compartments. A hyperoncotic solution such as 25% albumin expands blood volume to a extent greater than the volume infused by drawing water and electrolytes from the interstitium. However water does not diffuse from the intracellular space if extracellular osmolarity remains unchanged.

Starling defined the forces influencing the bulk movement of water between the vascular and interstitial compartments (Starling, 1896). Pappenheimer and Soto-Rivera derived a mathematical expression for these forces, referred to as the Starling equation of transcapillary exchange: (Pappenheimer and Soto-Rivera, 1948).

\[
Q_i = K_f [(P_c - P_i) - \delta (\pi_c - \pi_i)]
\]

where \(Q_i\) = total fluid flow across the capillary membrane; \(K_f\) = fluid filtration coefficient; \(P_c\) = capillary hydrostatic pressure; \(P_i\) = interstitial hydrostatic pressure; \(\delta\) = osmotic reflection coefficient; \(\pi_c\) = capillary oncotic pressure; \(\pi_i\) = interstitial oncotic pressure.

The four pressures in this equation are called the Starling forces. The net driving pressure favoring filtration is \(P_c - P_i\). The hydrostatic pressure within the capillary is the major force driving fluid into the interstitium and is essentially unopposed by the interstitial hydrostatic pressure. This is usually slightly negative and approaches zero or becomes slightly positive only when substantial amounts of edema accumulate (Meyer, Meyer and Guyton, 1968; Guyton, Granger and Taylor, 1971). The plasma COP is thus the only force acting to retain fluid within the intravascular space. The interstitial COP works in the opposite direction; the net effect of these opposing forces is described by \(\pi_c - \pi_i\).

\(K_f\), the filtration coefficient, has two components: \(L_p\), the hydraulic conductivity, which describes how rapidly fluid can pass through the microvascular exchange barrier (capillary membrane, interstitial gel and terminal lymphatics) and \(S\), the capillary surface area available for filtration (Granger, 1979; Demling et al., 1982). If either component of \(K_f\) increases, e.g. through damage to the endothelial membrane or dilatation of precapillary vasculature in response to increased cardiac output (CO), the rate and amount of fluid filtered increase independently of changes in the Starling forces (Peters and Hargens, 1981).

The reflection coefficient \(\delta\) defines the capacity of the capillary membrane to prevent translocation of proteins. If \(\delta = 1\), the membrane is totally impermeable and proteins are able to exert their full oncotic force; if \(\delta = 0\), the membrane permits protein to pass without impedance (Peters and Hargens, 1981). \(\delta\) varies in capillary membranes throughout the body, being approximately 0.9 for systemic and 0.7 for lung capillaries (Wittmers, Bartlett and Johnson, 1976). The net effect of the Starling forces across capillaries is to produce fluid movement from the intravascular to the interstitial space. Accumulation of interstitial fluid in the lung is much more life-threatening than peripheral edema formation and there has been great interest in evaluating factors that are likely to reduce the risk of clinically significant pulmonary edema (Allen et al., 1987; Civetta, 1979; Crandall et al., 1983).

Modest increases in pulmonary capillary hydrostatic pressure or decreases in plasma oncotic pressure do not result in pulmonary edema because the lung has mechanisms for resisting accumulation of interstitial fluid. In the first place, the pulmonary interstitial hydrostatic pressure (\(P_i\)) is normally slightly negative (Civetta, 1979; Levine et al., 1967; Taylor et al., 1982). When fluid first begins to accumulate in the interstitium, the pressure rapidly increases (i.e. compliance is low). This increase in hydrostatic pressure opposes any further fluid entry by decreasing the hydrostatic pressure gradient, \(P_c - P_i\) (Allen et al., 1987). However, as interstitial fluid pressure rises above atmospheric, resistance to fluid transport through the interstitium decreases markedly and further increases in fluid volume cause only minimal increases in interstitial hydrostatic pressure (Levine et al., 1967; Goldberg, 1980). \(P_i\) appears to level off between 1 and 5 mmHg in severe pulmonary edema (Battacharya, Gropper and Staub, 1984).

A second mechanism which resists the accumulation of pulmonary interstitial fluid is a decrease in the interstitial oncotic pressure resulting from the accumulation of protein-poor fluid (Granger, 1979). Pulmonary interstitial oncotic pressure is normally about 75% of the plasma level and the oncotic gradient across the pulmonary capillary membrane \((\pi_c - \pi_i)\) is only 4–6 mmHg. If serum COP decreases, interstitial oncotic pressure will decrease proportionately as fluid enters the interstitial space, avoiding a change in the oncotic gradient (Granger, 1979; Demling, 1980; Demling et al., 1979).

Thirdly, large protein molecules such as albumin are normally excluded from a substantial part of the interstitial fluid volume by the density of the interstitial matrix. However, as the degree of hydration increases the fibers in the interstitial matrix are stretched apart, allowing protein molecules to enter previously unavailable space (Granger, 1979). This lowers \(\pi_i\), widens the transcapillary oncotic gradient \((\pi_c - \pi_i)\), and thus opposes further pulmonary edema formation.
Lymphatic drainage is the fourth and probably most important safety factor. Experimental studies have shown that the lymph flow rate can increase tenfold when interstitial fluid volume or pressure increases.

The blood–brain barrier is formed by a closely woven mesh of capillary cells joined by a continuous array of tight junctions (zonula occludens) with an effective pore size of 0.7–0.9 nm. Because the blood–brain barrier is a lipid membrane with small pores, it is easily permeated by water and very small or lipophilic molecules. The blood–brain barrier is relatively impermeable to electrolytes, water-soluble non-electrolytes and plasma proteins. The endothelial cells in peripheral tissues are joined by interspersed tight junctions and the effective endothelial pore size is about 4–5 nm. Because of the large pore size in peripheral tissues, the endothelial membrane is freely permeable to water and electrolytes, but only partially permeable to plasma proteins. In the peripheral tissues there is an active lymphatic system, which helps reabsorb interstitial fluid. In the brain, however, there are no lymphatics. When the blood–brain barrier is injured, the barrier becomes permeable to electrolytes and large plasma proteins such as albumin (Zornow et al., 1988). Hypertonic fluids will only remove interstitial and intracellular fluid from regions of the brain where the blood–brain barrier is intact, and will have no effect on areas where the blood–brain barrier is permeable to electrolytes.

The difference in membrane function between the blood–brain barrier and the endothelium in peripheral tissues is of practical importance. For example, if the intravascular concentration of sodium is increased from 140 mmol/l to 150 mmol/l, there will only be a small and short-lasting effect on the peripheral interstitial tissues, owing to the free movement of both sodium and water across the endothelium. However such a change in sodium concentration will have a pronounced effect on the brain. The osmotic pressure gradient will increase drawing water from the brain interstitium to the intravascular space.

16.3.2 OSMOLALITY AND TONICITY

Osmolality is the number of dissolved particles in a kilogram of solvent (water) and determines the osmotic force of the solution (Shoemaker, 1982). Cell membranes are highly permeable to water, which will diffuse across them rapidly to maintain osmotic equilibrium between the extracellular and intracellular fluid compartments (Brobeck, 1973). Hence the relative volumes of the compartments will be determined by their sodium and potassium content.

Plasma osmolality can be measured directly or calculated approximately by means of the formula: \[ P_{OSM} = 2P_{Na^+} + \text{glucose} + \text{urea} \]

where the concentration of sodium, glucose and urea are all expressed in mmol/l (Worthley, Guerin and Pain, 1987).

The plasma sodium (\( P_{Na^+} \)) level is multiplied by two to account for anions. This rule of thumb does not take into account the low-concentration cations such as potassium, calcium and magnesium or organic molecules such as creatinine, amino acids and lactate. This error of exclusion is balanced by the presence of multivalent anions such as sulfate and phosphate which contribute fewer particles per equivalent than do univalent ions.

Although urea is included in the calculation of osmolality, it diffuses readily across cell membranes and does not influence relative compartment volumes (Brobeck, 1973). Exogenous solutes such as mannitol or alcohol may create an ‘osmolar gap’ between the measured and unmeasured osmolalities (Table 16.1).

This formula must be interpreted in conjunction with the clinical assessment of fluid status as, for example, an increased osmolality may result either from excess sodium or a deficit of water.

Tonicity defines effective osmolality, i.e. the osmotic force due to the particles which cannot permeate between compartments. Because all body fluids must be in osmotic equilibrium, changes in tonicity, regardless of their cause, will result in fluid shifts between the ECF and the ICF in order to re-establish osmotic equilibrium. The administration of hypertonic fluids such as 50% dextrose or hypertonic saline will increase the tonicity of the ECF and result in fluid shifts into the extracellular compartment. Thus patients with osmotic hypertonicity will have a contracted intracellular compartment.

This effect had been applied to the treatment of patients with cerebral edema in whom intracellular and extracellular volumes can be decreased by achieving hypernatremia. Conversely in hyponatremic states the tonicity of the ECF is decreased and water must shift into and expand the intracellular fluid to maintain osmolality. As brain expansion is limited by the confines of the cranial vault, severe hyponatremia

### Table 16.1 Osmotically active particles

<table>
<thead>
<tr>
<th>Extracellular fluid</th>
<th>Intracellular fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Potassium</td>
</tr>
<tr>
<td>Glucose</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Inorganic phosphate</td>
</tr>
<tr>
<td>Urea*</td>
<td>Urea*</td>
</tr>
<tr>
<td>Ethanol*</td>
<td>Ethanol*</td>
</tr>
</tbody>
</table>

*These particles are distributed freely in body water. Other particles are unable to permeate compartments.
may result in raised intracranial pressure (ICP). Urea increases osmolality but not tonicity because it passes freely through biological membranes, and will not alter the intracellular volume.

16.3.3 DISTRIBUTION OF ADMINISTERED FLUID IN THE BODY

All infused fluids may be considered as being composed of plasma equivalents (colloidal solutions), saline equivalents (crystalloid solutions) or water equivalents. Plasma equivalents remain essentially confined to the circulation as a result of their oncotic pressure. Saline equivalents are distributed between the interstitium and plasma, but remain restricted to the extracellular fluid compartment because of their sodium content. Water equivalents are distributed according to the distribution of water in the body (Figure 16.2).

(a) Plasma equivalents

Plasma equivalents include blood, its components and colloids. Blood may be administered either whole, or in its component form; the latter is preferred, as fractionation optimizes the availability of the various blood components for special situations and improves the survival of the stored blood elements. Its use is limited by cost and availability, the risks of allergic reactions and infection, the delays necessary for cross-matching and a limited shelf life.

Patients who are bleeding acutely are best treated in part with whole blood since this also replaces clotting components and platelets. Otherwise hypovolemia can be treated effectively by colloid or crystalloid solutions, and oxygen transport function can be restored by red-cell concentrates, although these take several hours to be fully effective since storage impairs oxygen dissociation.

The absolute minimum acceptable hematocrit in the trauma patient is difficult to determine. The goal of blood transfusion is to maintain an adequate level of tissue oxygenation, but the focus in clinical medicine has been on the level of serum hemoglobin or the hematocrit. It has been estimated that tissue $\dot{D}O_2$ is optimal when the hematocrit is 33% (Sutin, Ruskin and Kaufman, 1992), but the effect on $\dot{D}O_2$ may not be the same as the effect on oxygen utilization. A consensus development conference on perioperative red cell transfusion concluded that available evidence did not support the recommended practice of maintaining hemoglobin levels at 10 g/dl or hematocrits at 30% (Consensus Development Conference, 1988). In the United States, the National Blood Resource Education Program guidelines for red blood cell transfusion state that adequate oxygen-carrying capacity can be met by a hemoglobin of 7 g/dl (hematocrit of approximately 21%) or even less when the intravascular volume is adequate for perfusion. The guidelines add the caveat that the decision to transfuse a given patient should be based on consideration of the patient’s age, etiology and degree of anemia, hemodynamic stability and presence of coexisting cardiac, pulmonary or vascular disease. While the normal brain is very tolerant to anemia, the limits of iso-volemic anemia are unknown. Because autoregulation may be impaired after injury, it cannot be assumed that the safe lower limit of the hematocrit is the same as in the neurologically normal subject.

Colloidal solutions comprise preparations of plasma or high-molecular-weight synthetic substances (Table 16.2). These fluids do not cross capillary membranes readily and are initially confined mainly to the intravascular space. If the colloidal solution has an oncotic pressure that is higher than that of the plasma interstitial fluid will move into the intravascular space and expand the plasma volume by more than the administered volume of colloidal solution, hence the term ‘plasma expander’.

**Plasma-protein derivatives**

These include 5% normal serum albumin, which contains human albumin 50 g/l and sodium

<table>
<thead>
<tr>
<th>Type</th>
<th>Volume (ml)</th>
<th>Mean mol. wt (kDa)</th>
<th>Protein content</th>
<th>Sodium content (mmol/bottle)</th>
<th>Oncotic pressure</th>
<th>Other constituents</th>
<th>Half-life</th>
<th>Side effects (%)</th>
<th>Cost/bottle (Aust$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal serum albumin</td>
<td>500</td>
<td>69</td>
<td>5% (25g)</td>
<td>70</td>
<td>Iso-oncotic</td>
<td>–</td>
<td>5–10 d</td>
<td>0.02 (0.004)</td>
<td>60.00</td>
</tr>
<tr>
<td>Concentrated albumin</td>
<td>100</td>
<td>69</td>
<td>20% (20g)</td>
<td>10</td>
<td>$\times 5$</td>
<td>–</td>
<td>5–10 d</td>
<td>0.01 (0.003)</td>
<td>85.00</td>
</tr>
<tr>
<td>Dextran 70 (Macrodex)</td>
<td>500</td>
<td>70</td>
<td>6%</td>
<td>77 or 0</td>
<td>$\times 2.5$</td>
<td>–</td>
<td>12 h</td>
<td>0.07 (0.017)</td>
<td>8.00</td>
</tr>
<tr>
<td>Polygeline (Haemaccel)</td>
<td>500</td>
<td>35</td>
<td>3.5%</td>
<td>72</td>
<td>Iso-oncotic</td>
<td>Potassium, 5 mmol/l; calcium, 6 mmol/l</td>
<td>4 h</td>
<td>0.15 (0.05)</td>
<td>12.50</td>
</tr>
</tbody>
</table>

*Percentage incidence of all reactions. Percentage incidence of major (grade-3 and grade-4) reactions in parentheses.
vascular volume by 450–500 ml infusion of 5% albumin expands the intravascular space by 140 mmol/l, concentrated (20%) albumin, which contains 200 g/l of albumin and less sodium (100 mmol/l). The latter is usually restricted to hypoproteinemic patients with either hypernatremia or fluid overload. A 500 ml infusion of 5% albumin expands the intravascular volume by 450–500 ml (Lamke and Liljedahl, 1976). After 2 hours, under conditions of normal capillary permeability, 90% remains within the intravascular space (Rainey and English, 1988). Eventually the administered albumin is distributed throughout the extra cellular space (Rainey and English, 1988). After infusion of 100 ml of concentrated albumin (20%), the plasma volume continues to increase over the next 30–60 minutes to achieve a final blood volume expansion of 400–450 ml. Redistribution of 350 ml of interstitial fluid to the intravascular space is necessary for this to occur. In patients with extracellular or total body water depletion, equilibration is slow and incomplete (Beecher, 1945). Therefore, in acute hypovolemia, 5% albumin should be given rather than the hyperoncotic form. The 20% albumin solution is usually used in patients with concomitant hypovolemia and elevated extracellular fluid volume.

The duration of vascular retention and the hemodynamic effects of infused albumin solutions depend greatly on the patient’s disease state. This variability may result from ‘leakage’ into the interstitium, preferential binding of albumin in the skin and wound, or increased catabolism.

Albumin has several unique effects that differentiate it from other colloids as well as from crystalloids (Emerson, 1989). Albumin can bind reversibly with both anions and cations, which allows it to regulate the extracellular concentration of various substances such as iron, lipids and bilirubin (Emerson, 1989). Albumin also has the ability to act as a free radical scavenger and may limit lipid peroxidation (Holt, Ryali and Campbell, 1984; Wasil et al., 1987; Stocker, Glazer and Ames, 1987; Pirisino et al., 1988). These properties may in the future become the major reason for choosing albumin as a resuscitative fluid.

Albumin may also play a role in maintaining normal microvascular permeability to protein molecules. Endothelial cells contain pores through which protein molecules may leave the vascular space. Albumin may help regulate the permeability of these pores. Hypoalbuminemia increases capillary permeability and restoring the albumin level reduces permeability to normal (Harms et al., 1981; Denling et al., 1982). However, the intravascular albumin level necessary to maintain normal microvascular permeability is not known.

Plasma-protein solutions are heated to 60°C for 10 hours during processing and are free of transmissible diseases (Rainey and English, 1988). Severe side-effects, such as hypotension, which is probably due to kinin activation, are rare. Because of their long half-life care must be taken to avoid circulatory overload in patients who have been resuscitated with plasma-protein solutions and appropriate hemodynamic monitoring is required.

**Synthetic colloidal solutions**

Dextran are polysaccharides composed of glucose molecules polymerized into chains of various lengths. They are classified according to molecular weight and are available in isotonic saline or 5% dextrose. Because of their shape dextran molecules are hyperoncotic – i.e. they have the water-attracting equivalent of several individual molecules; thus they produce a plasma-volume expansion of about 120% of the infused volume (Scheinkestel et al., 1989).

Potentially life-threatening toxic effects may complicate dextran administration, including acute renal failure, anaphylaxis and bleeding diathesis (Atik, 1969). Dextran 40 has been associated with acute renal failure due to irreversible plugging of the renal tubules; Dextran 70 is rarely associated with the development of acute renal failure.

The incidence of anaphylactoid reactions after dextran administration was reported to be 0.032%. Dextran 40 produced fewer reactions than Dextran 70 and severe reactions were uncommon (Ring and Messmer, 1977).

Dextran 70 and, to a lesser extent, Dextran 40 produce a dose-related hemostatic defect. This has a number of mechanisms but is due primarily to a reduction in platelet adhesion and aggregation normally mediated by factor VIII:Rantigen activity (Alexander et al., 1975). Dextran also lowers the levels of all clotting factors by hemodilution, coats blood vessel walls and cellular elements and impairs the elasticity and tensile strength of fibrin clots (Atik, 1967; Weiss, 1967; Adelson, Crosby and Roeder, 1955; Karlson et al., 1967; Muzaffar et al., 1973). Primary hemostasis is affected and clinically the picture mimics von Willebrand’s disease. Bleeding is more likely in patients with pre-existing coagulation abnormalities. To minimize this risk, the volume of dextran infused should be limited to 20 ml/kg/d or 1.5 g/kg/d (Atik, 1967). Some 50–70% of infused dextran is excreted by the kidneys and the rest is slowly metabolized.

Because of their interference with coagulation, dextrans are rarely used in the management of severely injured patients.

Polygeline (Haemaccel, Hoechst) consists of urea-bridged gelatin, molecular weight range 5000–50 000; mean 35 000, derived from cattle-bone gelatin and suspended in saline. It is an effective plasma volume expander in critically ill patients (Edwards et al., 1989; Mishler, 1984). The low-molecular-weight gelatin portion distributes readily through the ECF and produces...
a plasma volume expansion of only about 70% of the infused volume. Renal excretion accounts for 85% of elimination, fecal excretion for 10% and the remainder is metabolized to non-essential amino acids. Polygeline contains potassium and calcium and this must be remembered when large volumes are infused. Rapid infusions cause histamine release, which usually takes the form of urticaria, but anaphylaxis has been reported (Scheinkestel et al., 1989). Gelatin products are not associated with renal failure or coagulopathy.

(b) Crystalloid solutions

Crystalloids are isotonic mixtures of sodium chloride and other physiologically active solutes (Table 16.3).

<table>
<thead>
<tr>
<th>Crystalloid solutions</th>
<th>Water-equivalent solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic (0.9%) saline</td>
<td>5% dextrose in water</td>
</tr>
<tr>
<td>Hartmann's (Ringer's lactate) solution</td>
<td>4% dextrose in 0.18% saline</td>
</tr>
<tr>
<td>Glucose (g)</td>
<td>–</td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>–</td>
</tr>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>150</td>
</tr>
<tr>
<td>K⁺ (mmol/l)</td>
<td>–</td>
</tr>
<tr>
<td>Cl⁻ (mmol/l)</td>
<td>131</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/l)</td>
<td>–</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>5</td>
</tr>
<tr>
<td>Osmolarity (mosmol/l)</td>
<td>300</td>
</tr>
<tr>
<td>pH</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Sodium is the major component of crystalloid fluids and the distribution of infused sodium will determine the distribution of infused crystalloid fluids. Since sodium is the major solute in the extracellular space and 80% is extravascular (Edelman and Leibman, 1959), infused sodium will reside primarily in the extravascular compartment.

Physiological saline and Hartmann's solution are the two most frequently used crystalloids and their volume-expanding effects are identical (Cervera and Moss, 1975). Figure 16.4 shows the effect of colloid and crystalloid infusions on blood volume in critically ill adults. Physiological saline and Hartmann's solution are both freely permeable across the vascular membrane and distribute evenly throughout

![Figure 16.4](image-url)
the extracellular space. In normal individuals approximately 25% of the infused volume remains within the blood vessels when equilibrium is reached (usually within 20–30 minutes). In other words, for every liter of infused crystalloid approximately 750 ml will pass into the interstitium and 250 ml will remain in the plasma. Thus interstitial edema is a necessary consequence of volume resuscitation with crystalloids and should not, unless excessive, be interpreted as evidence of fluid overload. However, the volume of crystalloid used in resuscitating patients with head injury should be tempered by the possibility of worsening brain edema.

Crystalloids are well suited for replacing extracellular fluid losses (dehydration); they are also used to replace blood loss, based on the notion that acute hemorrhage (or hypovolemia) causes an interstitial fluid deficit that must also be replaced. Indeed, crystalloids have proven effective in resuscitating patients following acute hemorrhage and continue to be widely used for this purpose (Moss and Gould, 1988; Dodge and Glass, 1982; Tranbaugh and Lewis, 1985; Shackford, 1987; Horton, Landreau and Tuggle, 1985; Lowe et al., 1979; Virgilio et al., 1979).

Crystalloids are non-toxic and do not produce anaphylactoid reactions.

(c) Water-equivalent solutions

Solutions of 5% dextrose or 4% dextrose in 0.18% isotonic saline are essentially water rendered isotonic to prevent local red-cell lysis at the infusion site. At most infusion rates insufficient dextrose is present to alter blood glucose levels, so the fluid is distributed evenly throughout total body water. Thus for every liter of solution administered, two-thirds will enter the intracellular space and one-third the extracellular space. Three-quarters of the extracellular fluid will be in the interstitium and one-quarter in the plasma. Thus about 8% only of the infused volume remains in the circulation. For this reason 5% dextrose solution is the fluid of choice for patients with ischemic heart disease or congestive cardiac failure, since it does not expand the circulation and increase the cardiac workload.

Dextrose and cerebral ischemia

The observation that carbohydrates promote ischemic damage in the central nervous system is not new but seems forgotten (Voll and Auer, 1988). The central nervous system relies on glucose for much of its energy needs. When cerebral ischemia develops, glucose infusion will promote anaerobic glycolysis and produce large quantities of lactic acid, which, accumulating locally, can reduce flow even further. Thus dextrose infusion during experimental cardiopulmonary resuscitation was associated with a much higher mortality (Lundy et al., 1987). At this stage, the routine infusion of glucose is not recommended in patients at risk of cerebral insufficiency.

Other fluids such as 1 liter of half-isotonic 0.45% saline can be regarded as comprising 500 ml of isotonic saline and 500 ml of free water.

(d) Hypertonic saline

Hypertonic saline will increase the osmolality of the ECF, causing a water shift from cells to re-establish osmotic equilibrium. One liter of a 3% saline solution contains 510 mmol each of sodium and chloride – a total of 1020 osmotically-active particles. These will be remain in the ECF, thus increasing its number of osmotically active particles by 25% and its volume by 7%. ECF osmolality will rise to 339 mmol/kg. To re-establish osmotic equilibrium, about 1.5 liters of water will shift from the ICF into the ECF. Thus the 1 liter of a 3% saline solution will increase the ECF volume by about 2.5 liters in total. As in other states of ECF expansion, three-quarters of this volume (1.9 l) is distributed to the interstitium and one-quarter (0.6 l) to the plasma, explaining the propensity of hypertonic saline to cause pulmonary and peripheral edema (Table 16.4).

Hypertonic saline is effective in restoring volume after hemorrhage (Gala et al., 1991), endotoxic shock (Horton and Walker, 1991), trauma (Mattox et al., 1991; Vassar et al., 1991) and burn injury (Griswold et al. 1991; Monafo, Halverson and Schechtman, 1984). Several clinical studies have suggested a better survival after resuscitation with hypertonic solutions compared with isotonic fluids (Mattox et al., 1991; Monafo, Halverson and Schechtman, 1984; Vassar et al., 1991).

Hypertonic solutions have a greater volume-expanding capacity than equal volumes of isotonic crystalloid solutions. Approximately three times the volume of 0.9% NaCl compared with 3.0% NaCl was

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Plasma</th>
<th>Interstitium</th>
<th>Intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloid</td>
<td>1000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isotonic (0.9%) saline</td>
<td>250</td>
<td>750</td>
<td>0</td>
</tr>
<tr>
<td>5% dextrose</td>
<td>83</td>
<td>250</td>
<td>667</td>
</tr>
<tr>
<td>Half isotonic (0.45%)</td>
<td>167</td>
<td>500</td>
<td>133</td>
</tr>
<tr>
<td>saline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3% saline</td>
<td>600</td>
<td>1900</td>
<td>-1500</td>
</tr>
</tbody>
</table>
required to restore MAP in a canine hemorrhage model, although the overall amount of sodium administered did not differ between the two experimental groups. Because small infusion volumes cause relatively large increases in intravascular fluid volume, blood volume restitution is rapid; however this effect is short-lived (Gala et al., 1991).

Hypertonic solutions may reduce edema formation in non-injured tissues (Battistella and Wisner, 1991; Cross et al., 1988; Wisner, Schuster and Quinn, 1990). This may be particularly useful in head-injured patients. Several studies of resuscitation in experimental brain injury have found that hypertonic solutions are more effective at lowering intracranial pressure and decreasing edema in the uninjured cerebral hemisphere than isotonic fluids (Battistella and Wisner, 1991; Wisner, Schuster and Quinn, 1990).

In a study of trauma victims with concomitant head injuries, hypertonic saline resuscitation was associated with increased survival compared with Hartmann’s solution (Vassar et al., 1991).

At present hypertonic saline, with or without the addition of colloid, is most commonly used for volume resuscitation after trauma or burns. The efficacy of small volumes and the rapidity of administration make its use convenient. Other reported benefits of hypertonic compared to isotonic solutions are improved pulmonary gas exchange (Boldt et al., 1991), increased renal cortical and gut mucosal blood flow (Behrmann et al., 1991), decreased bacterial translocation (Reed et al., 1991a) and the induction of natriuresis (Gala et al., 1991) and kaliuresis (Battistella and Wisner, 1991).

Although these properties would be advantageous in many clinical situations, the use of hypertonic solutions is not without problems. In an experimental model, increased bleeding, probably due to vasodilation, was reported if hypertonic fluid was administered within 15 minutes of injury (Krausz et al., 1992). If more than 10% of normal plasma volume is replaced with hypertonic saline, increases in prothrombin time and activated partial thromboplastin time and a decrease in platelet aggregation are observed (Reed et al., 1991b). If large volumes of hypertonic saline are used, potential complications include hypernatremia, hyperchloremia, hyperosmolality, hypokalemia, metabolic acidosis, intracellular dehydration, cerebral hemorrhage, inhibition of lipolysis, hyperosmolar coma and central pontine myelinolysis (Carvajal and Parks, 1988; Cross et al., 1988; Griffel and Kaufman, 1992). These complications are related directly to the solute load infused and inversely to the patient’s volume of distribution. When using hypertonic saline serum sodium levels (less than 160 mmol/l) and serum osmolality (less than 320 mosmol/l) require close monitoring.

16.4 Fluid resuscitation

16.4.1 SHOCK

When hypovolemia is severe, tissue oxygenation becomes impaired and the clinical and metabolic features of shock appear. The need for prompt restoration of adequate plasma volume under such circumstances is well recognized (Shoemaker, 1976; Shires and Canizaro, 1973). Hypotension has a markedly deleterious effect on the outcome from traumatic head injury and indeed from other injuries (Price and Murray, 1972; Siegel et al., 1991). Hence patients with head injury should receive sufficient intravascular fluid resuscitation to avoid hypovolemia and hypotension (Buchman, Menker and Lipsett, 1991; Levison and Trunkey, 1982). Few issues in critical care medicine have prompted as much diversity of opinion as the most appropriate asanguineous fluid to achieve this goal (Virgilio, Smith and Zarins, 1979; Shoemaker and Hauser, 1979; Velanovich, 1989).

The primary abnormality in hypovolemic shock is a reduction of plasma volume. Absolute or relative plasma volume deficits contribute to the disturbances of tissue oxygenation in the other three types of circulatory shock, cardiogenic, obstructive and septic, and these also may occur in the head-injured patient. Decreased plasma volume produces a decrease in left ventricular end-diastolic volume and stroke volume. Although sympathetic nervous system activation can initially maintain cardiac output (CO) by inducing tachycardia and arterial pressure by producing vasoconstriction, at some point compensatory limits are reached and CO and systemic blood pressure may suddenly fall.

There is clear agreement that the major goal of treatment of circulatory shock associated with hypovolemia is rapid restoration of blood volume and tissue oxygenation (Rackow et al., 1983; Weil and Henning, 1979). The use of asanguineous fluids for initial resuscitation provides better restoration of capillary blood flow than does immediate transfusion. Moderate hemodilution, for example, to a hemoglobin level of 10–12 g/dl, is well tolerated by most patients, and does not lower $\dot{D}O_2$, if intravascular volume is maintained (Messmer, 1975).

16.4.2 CHOICE OF FLUID

The hemodynamic response to fluid infusion is influenced by the choice of fluid, vascular tone and cardiac compliance. Several studies have directly compared the plasma volume-expanding and hemodynamic effects of colloids and crystalloids. In these studies, a preselected volume of fluid was administered rather than a volume adjusted on the basis of physiological
response. In stable postoperative patients plasma volume responses were compared to 1 liter infusions of 6% Dextran 70, 6% hetastarch, 5% albumin, 3.5% urea-bridged gelatin (Haemaccel) and physiological saline. Significant increases in plasma volume occurred with all colloids but not with physiological saline. The greatest increases occurred with Dextran 70 (790 ml) and 6% hetastarch (710 ml; Figure 16.5; Lamke and Liljedahl, 1976).

In acutely ill postoperative patients Lazrove and associates evaluated responses to infusion of 500 ml of 5% albumin and 6% hetastarch over 1 hour, using a prospective, randomized crossover design (Lazrove et al., 1980). Both solutions significantly increased plasma volume, CO, \( \dot{D}O_2 \), and \( \dot{V}O_2 \). Plasma volume expansion lasted for 1–5 hours with albumin and for at least 3 hours with hetastarch. Similar hemodynamic effects of 5% albumin and 6% hetastarch were reported in a series of critically ill patients by Puri and associates (1983).

The relative effectiveness in critically ill patients of 1 hour infusions of 500 ml of whole blood, 5% albumin, 6% Dextran 70, 10% Dextran 40 and 1 liter of Ringer’s lactate were compared (Shoemaker, 1976). Blood and colloid infusion produced significant increases in blood volume, CO, \( \dot{D}O_2 \), stroke volume, left ventricular stroke work index, central venous pressure (CVP) and pulmonary arterial wedge pressure (PAWP), but improvements after crystalloid infusion were insignificant, even though twice the volume was infused (Figure 16.6). In a later study by the same group involving critically ill patients with ARDS, 100 ml of 25% albumin was compared with 1000 ml of Ringer’s lactate (Hauser et al., 1980). Plasma volume increased by an average of 465 ml with 25% albumin but by only 194 ml with Ringer’s lactate. Significant increases in \( \dot{D}O_2 \) and \( \dot{V}O_2 \) occurred only in the albumin group.

Thus the more potent volume expanding properties of colloids compared to crystalloids may permit more rapid restoration of hemodynamic stability in hypotensive critically ill patients (Shoemaker et al., 1981; Modig, 1986). Our current clinical practice is to use both. In the resuscitative phase the emphasis is on volume restoration and we use mainly colloid; in the maintenance phase we use mainly crystalloid.

16.4.3 MONITORING

Changing vascular and cardiac compliances in the shock patient make it difficult to rely on any single hemodynamic measurement to define adequate resuscitation. The adequacy of volume resuscitation is measured by blood pressure, heart rate and urine output, which reflect a summation of many different processes and are only gross estimates of end-organ perfusion (Lowell et al., 1990). Mean arterial pressure (MAP), heart rate, central venous pressure (CVP) and pulmonary arterial wedge pressure (PAWP) do not reflect intravascular volumes in a linear fashion (Dawidson et al., 1991; Shippy, Appel and Shoemaker, 1984). CVP may fall during fluid infusion if blood volume expansion results in decreased autonomic-nervous-system-induced arteriolar and venous vasoconstriction (Baek et al., 1975). Changes in left ventricular compliance during fluid resuscitation may also limit the usefulness of PAWP as a measure of left ventricular end-diastolic volume (preload; Calvin, Driedger and Sibbald, 1981).

Even with sophisticated monitoring techniques, such as Swan–Ganz catheterization and oxygen saturation monitoring, the adequacy of resuscitation and
oxygen delivery to individual tissue beds in vital end organs cannot be determined. Poole et al. demonstrated this in an experimental canine shock model. Despite restoration of MAP and cardiac output (CO), cerebral blood flow did not return to preshock levels (Poole et al., 1986).

Nevertheless for clinical purposes the hemodynamic response to fluid resuscitation should be assessed by using the fluid challenge technique originally described by Weil and Henning (Table 16.5; Weil and Henning, 1979). When this is combined with sequential measurements of CO and measurements of tissue oxygenation (lactate, $\dot{D}O_2$, $\dot{V}O_2$ and mixed venous oxygen saturation) the risks of under- and over-resuscitation are minimized (Shoemaker and Czer, 1979).

### 16.4.4 CRYSTALLOIDS VERSUS COLLOIDS

The basic disagreement that initiated the colloid versus crystalloid controversy was a conceptual one. Those favoring crystalloids believe that an extracellular fluid deficit plays a primary role in the pathophysiology of hypovolemic shock and therefore repletion of this deficit is essential. Colloid proponents believe that decreased blood volume and reduced oxygen transport are the critical pathophysiological factors in hypovolemic shock; therefore, rapid and complete repletion of the intravascular compartment is critical for resuscitation.

In a series of experimental and clinical studies initiated in the early 1960s, Shires and associates showed that severe hemorrhagic shock was associated with a large decrease in extracellular volume, caused predominantly by intracellular shift of interstitial fluid in addition to external losses or shift in the intravascular space (transcapillary refill; Shires et al., 1964, 1972; Carrico, Canizaro and Shires, 1976). In a canine hemorrhagic shock model, animals resuscitated with whole blood and 50 ml/kg Ringer’s lactate (Figure 16.7; Shires et al., 1964). In a baboon model of hemorrhagic shock, microelectrodes were used to monitor transmembrane potential gradients across individual skeletal muscle cells. Sustained cell depolarization, a 49% decrease in extracellular water, and 6% increase in intracellular water increased intracellular sodium and decreased intracellular potassium were all recorded, suggesting a failure of the ATPase-dependent Na$^+$–K$^+$ pump (Shires et al., 1972). Resuscitation with balanced salt solution produced a return of the potential difference to normal together with a decrease in intracellular and an increase in extracellular volume. Similar alterations in water distribution were described in patients with circulatory shock and those undergoing major operative procedures (Shires, 1965; Shires, Williams and Brown, 1960). These changes also resolved with infusion of balanced salt solutions.

### Table 16.5 Guidelines for fluid challenge utilizing pulmonary arterial diastolic or pulmonary arterial wedge pressure monitoring: 7/3 rule for fluid challenge. PAWP = pulmonary arterial wedge pressure (mmHg); PADP = pulmonary arterial diastolic pressure (mmHg). (Source: adapted from Weil and Henning, 1979)

<table>
<thead>
<tr>
<th>PAWP/PADP</th>
<th>Fluid infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>For 10 min before challenge</td>
<td>200 ml × 10 min</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>100 ml × 10 min</td>
</tr>
<tr>
<td>&lt; 16</td>
<td>50 ml × 10 min</td>
</tr>
<tr>
<td>≥ 16</td>
<td></td>
</tr>
<tr>
<td>During 10 min infusion</td>
<td>Stop</td>
</tr>
<tr>
<td>Change &gt; 7</td>
<td>Continue infusion without interruption</td>
</tr>
<tr>
<td>Change ≥ 3</td>
<td></td>
</tr>
<tr>
<td>Immediately after 10 min infusion</td>
<td>Change &gt; 3, ≤ 7</td>
</tr>
<tr>
<td>Change &gt; 3</td>
<td>Stop</td>
</tr>
<tr>
<td>Change ≤ 3</td>
<td>Repeat fluid challenge</td>
</tr>
<tr>
<td>After 10 min wait</td>
<td></td>
</tr>
</tbody>
</table>

Figure 16.7 Survival after resuscitation of dogs from hemorrhagic shock. Each group consisted of 10 dogs, bled into shock by the Wiggers method. The RL group received fluid equivalent to 5% of body weight followed by return of shed blood. The plasma group received 10 ml/kg of donor plasma plus shed blood. The blood group received shed blood alone. (Source: reproduced from Shires et al., 1964, © 1964, American Medical Association, with permission.)
There is however, considerable controversy regarding the methods used by Shires and colleagues to measure extracellular fluid volume (Shoemaker, 1976; Roth, Lax and Malone, 1969). Using different techniques and models of hemorrhagic shock, other groups have found either a minimal decrease in extracellular volume, that subjects have found either a minimal decrease in extracellular volume account by the plasma volume loss or else an increase in extracellular volume (Roth, Lax and Malone, 1969; Serkes and Lang, 1966; Moore et al., 1966). There is similar debate about the changes in extracellular volume after major surgery, where no significant change was found in patients after cholecystectomy and increases were found in patients after cardiac surgery (Roth, Lax and Malone, 1969).

Despite this there is considerable evidence, from experimental models of severe hemorrhagic shock and from clinical studies of traumatic shock, that subjects can be successfully resuscitated with balanced salt solutions and blood (either whole blood or packed red blood cells) without the need for colloidal solutions (Lowe et al., 1979; Moss et al., 1981; Weaver et al., 1978). In the study of Lowe et al. (1979), patients with traumatic abdominal injuries requiring laparotomy were resuscitated randomly with either Ringer’s lactate or 4% albumin together with washed red blood cells for the entire emergency room and intraoperative period. Crystalloids alone were used postoperatively. Clinical criteria (systemic blood pressure, pulse and urine output) were used as the end points for resuscitation. Both groups of patients were resuscitated successfully and overall mortality was low (4.3%). There was no difference between the two groups in the need for postoperative ventilatory support. Since most patients in this study were not in shock on admission, the results might not be applicable to patients who are in severe hemorrhagic shock. Moss et al. (1981) repeated the study in a group of patients with traumatic shock, defined as systolic arterial pressure of 80 mmHg or the need for five or more red blood cell transfusions before surgery, with similar results. Pulmonary edema did not complicate the use of colloid or crystalloid in either of these studies. In both studies similar volumes of colloid and crystalloid were needed for resuscitation. This surprising finding may be due to the use of clinical rather than physiological end points for fluid resuscitation. Whether the successful outcome with crystalloid resuscitation in these studies is related to replacement of an interstitial fluid deficit or to the limited amount of the infused solution that remains in the circulation has not been ascertained. Despite the numerous studies comparing crystalloids to colloids, none has unequivocally demonstrated a distinct survival advantage with either therapy.

The current recommendations of the American College of Surgeons for initial resuscitation of patients with traumatic injury (hemorrhagic shock) include rapid infusion of up to 2 liters of Ringer’s lactate until hemodynamic stability is restored. If the patient remains unstable packed red blood cells are then infused. The use of two to four large-bore intravenous lines can compensate for the much more limited volume expansion produced by crystalloids. Complications of this approach to fluid infusion are minimal (Moss et al., 1981).

The choice of fluids in patients with massive bleeding that is difficult to control, or those with pre-existing medical problems, is more controversial. In these situations fluid administration may result in fluid overload and subsequent morbidity. The risk of pulmonary edema has been central to the debate over the relative merits of crystalloids versus colloids. As mentioned earlier, capillary membrane permeability, capillary hydrostatic pressure, colloid osmotic pressure (COP) and pulmonary lymph flow are all important factors in the development of pulmonary edema. Despite claims to the contrary (Virgilio et al., 1979), weight gain and systemic edema due to fluid infusion are not benign problems (Falk, 1991; Lowell et al., 1990). Decreased chest wall compliance due to tissue edema may occur following hydration with crystalloid (Brinkmeyer et al., 1981). Peripheral edema, particularly in a debilitated patient, can cause decreased mobility and subsequent skin breakdown. Tissue oxygenation is decreased when edema is present (Heughan, Niinikoski and Hunt, 1972) and wound healing may be impaired (Falk, 1991; Mangalore and Hunt, 1972; Niinikoski, Hengan and Hunt, 1972).

Edema of the gastrointestinal tract may result in ileus and intolerance for enteral alimentation (Falk, 1991). The potential for bacterial translocation and the development of systemic sepsis and multiple systems organ failure may also be increased (Baker et al., 1988; Wilmore et al., 1988).

In addition, systemic edema can increase time on mechanical ventilation, require diuresis or dialysis and lengthen the stay in the ICU.

16.5 Effects of intravenous fluids on the brain

Parenteral fluid therapy, particularly in patients with head injury, may increase brain swelling, intracranial pressure and neurological dysfunction and this may be reflected in increased mortality and morbidity (Vassar et al., 1991; Battistella and Wisner, 1991; Falk, 1991; Fein et al., 1982). However, there is little information available on the relative effects of colloid or crystalloid administration on cerebral edema formation in normal subjects or in patients with brain injury and decreased intracranial compliance (Zornow et al., 1988).
16.5.1 THE EFFECTS OF CRYSTALLOIDS AND COLLOIDS ON THE NORMAL BRAIN

Early studies in animals demonstrated brain shrinkage in response to infusion of hypertonic solutions and expansion in response to hypotonic solutions (Weed and McKibben, 1919a, b). In general, hypertonic fluids decrease both brain interstitial and intracellular volume and thus decrease ICP, and hypotonic fluids have the opposite effects. It was not possible to determine from these studies whether the increase in ICP and cerebral water content with hypotonic solutions was due to a decrease in plasma osmolality or a decrease in colloid oncotic pressure (COP). To clarify this issue, Zornow, Todd and Moore (1987) examined the acute effects of changes in plasma osmolality and plasma COP in normal rabbits with an intact blood–brain barrier. In one group COP was decreased without a change in plasma osmolality, whereas in a second group a hypo-osmolar condition was produced without change in the COP. Cerebral edema, estimated by changes in brain specific gravity, developed only in the hypo-osmolar group, suggesting that changes in COP do not influence intracranial water distribution in the absence of brain injury (Figure 16.8). These and other studies demonstrate that when the blood–brain barrier is intact, brain volume is strongly influenced by plasma osmotic pressure and is unaffected by changes in plasma oncotic pressure (Hindman et al., 1990). The brain, like a red blood cell, swells in a hypotonic solution and contracts in a hypertonic solution.

The effects of fluid resuscitation in experimental hemorrhagic shock on ICP and cerebral edema in animals with intact blood–brain barriers have been evaluated in several studies (Poole et al., 1986; Prough et al., 1985; Gunnar et al., 1986). In different models, fluid resuscitation with hypertonic crystalloid solutions was consistently associated with a lower ICP than fluid resuscitation with Ringer’s lactate, physiological saline or 10% Dextran 40 (Prough et al., 1985; Gunnar et al., 1986, 1988). Resuscitation with 6% hetastarch was associated with significantly lower ICP than resuscitation with Ringer’s lactate (Poole et al., 1986).

The unique structural characteristics of the cerebral capillaries (the blood–brain barrier) limit the effects of changes in COP on cerebral water distribution. The intercellular pores of non-cerebral capillaries are approximately 65 Å in diameter. Ionic solutes such as sodium and chloride are able to migrate freely between the interstitium and the intravascular space and therefore have no influence on water distribution (Zornow, Todd and Moore, 1987). High-molecular-weight compounds like albumin and unbridged gelatin are retained in the intravascular space and produce an oncotic gradient that tends to retain water in the capillaries. Because of the small pore size (8 Å) of cerebral capillaries, changes in serum electrolyte content (osmolarity) have significant effects on water movement. An osmotic gradient of 1 mosmol/l produces a hydrostatic gradient of 19.3 mmHg. Because there are so few protein molecules compared with the number of inorganic ions, their effect is minimal (Albright, Latchaw and Robinson, 1984). A 10 mm decrease in COP during crystalloid resuscitation has the same effect on cerebral water distribution as a decrease in osmolality of only 0.5 mosmol/l. Clearly the influence of changes in osmolality on cerebral water distribution dwarfs the effects of alteration of COP.

16.5.2 THE EFFECTS OF CRYSTALLOIDS AND COLLOIDS ON THE BRAIN AFTER INJURY

Patients with severe traumatic injuries often require resuscitation with large volumes of intravenous fluid to restore hemodynamic stability. When a head injury is also present, the choice of fluid for resuscitation may influence the development of brain edema. Animal studies confirm that damage to the blood–brain barrier (e.g. by cryogenic injury) increases the permeability of capillaries to both proteins and electrolytes so that osmotic and oncotic gradients cannot be established (Zornow et al., 1988; Weed and McKibben, 1919a). In these circumstances capillary hydrostatic pressure determines the rate at which edema forms. When hemorrhagic shock was combined with cryogenic brain injury, brain water fell in uninjured brain after resuscitation with hypertonic saline but not in areas of brain injury where the blood–brain barrier was damaged (Wisner, Schuster and Quinn, 1990).

Other animal studies evaluating the effects of fluid resuscitation in hemorrhagic shock on neurological

**Figure 16.8** Acute cerebral effects of changes in plasma osmolality and oncotic pressure in normal rabbits. The lower the specific gravity, the greater the brain water content **p<0.01 versus** other groups. (Source: from Zornow, Todd and Moore, 1987, with permission.)
function have shown that, although ICP in animals resuscitated with hypertonic saline was significantly lower, cerebral perfusion pressure was significantly higher in those receiving 6% hetastarch compared with those receiving hypertonic saline or physiological saline. Neurological function was also best in the hetastarch group, suggesting that restoration of cerebral perfusion pressure is a more important goal than change in ICP alone. The vasodilatory effect of hypertonic saline may have resulted in a lower mean arterial pressure compared with hetastarch.

These experimental results reaffirm that hypertonic saline will shift water from the extracellular to the intracellular space. Ringer’s lactate is a hypo-osmolar solution and 6% hetastarch is iso-osmolar; hence the differing effects of these solutions on ICP can be explained by their osmolarities.

The lower ICP after resuscitation with hypertonic crystalloid solutions may assist in restoring of cerebral blood flow and \( \dot{V}O_2 \), but there is not universal agreement on this issue (Prough et al., 1986).

The days of keeping the patient with a head injury ‘dry’ are over. There is no good evidence supporting fluid restriction as a means of limiting cerebral edema after brain injury (Morse et al., 1985). Dehydration increases sympathetic stimulation, metabolism and \( O_2 \) demand (Beckstead et al., 1978). Indeed, the therapeutic aim is now to maintain euvoeemia and normal physiological indices, especially cerebral perfusion pressure. Animal studies support this approach (Smith et al., 1982; Ito et al., 1979).

### 16.6 Metabolic response to injury

#### 16.6.1 OVERVIEW

Major injury, whether surgical or accidental, evokes predictable metabolic, hormonal and hemodynamic responses (Buckingham, 1985; Table 16.6). Changes in carbohydrate metabolism include increased endogenous hepatic glucose production (gluconeogenesis) and reduced glucose clearance (insulin resistance), which results in hyperglycemia. Fat becomes the major body fuel; therefore lipolysis is increased and lipogenesis is retarded. Changes in protein metabolism are manifested by negative nitrogen balance reflecting accelerated net protein breakdown (catabolism). The magnitude of these changes is proportional to the extent of the injury (Weissman, 1990).

#### 16.6.2 STARVATION

Starvation, i.e. lack of nutrient input, often accompanies injury, while nutrient utilization is normal at the cellular level. During starvation, metabolic adaptation occurs, with the aim of conserving essential tissues. There is little or no activation of metabolic mediators and the system is still able to respond to normal physiological stimuli. Glycogen reserves are only small, approximately 200–400 g; thus liver glycolysis is only useful for 24 hours. Decrease in insulin and increase in glucagon secretion result in protein and fat breakdown to provide energy. Amino acids are converted to pyruvic acid, acetyl CoA and tricarboxylic acid (Krebs) cycle intermediates. Glycerol from fat is fed into the glycolytic pathway and fatty acids form acetyl CoA, some of which enters the Krebs cycle inside the mitochondria; some is converted to ketones, which are used by skeletal muscle and brain. Protein catabolism results in increased urinary loss of urea, sodium, potassium, magnesium and calcium. As the new energy pathways become established, protein breakdown decreases and fat becomes the chief energy source, supplying 75–90% of the calories. The basal metabolic rate decreases as a result of decreasing lean body mass, decreased physical activity, and decreased thyroxine production. These changes are summarized in Figure 16.9.

In the absence of sepsis or injury, the starved patient can usually be rapidly converted to the anabolic state by administering moderate amounts of nutritional substrate.

#### 16.6.3 METABOLIC STRESS

When surgery, trauma or sepsis occur, a new process is activated (Cerra, 1986). Injured or dead tissue, dividing organisms, severe perfusion deficits and resolving hematomas activate mediator systems that affect end-organ function, producing the clinical, physiological and metabolic manifestations of the response to stress. This process is dynamic, and begins with a lag or ebb phase during which there is little metabolic activity. This is followed by a flow phase during which metabolic activity increases and peaks, usually on day 3 or 4 after injury. The processes then abate over another 3–4 days, unless a complication ensues. In the event of a new stress, the process reactivates and reaches a new peak.

The resting energy expenditure rises to an amount that depends on the type and severity of the stress. At high levels of stress, 30% or more of the increased

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**Table 16.6** Metabolic response to injury

- Altered protein homeostasis
- Hypermetabolism
- Altered carbohydrate metabolism
- Sodium and water retention
- Increased lipolysis
energy expenditure appears to come from the oxidation of amino acids, 30–40% from glucose and 30–40% from fat. With activation of metabolic mediators by trauma, gluconeogenesis becomes less responsive to exogenous nutritional substances (section 16.6.4(b)). Thus, administered glucose has progressively less inhibiting effect on lipolysis, proteolysis and gluconeogenesis. Glucose calories, as well as other calories, which are in excess of the existing demands promote lipogenesis, with excess CO₂ production and hepatic dysfunction.

Proteolysis increases and amino-acid flux attempts to meet the demands of energy production and protein synthesis. Ureagenesis is increased and more nitrogen is present in the urine. Gluconeogenesis is increased; peripheral glucose uptake is normal, but much of the glucose is recycled as lactate and alanine. Thus, increased plasma glucose and lactate levels are a normal part of the response. Ketosis is relatively depressed. These changes are summarized in Figure 16.10.

Malnutrition usually develops rapidly in post-traumatic patients, taking days instead of the weeks needed in simple starvation. It is difficult to exclude the effects of bedrest (disuse) on some of the parameters. Indeed, in patients with isolated closed-head injuries many reports have described persistent excretion of large amounts of urinary nitrogen up to weeks after severe head injury. However some studies indicate that the response abates in 5–7 days unless a complication ensues. The early nitrogen excretion appears to reflect the stress response, whereas the persistent nitrogen excretion may be due to bedrest and disuse in a largely young and muscular group of patients.

In some instances under new stimuli the process reacts and the state of persistent hypermetabolism with or without the development of multiple system organ failure ensues (Cerra, 1986). Risk factors include severe perfusion shock, severe septic shock, persistent septic sources, and recurrent septic episodes.

16.6.4 MEDIATORS OF THE RESPONSE TO INJURY

(a) The neuroendocrine axis

The mechanisms initiating, regulating and sustaining this response are not all identified. It is known that injured patients have elevated levels of the anti-insulin hormones: cortisol, glucagon, and the catecholamines. Insulin levels are usually elevated, but not sufficiently to prevent the commonly noted hyperglycemia. Growth hormone, aldosterone and ADH are also elevated. These elevations may in part be neurally mediated via the hypothalamus (Hume and Egdahl, 1959). Patients with severe head injury may develop abnormalities of fluid and electrolyte balance because of damage to the neuroendocrine axis (e.g. diabetes insipidus following pituitary damage; Figure 16.11).
(b) Cytokines

Several non-endocrine factors play important roles in the response to stress. These include interleukin-1 (IL-1), tumor necrosis factor (TNF), IL-2 and gamma-interferon (IFN). The reader is referred to the extensive review of this subject by Weissmann (1990).

16.6.5 EFFECT OF STRESS ON FLUID AND ELECTROLYTE MOVEMENTS

The changes in electrolyte concentrations and fluid distribution after trauma and critical illness have been extensively studied. In the normal subject neural, hormonal, hemodynamic and renal mechanisms function in a highly integrated manner to preserve sodium and water homeostasis. There are two main objectives. The first is to keep the concentration of sodium in the ECF within a very narrow range. Together with its associated anions, sodium constitutes more than 90% of the total solute in the ECF and controls the distribution of water between the cells and the extracellular space. Large deviations from normal in ECF sodium concentration cause cells to shrink or swell, which may have serious consequences for brain function. Sodium concentration is kept constant by finely adjusting the water content of the ECF through the secretion of antidiuretic hormone (ADH, vasopressin; Figure 16.12). At least four independent physiological stimuli release ADH into the blood stream: osmotic, hemodynamic (hypotension and/or hypovolemia), nausea and emesis, and hypoglycemia. Of these, osmotic stimulation is the most important for fine control of ADH secretion and maintenance of water balance. A number of drugs used in critically ill patients affect ADH secretion. Halothane and morphine in high doses increase ADH release, while phenytoin and chlorpromazine inhibit ADH release. Positive pressure ventilation also increases secretion. The thirst mechanism assists by controlling fluid intake to some extent in the conscious patient.

The second objective is to keep the total sodium content of the ECF within normal limits and thus maintain a normal ECF volume. Since sodium is the major cation of the ECF and the body adjusts the water around it to maintain a normal sodium concentration, the total number of sodium ions in the ECF will determine the ECF volume. Large deviations from normal in the ECF sodium content cause fluctuations in the circulating blood volume. Both volume contraction and expansion can have serious effects on brain function, particularly in the presence of pre-existing brain damage (Aubry and Nankin, 1965). Normally, ECF sodium is regulated by several closely coordinated mechanisms that adjust the amount of sodium lost through the kidneys.

- The relative fullness of the ECF is sensed by receptors located in low- (intrathoracic) and high-pressure (intra-arterial) areas of the cardiovascular system. When changes in ECF volume occur, renal, neural and hormonal mechanisms modulate renal
Figure 16.11  Hypothalamic control of pituitary secretion. (a) Vasopressin and oxytocin are secreted in the paraventricular and supraoptic nuclei of the hypothalamus and transported in the axons of the supraoptico-hypophyseal tract to the posterior lobe of the pituitary gland; these hormones are then released into the circulation. (b) Hypothalamic releasing hormones are formed in the hypothalamus and are transported to a capillary plexus formed by the superior hypophyseal arteries around the median eminence and infundibular stem of the hypothalamus; these hormones there enter into the vascular system and are taken by the portal veins to the adenohypophysis. (Source: reproduced from Brown, David and Reilly, 1995, with permission.)
sodium excretion such that renal sodium and water excretion fall when absolute or relative ECF volume is low and increase when ECF volume is high. The renal mechanisms influencing sodium excretion in response to changes in ECF volume are listed in Table 16.7.

- Physical factors in the peritubular capillary environment are one of the principal mechanisms influencing Na⁺ excretion in response to changes in ECF volume. When renal perfusion pressure falls or oncotic pressure in the peritubular capillary increases, the balance of Starling forces favors sodium and water reabsorption in the proximal tubule. Conversely, if the hydrostatic pressure in the peritubular capillary is increased, sodium excretion occurs. Changes in the resistance of the glomerular afferent or efferent arteriole affect renal sodium reabsorption independent of changes in renal perfusion pressure or oncotic pressure. Vasodilatation (e.g. with low-dose dopamine) increases capillary

| Physical factors in peritubular capillary environment (i.e. hydrostatic and oncotic pressure) |
| Changes in resistance of afferent or efferent arteriole |
| Renal adrenergic nerve fibers |
| Hormonal mechanisms—renin–angiotensin–aldosterone; atrial natriuretic peptide (ANP) |

Figure 16.12 Control of body fluids. This shows the pituitary gland at the top of the diagram, the heart in the center and the two kidneys. The factors affecting ACTH, ADH and catecholamine release are shown and the effects on the kidney of these two hormones are simplified at the bottom of the diagram. The possible results of the kallikrein system, natriuretic hormone and angiotensin are also included.
hydrostatic pressure and renal sodium excretion, while vasoconstriction (e.g. heart failure) reduces hydrostatic pressure and renal sodium excretion. Adrenergic nerve fibers innervate the renal tubules and may influence renal sodium excretion independent of changes in renal hemodynamics. Stimulation enhances sodium reabsorption, while denervation reduces renal Na+ reabsorption.

- The major hormonal mechanism influencing renal sodium excretion is the renin–angiotensin–aldosterone system. The juxtaglomerular apparatus senses a reduction in effective blood volume, renin is released from the kidney, ultimately increasing angiotensin II and aldosterone levels. Aldosterone increases distal tubular sodium reabsorption and potassium excretion. Angiotensin II also increases systemic vascular resistance and proximal tubular sodium reabsorption by increasing resistance in the efferent arteriole.

ANP is produced both in atrial myocytes and within the CNS is also important in body sodium regulation (Needleman and Greenwald, 1986; Samson, 1987). Its actions tend to oppose those of ADH and angiotensin, and so it appears to play a role in regulating fluid and electrolyte balance. ANP may play a role in local control of brain volume as well as electrolyte and water content. ANP is released into the systemic circulation from the atria, stimulated by increased intravascular volume or by increased atrial pressure independent of intravascular volume, and under salt-loading conditions as with infusion of hypertonic saline. ANP decreases renal vascular resistance and increases glomerular filtration rate. It induces natriuresis and diuresis and inhibits the renin–angiotensin–aldosterone axis. ANP also reduces systemic vascular resistance and blood pressure.

Fluid balance disturbances are common among patients with head injury and are often multifactorial. Hyponatremia has often been attributed to a cerebral salt-wasting state or to inappropriate secretion of antidiuretic hormone (SIADH; as noted earlier, a moderate degree of ADH secretion is part of the response to stress). However, hyponatremia may in fact often be iatrogenic (Bouzarth et al., 1982; Nelson et al., 1981). Hypernatremia and hyperosmolarity are present in many head-injured patients as a consequence of the fluid restriction and hyperosmolar agents used to manage the increases in intracranial pressure. Hypothalamic dysfunction can cause diabetes insipidus with hyponatremia.

The major fluid/electrolyte changes immediately after acute injury are:

- release of K+ by the cells, leading to transient relative hyperkalemia, increased K+ excretion and subsequent reduction of total body K+;
- retention of Na+ and water; water is retained relatively more than Na+, leading to dilutional hyponatremia.

These changes are maximum on the first and second day after injury and persist for 4–7 days. They are more pronounced after severe trauma (Verney, 1954).

### 16.7 Fluid therapy in uncomplicated postoperative and post-traumatic states

#### 16.7.1 FLUID AND ELECTROLYTE REQUIREMENTS

Abnormal fluid losses occur through:

- external routes, such as hemorrhage, GI losses, wounds and burns; CSF otorrhea in young children can sometimes be clinically significant;
- internal shifts into the interstitial water or extracellular water;
- local edema due to surgical wounds, crushing injuries, burns, venous thrombosis;
- fluid accumulation in the transepidermal space, e.g. pleural effusion, ascites and paralytic ileus.

Fluid replacement must take into account basal losses, additional extrarenal losses and distributional changes, based on an understanding of the underlying physiological and metabolic changes.

Once a stable circulation has been established, water replacement in adult patients with no oral intake should equal urinary losses, usually 1000–1500 ml/d, plus insoluble water losses, usually 600–800 ml/d, minus the volume of endogenous water released by tissue breakdown during semistarvation. In uncomplicated, afebrile postoperative patients, the latter is usually only 100–200 ml but may be as much as 1000 ml in a critically ill trauma patient with sepsis. Thus, replacement volume is approximately 1500–3000 ml/d, depending on weight, age, sex and overall status. Elderly patients with underlying cardiac or renal disease usually require less.

Water requirements increase by about 300 ml/d for each 1°C elevation in body temperature. Fluid requirements are greatly increased by shock, multiple trauma, sepsis, postoperative complications and other critical illnesses. Under these conditions, criteria for fluid therapy are based primarily on hemodynamic factors and adequate oxygen delivery.

Basal sodium requirements are met by the daily administration of 500 ml of physiological saline (75 mmol/d) plus the estimated volume of extrarenal fluid losses (e.g. nasogastric suction, diarrhea, CSF and other fistulae, and pleural or peritoneal drains).

In an uncomplicated postoperative patient, 40 mmol potassium per day is usually sufficient, unless the patient is suffering from renal failure or upper GIT...
bleeding. Such patients may develop hyperkalemia and thus usually need less K⁺ replacement. Fluid therapy of brief duration does not usually require magnesium, but debilitated patients who do not have renal failure may benefit from 10–15 mmol Mg²⁺ daily.

Nutritional support plays an integral role in the management of metabolic stress. The time to initiate nutritional support is not completely settled. It is generally agreed that oxygen transport must be restored, stabilized and maintained prior to beginning nutritional therapy. In a previously well nourished patient, our practice is to wait a few days, whereas in a severely malnourished patient, therapy should begin as soon as O₂ transport is stabilized.

16 7.2 NUTRITIONAL REQUIREMENTS

Nutrition may be administered via the enteral or parenteral route. The essential requirements are as follows.

(a) Calories

Energy as carbohydrate or fat is given to meet the metabolic needs of the patient (i.e. basal metabolic rate plus additional demands). Sufficient energy of non-protein origin must be given to prevent infused protein being used as an energy source. Energy is measured in kilocalories (kcal) or kilojoules (kJ) – one kilocalorie = 4.184 kilojoules. A satisfactory ratio of non-nitrogen kilocalories per gram of nitrogen is 150:1 (each 6.25 g protein yields 1 g nitrogen).

Although numerous equations and nomograms have been used to estimate metabolic rate and nitrogen requirements, none predict accurately which caloric or nitrogen substrate will be utilized most effectively. Furthermore, substrate utilization varies during the course of an illness.

The increase in metabolism during the acute phase of injury is short-lived, and nutritional requirements fall rapidly within 2–5 days as shock, pain and sepsis resolve and recovery begins. During convalescence very few hospital patients expend more than 1500–2000 kcal (6300–8400 kJ) per day.

Glucose

Glucose and lipid solutions are the standard intravenous energy substrates. In a normal person a daily infusion of 4 mg/kg/min of glucose suppresses gluconeogenesis maximally. Approximately one-third of the infused glucose is oxidized immediately and the remainder is stored as glycogen or lipid. Increasing the infusion rate increases the amount of glucose stored, thus increasing O₂ utilization and CO₂ production. A greater caloric intake is unnecessary in most patients and may be detrimental in those with severe respiratory failure, particularly if infusion rates of greater than 7 mg/kg/min (equivalent to 700 g of dextrose or 2800 kcal/d in a 70 kg subject) are used. Excessive glucose administration may lead to hepatic steatosis, hyperbilirubinemia and an elevated alkaline phosphatase.

In patients requiring parenteral nutrition, glucose should be used as the major caloric source and infused at a rate no greater than 30 kcal/kg/d (equivalent to 500 g of dextrose or 2000 kcal/d in a 70 kg subject). Each gram of glucose provides approximately 4 kcal.

Lipid

Intravenous lipids are available as emulsions similar in particle size to chylomicrons, and are cleared as such by the body. Chylomicrons are acted upon by plasma lipoprotein lipase to form free fatty acids and glycerol, which are either oxidized or stored as lipid. Although there is an increasing trend toward the routine use of lipid solutions as an energy source, these expensive substances have no advantages over dextrose. Lipid solutions are only necessary to provide the essential fatty acids linolenic and linoleic. In the absence of essential fatty acids, linoleic and hence arachidonic acid levels fall and skin lesions (desquamative dermatitis) may result. Approximately 9 kcal is provided for each gram of fat used by the body.

(b) Protein

The normal adult only needs an oral intake of 20 g of protein to meet daily protein requirements. Protein ingested in excess of this amount is broken down to provide energy and nitrogenous wastes. In the acutely ill patient, the minimal quantity of protein required is unknown, but it is unlikely to exceed 50 g/d in a patient who is not losing protein externally. The usually quoted requirement is 1–2 g/kg body weight per day.

Normal adults require 20 L-amino acids for protein synthesis, although only leucine, isoleucine, valine, lysine, threonine, phenylalanine, methionine and tryptophan cannot be synthesized and are therefore essential. In patients requiring parenteral nutrition, histidine, arginine and cysteine may also be required.

For effective nitrogen utilization, a ratio of essential to total amino acids of 2:5 is advisable, and should reflect the amino acid profile of a normal diet. To reduce the oxidation of amino acids as an energy substrate, a source of alternate energy should be administered simultaneously in a ratio of 150 kcal for each 1 g of nitrogen.
(c) Vitamins and trace elements

Vitamins are dietary compounds that act as cofactors for intermediary metabolism. Patients may develop a deficiency of the water-soluble C and B group vitamins and vitamin K within 4 weeks of parenteral nutrition; hence they should be administered to all patients receiving intravenous nutrition at doses equivalent to normal daily requirement (Table 16.8). Vitamin deficiency may rarely affect neurological assessment.

The essential trace elements are those present in the body in amounts of less than 50 μg/g tissue, and are required in the diet in milligram quantities or less per day. They are usually defined by their deficiency states, i.e. a reproducible functional and/or structural abnormality associated with a specific biochemical change which is prevented or reversed by the element.

With the exception of zinc, the body stores of the essential trace elements, copper, iodine, iron, manganese, cobalt, selenium, chromium and molybdenum are usually adequate for patients requiring parenteral nutrition for less than 3 months. A total of 2.5 mg of zinc per day will normally maintain the zinc balance, although, in patients with diarrhea, up to five times this amount may be required. Table 16.9 summarizes parenteral nutrient intake for adults. Trace element deficiency can result in neurological manifestations, which may interfere with the neurological assessment of the head-injured patient and wound healing, as is the case with some vitamin deficiency syndromes. There is little data regarding the optimal amounts of provision of trace elements to critically ill patients. Guidelines will only be established when more accurate methods are developed for assessing and monitoring trace element status in patients in intensive care.

Gastric atony is usually present during states of metabolic stress and responds poorly to motility enhancers. Gastric feeding is associated with a very high incidence of aspiration and great care must be taken to avoid this. These problems are alleviated by using sites for feeding distal to the pylorus and in our view enteral nutrition should be used whenever possible. In many patients the gut provides an adequate portal of entry for nutritional support at a much reduced risk. By keeping bacteria and toxins within its lumen, the gut has a role in host defense. In states of metabolic stress, especially coupled with gut starvation, mucosal permeability increases, allowing movement of enteric bacteria to the regional lymph nodes and thence to the systemic circulation.

Proven benefits of enteral feeding include maintenance of an intestinal ‘barrier’ and better immune function, improved liver blood flow following shock and better wound healing. Gut feeding can be started early even in the presence of a mild ileus, although early feeding does not attenuate the metabolic response to blunt trauma (Eyer et al., 1993). Exercise, even when done passively, is a potent anabolic stimulus and retards nitrogen mobilization in critically ill and injured patients. While vigorous nutritional support appears to affect mortality favorably and speed recovery from head injury, nutrient administration alone cannot override the metabolic response to head injury (Clifton et al., 1984; Young et al., 1985). Despite adequate caloric administration, severe head

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### Table 16.8 Recommended daily allowance (RDA) of vitamins for adults (MVI-12 contents)

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>RDA (mg)</th>
<th>MVI-12 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>E</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>K</td>
<td>0.1</td>
<td>–</td>
</tr>
<tr>
<td>B1 (thiamin)</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>B2 (riboflavin)</td>
<td>1.6</td>
<td>3.6</td>
</tr>
<tr>
<td>B6 (pyridoxine)</td>
<td>2.2</td>
<td>4</td>
</tr>
<tr>
<td>Niacin</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>B12</td>
<td>0.003</td>
<td>0.005</td>
</tr>
<tr>
<td>Biotin</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

MVI-12 does not contain vitamin K

### Table 16.9 Usual daily dose range of parenteral nutrient intake for the adult

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>2500–3500 ml</td>
<td>30–40 ml/kg/d</td>
</tr>
<tr>
<td>Calories</td>
<td>2500–3500</td>
<td>30–40 kcal/kg/d</td>
</tr>
<tr>
<td>Glucose</td>
<td>600–900 g</td>
<td></td>
</tr>
<tr>
<td>Protein equivalent (as amino acids)</td>
<td>60–130 g</td>
<td>1–2 g/kg/d</td>
</tr>
<tr>
<td>Na⁺</td>
<td>100–120 mmol</td>
<td>↑ with GI losses; ↓ in elderly, CCF</td>
</tr>
<tr>
<td>K⁺</td>
<td>80–120 mmol</td>
<td>↓ with renal failure</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>4–10 mmol</td>
<td></td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>12–15 mmol</td>
<td>↑ with GI losses</td>
</tr>
<tr>
<td>PO₄</td>
<td>10–15 mmol</td>
<td>↑ when glucose alone is given; ↓ with renal failure</td>
</tr>
</tbody>
</table>
(d) Nutrition and outcome

Since protein-calorie malnutrition can adversely affect the structure and function of many organs, including the lungs (Arora and Rochester, 1982), heart (Heymsfield et al., 1978), gastrointestinal tract (James, 1971) and musculoskeletal system (Jeejeebhoy, 1986) as well as wound healing (Haydock and Hill, 1987) and immune function, nutritional support might be expected to have a beneficial effect on mortality and morbidity following head injury.

However, although there are studies that suggest that nutritional support is beneficial in supporting general metabolism following head injury (McMahon et al., 1993), a significant relationship between nutrient intake and outcome has not been proved.

16.8 Disorders of water and electrolyte balance

Hypovolemia (from aggressive use of diuretics), hyperosmolarity (from osmotic diuretics, hyperglycemia resulting in glycosuria, and diabetes insipidus) and disorders of sodium metabolism (especially the syndrome of inappropriate ADH secretion – SIADH) are common problems in head-injured patients. These and other disorders may cause secondary brain injury through their effects on cerebral perfusion, intracranial pressure and neuronal function.

16.8.1 HYponATREMIA

Hyponatremia (plasma Na⁺ < 135 mmol/l) is seen in 5–12% of patients with severe head injury (Steinbok and Thompson, 1978). It is especially important, since the osmotic buffering capacity of the brain may be impaired following primary brain injuries. ECF osmolality is reduced in all cases of hyponatremia in the absence of abnormal solute accumulation, and even small decreases in osmolality may cause brain edema, impairing brain function and increasing ICP. The pathogenesis of hyponatremia is summarized in Table 16.10.

Hyponatremia may occur in association with different levels of body fluid tonicity (Table 16.11) and so be classified as isotonic, hypertonic or hypotonic, based on the measured plasma osmolality. Hyponatremia following head injury is hypotonic and is usually thought to be due to SIADH. The risk of hyponatremia seems greater in those with severe head injuries, chronic subdural hematoma and basal skull fracture (Steinbok and Thompson, 1978; Doczi et al., 1982). There are numerous reports alleging that this type of hyponatremia is due to renal salt wasting caused by an unknown humoral substance released in response to cerebral injury (‘cerebral salt wasting’); however, the evidence is not strong and the reported cases most probably represent SIADH (Oh and Carroll, 1992). Deterioration in level of consciousness, new focal deficits, myoclonus, seizures or increasing ICP should alert the physician to the possibility of hyponatremia and hypo-osmolality in the patient with a severe brain injury.

(a) Isotonic hyponatremia

An apparent decrease in serum sodium concentration (measured by flame photometry) occurs when the mass of the non-aqueous components of serum is increased by severe hyperlipidemia or hyperproteinaemia. This is usually referred to as pseudo-hyponatremia and can be readily identified by finding a normal serum osmolality (Weisberg, 1989).

(b) Hypertonic hyponatremia

In patients with an increased amount of an impermeant solute (i.e. one that is unable to cross the blood–
brain barrier), such as glucose, mannitol, glycerol or sorbitol, osmotic equilibration occurs by water shifting from the ICF to the ECF, thus diluting the ECF sodium. In such circumstances, hyponatremia is often associated with an elevated measured osmolality. For every 1 mmol/l rise in glucose above a plasma glucose level of 5.6 mmol/l, the plasma sodium decreases by 0.288 mmol/l (Katz, 1973; Crandall, 1974; Jenkins and Larmore, 1974; Robin et al., 1979). The corrected sodium value is derived from the formula:

$$\text{Corrected Na value} = \frac{\text{measured plasma Na}^+}{(\text{plasma glucose value} - 5.6)} \times 0.288.$$

(c) **Hypotonic hyponatremia**

Hyponatremia is almost always caused by an excess of total body water. This may be due to excessive infusion of hypotonic or water-generating intravenous fluids such as 5% dextrose, 1.5% glycine or 0.45% saline, particularly when administered rapidly or in the presence of high circulating ADH levels. Hyponatremia may rarely be due to loss of exchangeable sodium or potassium (Fuisz, 1963).

Since hyponatremia may be associated with an alteration in both total body water and total body solute the ECF volume may be increased (hypervolemia), decreased (hypovolemia) or unchanged (isovolemia; Humes, 1986).

In health, a fluid intake of up to 15–20 liters may be tolerated before water is retained. However, less water is needed to produce hyponatremia in individuals in whom there is also an increase in non-osmotic stimulation of ADH by hypovolemia, hypotension, pain, nausea or postoperative stress (Hayes, 1968; Chung et al., 1986; Sinnatamby et al., 1974), or a reduction in urinary osmotic excretion, as in patients with a reduced urea production, or a reduction in renal capacity to respond to ADH.

The proposal that disease may cause a ‘sick cell’ syndrome (Flear and Singh, 1973; Flear, Gill and Burn, 1981) in which ECF sodium leaks into cells and produces hyponatremia is a misconception (Leaf, 1974; Bichet and Schrier, 1982).

Loss of potassium may cause hyponatremia as sodium shifts into the cell in exchange for K+

**Syndrome of inappropriate ADH secretion (SIADH)**

This syndrome is defined as hyponatremia due to an elevated level of ADH inappropriate for the prevailing osmotic or volume stimuli (Robinson, 1985; Barter and Schwartz, 1967). ADH secretion from the neurohypophysis is no longer under normal regulatory influences. The criteria for the diagnosis of SIADH are listed in Table 16.12.

**Table 16.12** Criteria for the diagnosis of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

- Hypotonic hyponatremia
- Urine osmolality greater than plasma osmolality
- Urine sodium excretion greater than 20 mmol/l
- Normal renal, hepatic, cardiac, pituitary, adrenal and thyroid function
- Absence of hypotension, hypovolemia, edema and drugs
- Correction by water restriction

SIADH is a form of dilutional hyponatremia; ECF volume is usually increased by 3–4 liters and peripheral edema does not occur. Because of the expanded ECF volume, glomerular filtration rate is increased and the renin–angiotensin–aldosterone mechanism is suppressed, resulting in a decrease in the renal absorption of sodium.

**Syndrome of inappropriate antidiuresis (SIAD)**

This syndrome is defined as hyponatremia due either to increased ADH secretion initiated by stimulation of high- or low-pressure baroreceptors, or to a reduction in non-ADH renal water excretion mechanisms (Robertson, 1989). The causes of SIAD are listed in Table 16.13.

**Table 16.13** Causes of syndrome of inappropriate antidiuresis

<table>
<thead>
<tr>
<th>Baroreceptor-mediated</th>
<th>Cortical influences</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>Pain, anxiety and nausea</td>
<td>Narcotics, barbiturates, chlorpropamide, phenothiazines, carbamazepine, tricyclics, nicotine derivatives, clofibrate, vincristine, vinblastine, cyclophosphamide</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Postoperative</td>
<td>Reduction in renal response to antidiuretic hormone</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Trauma</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Drugs: frusemide, thiazides</td>
<td></td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
<td>Drugs: indomethacin, frusemide, thiazides</td>
</tr>
</tbody>
</table>

(d) **Clinical features of hyponatremia**

Hypotonic hyponatremia is almost always caused by excess total body water, and the symptoms are due...
to the cerebral water excess (cerebral edema; Waste-rlain and Posner, 1968). Normally the brain partially adapts to the hypo-osmolality within 24 hours, reducing the cerebral water excess by losing or inactivating intracellular osmotically active solutes (Arieff, 1984, 1985; Arieff and Guisado, 1976; Arieff, Liach and Massry, 1976).

If the patient develops hyponatremia of 125 mmol/l (osmolality 260 mosmol/kg) acutely, that is within 3 days, then symptoms of cerebral edema usually occur. These include headache, anorexia, nausea, weakness, lethargy, confusion, disorientation, blurred vision, muscle cramps, coma and seizures (Arieff, 1984; Arieff, Liach and Massry, 1976; Plum and Posner, 1980).

Chronic hyponatremia, on the other hand, with plasma sodium values well below 125 mmol/l, may be well tolerated because of cerebral osmotic compensation (Arieff, 1984). Thus the mortality associated with hyponatremia is usually related to its rate of development rather than its severity. Chronic hyponatremia has a mortality of less than 10% (Sterns, 1987), whereas a mortality up to 50% has been reported with acute hyponatremia (Robertson, 1989).

(e) Diagnosis of hyponatremia

The evaluation of hyponatremia with hypo-osmolality begins with a clinical assessment of volume status and measurement of urinary indices (Table 16.14). However, volume status can be difficult to assess clinically in a critically ill patient. ECF volume may be affected by blood loss, the amount and type of fluid administered and the use of diuretics. Urinary Na⁺ measurements are affected by the use of osmotic and non-osmotic diuretics. Figure 16.13 summarizes our diagnostic approach to hyponatremia.

Acute hyponatremia is usually due to excess water, as in dextrose solutions administered inappropriately to patients in the postoperative period. Diagnosis is based on measurement of plasma osmolality, osmolar gap and urinary sodium. The osmolar gap is the difference between the measured osmolality and the calculated osmolality (2 × Na⁺ + glucose + urea, where plasma sodium, glucose and urea are measured in millimoles per liter; Worthley, Guerin and Pain, 1987). When there is an excess of total body water, urinary sodium is usually greater than 40 mmol/l and plasma urea is low. In the rare case of hyponatremia due to salt depletion, urinary sodium is usually less than 20 mmol/l and the plasma urea and uric acid are often high (Humes, 1986). In patients with head injuries hyponatremia will almost always be associated with a urinary osmolality of greater than 100 mosmol/kg.

The presumptive diagnosis of SIADH can be confirmed if simply restricting fluids results in a reduction of urinary Na⁺ losses and correction of hyponatremia. The clinical picture most often confused with SIADH is a patient with isotonic fluid loss, usually due to diuretics, who is treated with hypotonic fluid replacement. In this situation, the body preserves volume at the expense of tonicity – a form of hypotonic dehydration. It should be stressed that the absence of an increase in ECF volume excludes a diagnosis of SIADH.

Chronic hyponatremia accompanies other diseases and it is important to differentiate SIADH from sodium depletion due to prolonged vomiting, adrenal insufficiency or hypopituitarism.

(f) Treatment of hyponatremia

Treatment aims to remove excess water and treat of the underlying cause.

Chronic hyponatremia (> 3 days’ duration)

If the patient is asymptomatic and hyponatremia has been present for more than 3 days, fluid restriction and removal of any precipitating factor is often all that is required (Cluitmans and Meinders, 1990). Fluid should be restricted to less than 500 ml/d. The rate of correction should be no greater than 12 mmol/l/d (0.5 mmol/l/h) and is continued only until the plasma sodium is 130 mmol/l (Laureno and Karp, 1988; Sterns, Riggs and Schochet, 1986; Plum and Posner, 1980; Cluitmans and Meinders, 1990; Norenberg and Papendick, 1984). If fluid deprivation is difficult to sustain in patients with SIADH or SIAD then patients with hyponatremia and chronic CCF may benefit from an ACE inhibitor added to frusemide (furosamide). This will inhibit the stimulation of thirst and ADH release by angiotensin II (Dzau and Hollenberg, 1984; Packer, Medina and Yushak, 1984). However, in these patients a direct ADH inhibitor such as phenytoin may be of greater value (Mulinari et al., 1990). This has been used to reduce ADH release from the hypophysis in

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ECV</th>
<th>uNa⁺ (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>Decreased</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Congestive heart failure, cirrhosis</td>
<td>Increased</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Renal disease, adrenal insufficiency, diuretics</td>
<td>Decreased</td>
<td>&gt;25</td>
</tr>
<tr>
<td>SIADH</td>
<td>Normal or increased</td>
<td>&gt;25</td>
</tr>
</tbody>
</table>
patients with SIADH due to CNS disorders including head injury (Martinez-Maldonado, 1980).

Complications of treatment of chronic hyponatremia

In chronic hyponatremia the brain is less able to tolerate rapid correction and may develop central pontine and extrapontine myelinolysis if hypertonic saline is used. The lesions of central pontine myelinolysis (CPM) are caused by the destruction of myelin sheaths in the center of the basilar portion of the pons and may extend from the midbrain to the lower pons. The clinical features range from coma, flaccid quadriplegia, facial weakness and pseudobulbar palsy to minor behavioral changes without focal findings. The onset may be from one to several days after the hyponatremia has been corrected and may require MRI to confirm the diagnosis (Brunner et al., 1990).

While an association with CPM and correction of hyponatremia has been reported, the relationship between CPM and the rapidity of correction of hyponatremia has not been firmly established in clinical practice. In 170 cases of CPM, hyponatremia occurred in only 28% of patients, most of whom were corrected slowly (Ayu, Krothapalli and Arieff, 1985), an observation that has been confirmed by others (Tormey, 1990). Nevertheless, there is persuasive experimental evidence for the association between rapidity of correction of chronic hyponatremia and CPM (Norenberg and Papendick, 1984).
Acute hyponatremia (<3 days duration)

In this condition, the rate of reduction of plasma sodium is 0.5 mmol/l/h or greater and/or the hyponatremia is of less than 3 days duration (Cluitmans and Meinders, 1990). It is often associated with inappropriate intravenous fluid administration and with the postoperative period (Arieff, 1986). The total water excess in adults ranges from 5–10 liters.

The rate of correction of acute hyponatremia should be no greater than 2 mmol/l/h of sodium until the plasma level has increased to 120 mmol/l or by a maximum of 20 mmol/l during the first 24 hours (Arieff and Guisado, 1976; Ayus, Krothapalli and Arieff, 1987, 1988).

This is achieved initially by intravenous administration of hypertonic saline given at 50–70 mmol/h. It is important to note that the purpose of using hypertonic saline is not to correct a saline deficit, since there is in fact not a total Na⁺ deficiency, but rather the hypertonic saline draws water into the intravascular compartment and reduces brain edema. A spontaneous or frusemide-induced diuresis (e.g. by 20–40 mg intravenously) is then required to excrete the water excess. When the plasma sodium has increased to 120 mmol/l, precautions should be taken to prevent the plasma sodium rising to greater than 130 mmol/l over the next 24 hours. If the hyponatremia presents with convulsions, then urgent correction of the cerebral edema using 250 mmol of hypertonic sodium chloride over 10 minutes (equivalent to 500 ml of 20% mannitol), has been used. This will immediately elevate the plasma sodium in adults by about 7 mmol/l (Table 16.15; Worthley and Thomas, 1986).

Complications of treatment of acute hyponatremia

The complications reported with the use of hypertonic saline include congestive cardiac failure, cerebral hemorrhage – intracerebral and subdural, presumed due to tearing of bridging veins – and CPM. To reduce the incidence of congestive cardiac failure, CVP or PAWP should be monitored throughout saline administration. Cerebral hemorrhage will only occur if there is an inappropriate administration of hypertonic saline in normonatremic states (Finberg, Luttrell and Redd, 1959).

16.8.2 HYPERNATREMIA

Hypernatremia is defined as a plasma sodium greater than 145 mmol/l. It is always associated with hyperosmolality and may be caused by water depletion, excessive administration of sodium salts or both (Table 16.16).

In water-depleted states, the thirst mechanism normally stimulates a conscious individual to drink water. Thus water loss only produces hypernatremia if the patient is unconscious or otherwise physically unable to drink. Excessive administration of sodium salts is a rare cause of hypernatremia and usually only occurs through therapeutic misadventure.

Hypernatremia is the usual cause of hyperosmolar states in neurosurgical patients, although marked

---

Table 16.15 Treatment of severe hyponatremia (ACE = angiotensin-converting enzyme; ADH = antidiuretic hormone)

<table>
<thead>
<tr>
<th>Acute hyponatremia</th>
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</thead>
<tbody>
<tr>
<td>Fluid restrict to 500 ml/d or less</td>
</tr>
<tr>
<td>Hypertonic saline (50–70 mmol/l/h)</td>
</tr>
<tr>
<td>Diuresis of 160 ml/h or greater</td>
</tr>
<tr>
<td>Rate of correction:</td>
</tr>
<tr>
<td>First day: no greater than 20 mmol/l/d (2 mmol/l/h) until plasma sodium 120 mmol/l</td>
</tr>
<tr>
<td>Second day: attempt to keep plasma sodium between 130 and 135 mmol/l</td>
</tr>
<tr>
<td>Seizures: 100–250 mmol hypertonic saline over 10 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid restrict to 500 ml/d or less</td>
</tr>
<tr>
<td>Rate of correction:</td>
</tr>
<tr>
<td>No greater than 12 mmol/l/d (0.5 mmol/l/h) until the plasma sodium is 130 mmol/l</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Lithium, demeclocycline</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>ADH inhibitor</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 16.16 Causes of hypernatremia</th>
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</thead>
<tbody>
<tr>
<td><strong>Water depletion</strong></td>
</tr>
<tr>
<td><strong>Extrarenal loss</strong></td>
</tr>
<tr>
<td>Exposure</td>
</tr>
<tr>
<td>GIT losses</td>
</tr>
<tr>
<td><strong>Renal loss</strong></td>
</tr>
<tr>
<td>Osmotic diuresis</td>
</tr>
<tr>
<td>Urea, mannitol, glycosuria</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Central (neurogenic)</td>
</tr>
<tr>
<td>Post-traumatic, postoperative</td>
</tr>
<tr>
<td>Metastatic tumors, craniopharyngioma, pinealoma, cysts</td>
</tr>
<tr>
<td>Meningitis, encephalitis</td>
</tr>
<tr>
<td>Fat embolism</td>
</tr>
<tr>
<td>Granulomas (TB sarcoid)</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Nephrogenic</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Drugs: lithium, amphotericin B</td>
</tr>
<tr>
<td>Renal diseases: chronic pyelonephritis; medullary sponge kidney; polycystic kidney; analgesic nephropathy; postobstructive uropathy; multiple myeloma; amyloid; sarcoid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Salt gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic saline or sodium bicarbonate</td>
</tr>
</tbody>
</table>
hyperglycemia may contribute to hyperosmolality in states of insulin resistance, such as in sepsis, or as a result of inadequate insulin administration with parenteral nutrition.

(a) Clinical features

Hypernatremia is usually symptomatic if plasma sodium is 155–160 mmol/l or greater (equivalent to an osmolality of 330 mosmol/kg or greater). This equates to a water depletion of 6 liters or greater in a 70 kg man (Arieff, 1984). Clinical features include pyrexia, restlessness, weakness, paralysis, irritability, drowsiness, lethargy, confusion, tremor, hyper-reflexia, seizures and coma (Ross and Christie, 1969). The signs of hypernatremia are due mainly to increased effective osmolality, which reduces brain cell volume (Oh and Carroll, 1992). As already noted, hypernatremia is much better tolerated if it develops slowly. Increase of the brain volume may be accomplished by intracellular shift of sodium, potassium and chloride, and the accumulation of organic solutes, mainly taurine and other amino acids (Lohr, McReynolds and Grimaldi, 1988). Normalizing brain volume in chronic hypernatremia therefore requires an increase in the total solute content of the brain. A sudden lowering of the osmolality of the ECF may cause a shift of water into the brain cells with resultant cerebral edema.

(b) Diabetes insipidus

Diabetes insipidus (DI) is characterized by polyuria (3–15 l/d) and polydipsia due to the complete or partial failure of ADH secretion (central or neurogenic DI), or decrease in the renal response to ADH (nephrogenic DI; Table 16.16). Both situations result in an inability to concentrate urine and to conserve solute-free water in the face of appropriate stimuli. Head injury is a common cause of central DI. A very early onset is characteristic of major hypothalamic damage and is associated with a high mortality (Seckl, Dunger and Lightman, 1987).

Head-injured patients with fractures involving the base of the skull and sella turcica appear to be at increased risk of DI (Crompton, 1971; Edwards and Clark, 1986). Diabetes insipidus is common in patients prior to brain death. Traumatic DI is thought to be caused by a shearing injury to the pituitary stalk. The time of onset is variable, but it usually appears after 5–10 days (Kern and Meislin, 1984). In most cases of post-traumatic DI the onset is characterized by polyuria, hypernatremia and plasma hyperosmolality, sometimes as early as 12–24 hours after injury. If the damage is limited to the pituitary or lower pituitary stalk, the DI may only be transient, and this is usually the case. High stalk lesions or injury to the hypothalamus usually cause permanent DI. Since most patients in ICU are unable to control their own water intake, hemodynamic instability may occur with untreated DI.

Nephrogenic DI is often mild because the patient can usually produce an isotonic urine; thus the diuresis is limited to 3–5 l/d.

(c) Diagnosis

Every patient with hypernatremia may be considered to have an inadequate water intake, either absolute or relative. Excessive sodium administration as the cause of hypernatremia is usually obvious from the history. Whether hypernatremia is due to insufficient water intake or to excessive water loss can be determined by measurements of urine osmolality (Figure 16.14). Normal concentration of urine (urine osmolality

![Figure 16.14](image-url) Differential diagnosis of hypernatremia. $P_{osm}$ = plasma osmolality; DI = diabetes insipidus.)
>700 mosmol/l) suggests that the main problem is insufficient water intake, with or without excessive extrarenal water loss. Urine osmolality between 700 mosmol/l and the osmolality of plasma suggests partial central DI, osmotic diuresis, diuretic therapy, acquired (partial) nephrogenic DI or renal failure. A high (>30 ml/kg/h) urine volume may be the first sign of diabetes insipidus, but is also seen in osmotic diuresis. A urine osmolality below that of plasma suggests either complete central DI or nephrogenic DI.

Laboratory investigations show hypernatremia, persistently hypotonic urine and low urine osmolality, usually less than 200 mosmol/l. In milder cases urine osmolality may not be below that of plasma, and may be 300–600 mosmol/l. Patients with central DI are unable to increase urinary osmolality during fluid restriction, but remain sensitive to exogenous ADH. Patients with partial DI have urinary volumes much less than those with complete DI. Other causes of polyuria which should be considered in the head-injured patient include osmotic diuretics (mannitol, iodinated contrast-medium), severe hyperglycemia and fluid overload. In contrast to DI, a solute diuresis is usually accompanied by a higher urinary osmolality (between 250 and 320 mosmol/l; Shucart and Jackson, 1976).

(d) Treatment of hypernatremia

Hypotension due to a reduction in intravascular fluid volume should be treated by isotonic saline infusions to replace the intravascular volume and improve tissue perfusion before hypotonic solutions are used.

Pure water depletion is treated by water administration. (In a conscious patient with normal gastrointestinal function, oral ingestion of water is encouraged.) If intravenous fluid is required, 5% dextrose or hypotonic saline solutions (e.g. 0.45% saline) are often used, as sterile water through a peripheral vein causes hemolysis (Krumbhaar, 1914). In rare cases, where saline and dextrose solutions are deemed inadvisable; for example, in a patient who is volume-depleted and severely hypernatremic, central venous administration of sterile water can be used without causing hemolysis (Worthley, 1986).

The rate of increase in osmolality should be no greater than 2 mosmol/kg/h (Arieff, 1984; Arieff and Guisado, 1976). Hypernatremia due to excess sodium is treated by water and diuretic administration (Addleman, Pollard and Grossman, 1985). The management of DI depends on the cause (Table 16.17).

(e) Hyperosmolar therapy

Intravenous 20% mannitol (1098 mosmol/l) a six-carbon sugar similar to glucose, is often used to lower ICP. The aim is not to induce hypovolemia, which may be detrimental, but rather to maintain a normovolemic state while increasing serum sodium, osmolality and tonicity, thus decreasing the extracellular fluid volume within the brain. A serum sodium level of 145–155 mmol/l and serum osmolality of 300–320 mosmol/l are often generated, and excessive dehydration may precipitate prerenal renal failure. Fluids are administered to maintain CVP

<table>
<thead>
<tr>
<th>Table 16.17</th>
<th>Treatment of diabetes insipidus (DI) in the critically ill ICU patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remarks</strong></td>
<td></td>
</tr>
<tr>
<td>1 Confirm diagnosis</td>
<td>Altered conscious state or inability to detect thirst or take oral fluids. Hypertonicity (&gt;295 mosmol/kg), hypernatremia, inappropriately dilute urine. DI may be transient or permanent; permanent form seen in one-third of patients with trauma or neurosurgery. Presence of associated anterior pituitary hypofunction not uncommon in patients with severe head trauma.</td>
</tr>
<tr>
<td>2 Replace free water deficit</td>
<td>Free H₂O deficit (liters) = 0.6 × (body weight [kg]) × ([Na⁺/140] – 1) Parenteral replacement of half of deficit immediately; rest over 24–36 hours. Use 5% dextrose, not saline solutions</td>
</tr>
<tr>
<td>3 Give maintenance fluids and replace urine output hourly with dextrose solutions</td>
<td>Labor-intensive; inaccurate fluid balance may occur with high volumes of urine</td>
</tr>
<tr>
<td>4 Daily weight</td>
<td>Not always available in adult ICU</td>
</tr>
<tr>
<td>5 Close monitoring of electrolytes and fluid balance</td>
<td></td>
</tr>
<tr>
<td>6 Aqueous vasopressin (AVP)</td>
<td>If urine output remains excessive (&gt;200–250 ml/h) in the absence of diuretics or, if maintenance of fluid balance is difficult or hyperosmolality is present give 5–10 U subcutaneously or i.m.</td>
</tr>
<tr>
<td>7 Desmopressin (DDAVP) for patients with severe DI</td>
<td>More recent regimen. Synthetic analog of AVP with longer half-life and fewer vasoconstrictive effects. Give 1–2 µg subcutaneously or i.v. every 12–24 h or by nasal insufflation of 5–20 µg every 12 h. Watch for water intoxication (hyponatremia and elevated urinary osmolality) during therapy; withhold DDAVP periodically to document persistence of DI.</td>
</tr>
</tbody>
</table>
between 5 and 10 mmHg. In young, otherwise fit head-injured patients, pulmonary artery catheterization is rarely indicated.

Mannitol is administered as an intermittent intravenous bolus (0.25–0.5 g/kg body weight) up to 4-hourly. Where the blood–brain barrier is intact, mannitol remains within the intravascular and extracellular spaces (Sutin, Ruskin and Kaufman, 1992). It has several effects, including an immediate increase in circulating blood volume and arterial blood pressure (Wise and Chater, 1962; Roberts et al., 1987). It also reduces blood viscosity by hemodilution (Burke et al., 1981; Muizelaar et al., 1983) and by increasing red blood cell deformability. It causes osmotic dehydration of the brain, which reduces the volume of extracellular free water (Roberts et al., 1987), thus decreasing brain volume and ICP as well as causing a urinary osmotic diuresis. Repeated administration of mannitol may result in a systemic hyperosmolar state and dehydration, which should be avoided since cerebral perfusion may decrease and renal failure may occur.Repeated administration of mannitol may result in its eventual movement through the blood–brain barrier into the extracellular space, where the increased oncotic pressure may retain free water and worsen edema. Thus mannitol use should be restricted to the minimum amount needed to control ICP and CPP. Our practice is to measure serum osmolality daily and cease mannitol if serum osmolality exceeds 320 mosmol/l.

Mannitol induces diuresis primarily by elevating the osmotic pressure of the glomerular filtrate to such an extent that the tubular reabsorption of water and solutes is hindered. It promotes the excretion of sodium; however, proportionately more water than sodium is excreted. Excretion of potassium, chloride, calcium, phosphorus, magnesium, urea and uric acid are also increased. Mannitol is only very slightly metabolized, if at all, to glycogen in the liver. It is freely filtered by the glomeruli, with less than 10% tubular reabsorption, and is not secreted by tubular cells. The elimination half life in adults is about 100 minutes. Approximately 80% of a 100 g dose is excreted unchanged in the urine within 3 hours. In the presence of renal disease in which glomerular function is impaired or in conditions that impair small vessel circulation, such as congestive cardiac failure, cirrhosis with ascites, shock or dehydration, mannitol clearance is lower than normal. Mannitol does not cross the intact blood–brain barrier unless very high concentrations are present in the plasma or the patient has acidosis.

Hypertonic saline (7.5%) has also been used to lower ICP in animal models of head injury (Freshman et al., 1993). It was as effective as 20% mannitol in treating elevated ICP caused by a space-occupying lesion. Hypertonic saline has the additional benefit of rapid small volume resuscitation of associated hemorrhagic shock (section 16.5.2).

16.8.3 HYPOKALEMIA

Hypokalemia is defined as a serum potassium of less than 3.5 mmol/l or plasma potassium less than 3.0 mmol/l. It may be due to a reduction in total body potassium, caused by a decreased oral intake, increased renal or gastrointestinal loss, or to a compartmental shift of potassium from the ECF to the ICF (Tannen, 1986). In contrast to Na\(^+\) and Cl\(^-\), which are predominantly in the ECF and regulated by the kidneys, K\(^+\) is predominantly in the ICF; its movements are primarily determined by nutritional and metabolic factors (e.g. pH) and are mediated by neural and hormonal influences (Schultze and Nissenson, 1980).

Hypokalemia may be caused by osmotic diuretics, diabetes insipidus, steroids, catabolic losses in trauma and secondary hyperaldosteronism (commonly caused by hypovolemia or cardiac failure). Excessive renal K\(^+\) loss also occurs in the presence of alkalosis and hypomagnesemia. Gastrointestinal K\(^+\) losses may be due to vomiting, nasogastric suction or diarrhea. Intracellular shift of K\(^+\) occurs in metabolic or respiratory alkalosis, exogenous insulin administration and endogenous or exogenous catecholamine administration.

(a) Clinical features

The clinical features of hypokalemia are listed in Table 16.18. These include ventricular and supraventricular arrhythmias, ileus, enhancement of digitalis toxicity and hypokalemic nephropathy; nephropathy occurs if hypokalemia is severe and prolonged and results in impaired renal water conservation and polyuria. If K\(^+\) depletion is severe neuromuscular manifestations include weakness, hyporeflexia and even paralysis. The muscular weakness can interfere with attempts to wean patients from ventilatory support in the ICU.

(b) Treatment

Treatment of hypokalemia is usually commenced when plasma K\(^+\) is less than 3.0 mmol/l. While there is normally a linear relationship between serum K\(^+\) and total body K\(^+\) (Sterns et al., 1981), acid–base disturbances and other causes of compartmental K\(^+\) shift make estimates of total body K\(^+\) difficult in severely ill patients. Thus K\(^+\) therapy must be monitored by frequent estimations of serum K\(^+\). Serum magnesium levels should be measured in patients with refractory...
16.8.4 HYPERKALEMIA

Hyperkalemia is defined as a serum potassium greater than 5.0 mmol/l or plasma potassium greater than 4.5 mmol/l. It may be due to excessive intake, severe tissue damage, decreased excretion or body fluid compartment shift, or may be artifactual, due to hemolysis after collection.

Hyperkalemia is uncommon in patients with an isolated head injury unless overzealous use of osmotic diuretics has caused renal failure. Apparent hyperkalemia may be seen with hemolysis or acidosis. In patients with additional trauma, rhabdomyolysis and massive transfusion of old blood may result in hyperkalemia.

(a) Hypoaldosteronism (Barratt, 1981)

Hyporeninemic hypoaldosteronism

This usually occurs in patients who have non-insulin-dependent diabetes mellitus and mild renal failure, and may be provoked by cyclo-oxygenase inhibitors. The patient is hyperkalemic with metabolic acidosis (Type 4 renal tubular acidosis, RTA) and has an elevated plasma creatinine and urea nitrogen. The etiology is not known, although hyporeninemia, prostacyclin deficiency and excess atrial natriuretic hormone have all been implicated. Non-steroidal anti-inflammatory drugs (NSAIDs), calcium-channel blockers and beta-adrenergic blockers should not be administered as they will contribute to the hyporeninemic state (Williams, 1986).

Primary hypoaldosteronism

This is characterized by normal or high renin levels and is due to an enzymatic defect in the aldosterone pathway.

Pseudo-hypoaldosteronism

This is characterized by normal or high levels of aldosterone with a renal tubular resistance to the action of the hormone. This disorder is commonly caused by spironolactone and amiloride. The suppression of aldosterone production with hyperkalemia (Edes and Sunderrajan, 1985) described with heparin use is due to the antiseptic in commercial heparin solutions and not to heparin (Jaques, 1985).

(b) Clinical features of hyperkalemia

The clinical features of hyperkalemia include tingling, paresthesias, weakness, flaccid paralysis and hypotension. ECG changes include T-wave peaking, P-wave flattening, PR prolongation (until sinus arrest with nodal rhythm occurs), QRS widening, shortened QT interval and deep S wave. Finally, a sine-wave ECG pattern develops, which deteriorates to asystole, occurring at plasma potassium levels of 7 mmol/l or greater.
For mild hyperkalemia (i.e. plasma K⁺ > 4.5 and < 5.5 mmol/l) treatment usually involves reducing the potassium intake, correcting renal failure, and treating the cause (e.g. ceasing NSAIDs or spironolactone). Treatment of severe hyperkalemia (i.e. plasma K⁺ > 5.5 mmol/l) often involves the administration of intravenous glucose and insulin, sodium bicarbonate and calcium chloride (Table 16.19; Tannen, 1986), although nebulized salbutamol (10–20 mg) may also be useful as it can reduce the plasma potassium by 0.6–1.0 mmol/l after 30 minutes and will last for 2 hours (Williams, 1986). Resonium A has the capacity to bind 3.1 mmol of potassium per gram by releasing 3.1 mmol of sodium. Calcium chloride (or gluconate) does not reduce the plasma potassium and is used only to counteract the toxic cardiac effects of hyperkalemia. Since all the methods of reducing the potassium level are only temporary, treatment should also be directed at the underlying cause, and may also include dialysis.

**16.8.5 HYPOCALCEMIA**

Hypocalcemia occurs in up to 70% of patients in ICU (Desai, Carlson and Geheb, 1988; Zaloga and Chernow, 1986). It is defined as a total plasma calcium less than 2.2 mmol/l and may be caused by either a reduced ionized or protein-bound calcium. In critically ill patients calcium loss due to increased tissue sequestration of calcium may be associated with pancreatitis, sepsis, burns or toxic shock (Chernow et al., 1982a; Zaloga, 1991). However, hypocalcemia is only important clinically when the physiologically active, ionized fraction (40% of total) is reduced. Ionized calcium is lowered by alkalosis, by high circulating free fatty acids, as in pancreatitis or sepsis, and by agents that chelate calcium, such as albumin infusions, bicarbonate administration and high citrate loads administered with massive blood transfusion (Zaloga and Chernow, 1986). Ionized hypocalcemia (less than 1.15 mmol/l) occurs in 15–20% of patients in the ICU (Zaloga, Chernog and Cook, 1985) but cannot be predicted by estimation of either total serum calcium or of ionized calcium corrected for pH and serum albumin concentration (Desai, Carlson and Geheb, 1987).

Common causes of hypocalcemia in head-injured patients include respiratory alkalosis, sepsis, hypomagnesemia and rhabdomyolysis in the polytrauma patient. Hypomagnesemia impairs both parathyroid hormone (PTH) release and action. Critically ill patients who are septic or who have unexplained ionized hypocalcemia may be vitamin-D-deficient, have an impairment of vitamin D metabolism or action, or have impaired release of PTH (Desai, Carlson and Geheb, 1987; Zaloga et al., 1984; Knochel, 1977). Hyperphosphatemia in severe rhabdomyolysis causes hypocalcemia by calcium precipitation or impaired vitamin D metabolism.

(a) **Clinical features**

Clinical manifestations of ionized hypocalcemia are generally not evident until ionized calcium is less than 0.7 mmol/l. Signs include hypotension, impaired ventricular function, bradycardia, bronchospasm and laryngospasm. Weakness, tetany, hyper-reflexia, agitation, confusion and seizures may occur, but are less common than in patients with hypoparathyroidism. The response to digoxin and catecholamines may also be impaired by hypocalcemia.

(b) **Treatment**

Treatment is only undertaken if the patient is symptomatic. Acute hypocalcemia may be corrected by intravenous 10% calcium chloride (0.7 mmol calcium per milliliter). Before initiating treatment, hypomagnesemia should be excluded, as hypomagnesemic patients respond poorly to calcium. Calcium chloride 10%, 5 ml intravenously (i.e. 3.4 mmol) or 10 ml of calcium gluconate 10% (i.e. 2.3 mmol) may be administered over 3–5 minutes. Rapid infusion of calcium may result in unpleasant flushing, hypertension,

<table>
<thead>
<tr>
<th>Table 16.19</th>
<th>Treatment of life-threatening hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
</tr>
<tr>
<td>Dextrose and insulin</td>
<td>50 g dextrose</td>
</tr>
<tr>
<td></td>
<td>20IU insulin</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>50–100 mmol</td>
</tr>
<tr>
<td>Calcium chloride (10%)</td>
<td>5–10 ml (3.4–6.8 mmol)</td>
</tr>
<tr>
<td>Oral or rectal resonium A</td>
<td>50 g</td>
</tr>
<tr>
<td>Nebulized salbutamol</td>
<td>10–20 mg</td>
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bradycardia and atrioventricular nodal blockade, and may precipitate digitalis toxicity. Persistent unexplained hypocalcemia requires further evaluation to exclude hypoparathyroidism and vitamin D deficiency.

16.8.6 HYPOPHOSPHATEMIA

Hypophosphatemia is defined as a fasting plasma phosphate level of less than 0.8 mmol/l. Moderate hypophosphatemia exists if the phosphate level is between 0.32 and 0.8 mmol/l (Bohannon, 1989). Severe hypophosphatemia exists when the plasma level is less than 0.32 mmol/l (Hayek and Eisenberg, 1989). It may be caused by decreased intake, increased excretion or intracellular redistribution.

Parenteral or enteral nutrition induces a transcellular shift of phosphate from the ECF to the ICF via insulin-mediated intracellular transport of phosphate with glucose (‘refeeding syndrome’; Solomon and Kirby, 1990; Aubier et al., 1985). Respiratory alkalosis causes intracellular shift of phosphate by stimulating glycolysis and intracellular phosphate trapping. Hypophosphatemia induced by transcellular shift is associated with hypophosphaturia and the normal body stores of phosphate are maintained. Hypokalemia and hypomagnesemia may also promote hypophosphatemia by impairing renal phosphate reabsorption.

(a) Clinical features

Clinical manifestations of hypophosphatemia are not usually seen unless levels are markedly reduced, i.e. to less than 0.3 mmol/l. Patients who are hyperventilated or malnourished, alcoholic, septic or have diabetic ketoacidosis are at increased risk of severe hypophosphatemia, and diaphragmatic weakness and respiratory failure may occur (Lau, 1986).

(b) Investigations

Patients with hypophosphatemia in the absence of alkalosis and a urinary phosphate greater than 25 mmol/d, are suffering excessive renal loss. If the urinary loss is less than 5 mmol/d, then renal loss is excluded (Knochel, 1981). If hypophosphatemia is associated with hypercalcemia, hyperparathyroidism should be considered.

(c) Treatment

Hypophosphatemia is usually asymptomatic. If hypophosphatemia is due to compartmental shift resulting from respiratory alkalosis or to catecholamine infusions, even though phosphate levels may decrease to 0.4 mmol/l, treatment with phosphate may not be necessary. Generally, however, in the critically ill patient, the phosphate level should be kept above 0.8 mmol/l, to ensure adequate respiratory, cardiac and intracellular function. Phosphate at 40–80 mmol/24 h may be administered orally or intravenously as sodium or potassium phosphate (Chernow et al., 1989). If an intravenous solution is administered as the dihydrogen salt, an equimolar amount of Na⁺ or K⁺ and 80% of the molar amount as H⁺ is administered with the phosphate. If it is administered as the monohydrogen salt, then twice the molar amounts of sodium or potassium are administered with the phosphate.

16.8.7 HYPOMAGNESEMIA

Hypomagnesemia is defined as a plasma level of less than 0.7 mmol/l and is associated with a 24-hour urine magnesium of less than 1 mmol/l in the absence of abnormal renal magnesium losses. This is a common electrolyte disturbance in ICU patients (Chernow et al., 1982b; Kingston, Al-Siba and Skooge, 1986; Paymaster, 1976) and is caused by decreased intake or increased loss. The causes are similar to those for hypophosphatemia. Common causes in patients with head injury include diuretics (osmotic and non-osmotic), diabetes insipidus, respiratory alkalosis, sepsis and certain drugs including aminoglycosides.

(a) Clinical features

Clinical features tend only to occur when the plasma level is less than 0.5 mmol/l (Table 16.20; Paymaster, 1976; Fishman, 1965; Whang et al., 1984). The clinical diagnosis of magnesium depletion is difficult because only 1% of total body magnesium is contained in plasma and because total plasma magnesium does not accurately reflect the ionized fraction (55% of the total), which is the physiologically active form. The remaining plasma magnesium is bound to protein (33%) or is chelated. Measurement of ionized magnesium is not available. Hypomagnesemia may be associated with hypokalemia (due to renal loss),

<table>
<thead>
<tr>
<th>Table 16.20 Clinical features of hypomagnesemia</th>
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<tbody>
<tr>
<td>Neurological</td>
</tr>
<tr>
<td>● Confusion, irritability, delirium, convulsions</td>
</tr>
<tr>
<td>● Ataxia, athetoid movements</td>
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<tr>
<td>● Weakness, tremors, cramps, tetany</td>
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<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>● Tachyarrhythmias (torsades de pointes)</td>
</tr>
<tr>
<td>● Enhanced digoxin toxicity</td>
</tr>
<tr>
<td>Biochemical</td>
</tr>
<tr>
<td>● Resistant hypokalemia, hypocalcemia, renal tubular acidosis</td>
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hypokalemia (due to impaired release of PTH and impaired peripheral action of PTH) and renal tubular acidosis (RTA). In one study, more than 40% of hypokalemic patients revealed an associated hypomagnesemia (Gums, 1987).

(b) Investigations

With magnesium deficiency, the renal loss is usually minimal (0.05–0.10 mmol/d). An intravenous dose of magnesium is normally excreted in the urine in 24 hours; thus 30 mmol administered over 8–12 hours and a 24-hour collection of urine can be used as an estimate of magnesium balance. Normally more than 60% of the dose is excreted; if less than 50% is excreted the patient has a magnesium deficiency (Salem, Munoz and Chernow, 1991).

(c) Treatment

Symptomatic hypomagnesemia (e.g., causing refractory arrhythmias or seizures) is treated by intravenous bolus injection of 5–10 ml of 49.3% MgSO$_4$ solution (2 mmol/ml magnesium; Cohen, Gambill and Eggers, 1977). Less severe degrees of hypomagnesemia are treated by adding magnesium salts to the enteral or parenteral solutions.

16.9 Special fluid and electrolyte problems in the neurosurgical patient

16.9.1 NEUROGENIC PULMONARY EDEMA

Patients with a variety of central nervous system disorders, including head injury, may develop acute pulmonary edema in the absence of cardiopulmonary disease or other apparent causes. This neurogenic pulmonary edema may follow head trauma (Ducker, Simmons and Martin, 1969), intracranial tumors, subarachnoid hemorrhage, stroke, seizures (Bonbrest, 1965), Guillain-Barré syndrome and meningitis. Although the cause is unclear, it is thought that neurogenic pulmonary edema may be due to massive alpha-adrenergic discharge (Wray and Nicotra, 1978). The sympathetic discharge increases systemic and pulmonary vascular resistances. This transiently increases left atrial pressure and pulmonary artery wedge pressure (PAWP), and pulmonary capillary disruption occurs. An animal model has also implicated endothelial injury in its development (Minnear et al., 1987). The altered pulmonary capillary permeability results in the accumulation of pulmonary edema fluid, which has a high protein content.

A previously healthy 24-year-old male was admitted to ICU following a gunshot wound to the head (Figure 16.15(a)). Frothy pulmonary edema fluid issued from the endotracheal tube and marked oxygen desaturation was noted on pulse oximetry. He required ventilation with 100% O$_2$ and positive end-expiratory pressure (PEEP); chest X-ray confirmed the presence of pulmonary edema (Figure 16.15(b)). The CVP was 10 mmHg. A Swan–Ganz catheter was inserted to facilitate fluid management in this patient, who subsequently made a satisfactory recovery.

The treatment of neurogenic pulmonary edema is similar to the treatment of adult respiratory distress syndrome (ARDS) from any cause. In addition to
ventilatory support with positive-pressure ventilation and positive end-expiratory pressure (PEEP), fluid management is of the utmost importance. Fluid intake should be crystalloid solution, rather than protein-containing solutions, and should be minimal. If PAWP is monitored, it should be kept low (5–7 mmHg) to minimize further extravasation of proteinaceous fluid. If mean arterial pressure or perfusion is inadequate, inotropes should be used to maintain cerebral and peripheral tissue perfusion. For a detailed account of the respiratory management of neurogenic pulmonary edema see Chapter 17.

16.9.2 NON-KETOTIC HYPERGLYCEMIC HYPEROSMOLAR COMA
Non-ketotic hyperglycemic hyperosmolar coma (NHHC) may occur following head injury, intracerebral hemorrhage, brain tumor or cerebral infarction (Park, Meacham and Netsky, 1976). About two-thirds of patients who develop NHHC have no history of diabetes mellitus. Many have intercurrent infections, or are taking drugs that alter glucose tolerance, such as steroids, phenytoin and thiazides, or are dehydrated.

The diagnosis of NHHC is based on the findings of hyperglycemia, glycosuria and a plasma osmolality greater than 330 mOsm/l in the absence of ketosis. Patients who have NHHC and are dehydrated because of the osmotic diuresis are often potassium-depleted. They may also have evidence of prerenal renal failure which, if untreated, can progress to acute renal failure.

Treatment is primarily correction of dehydration and hypertonicity. Physiological saline is used for volume replacement, together with careful monitoring of serum and urine electrolytes and osmolality. After sodium deficits have been corrected with physiological saline, half physiological saline or dextrose/saline (4% dextrose in N/5 saline) should be used to replace water deficits. The hyperglycemia is usually responsive to insulin.

16.9.3 SPINAL-CORD-INJURED PATIENTS
Cervical cord injury may cause spinal shock due to anatomical or functional transection of the cord and this may last for 1–3 weeks. The interruption to sympathetic outflow results in vasodilatation, pooling of blood in peripheral vascular beds and hypotension. Reflex bradycardia also occurs, because the cardiac accelerator nerves arise from segments T1–T4. The hypotensive phase is usually preceded by a rise in systemic pressure over 3–4 minutes as a result of widespread initial sympathetic activation. This may be particularly important in the presence of brain injury, because cerebral autoregulation may be overcome and cerebral edema exacerbated.

Because the heart cannot compensate for overt transfusion or increased venous return, careful monitoring is mandatory. Circulating volume is critical, and observation of the CVP or PAWP to fluid challenge may be used to assess the volume status of the patient.

Electrolyte abnormalities may develop as a result of immobility and absent muscle activity. Mobilization of calcium may increase, causing hypercalcemia and hypercalciuria, from about 10 days after injury. The increase in serum calcium levels may predispose to ventricular arrhythmias during anesthesia. Thus calcium levels should be measured preoperatively in these patients.

16.10 Conclusions

- The goal of fluid therapy in the critically ill patient is to restore and maintain normal O₂ delivery to the tissues before the sequelae of shock (including secondary neuronal damage) occur.
- Abnormalities of fluid, electrolyte and acid–base metabolism may result in alterations in neurological status and thus interfere with neurological assessment, as well as contributing to secondary neuronal damage and thus worsening outcome.
- Maintenance of normal cerebral perfusion pressure (CPP) is a key aspect of the management of patients with head injuries, since impairment of cerebral autoregulation following traumatic brain injury causes cerebral oxygen delivery to be influenced by CPP.
- Correction of hypovolemia is best achieved with colloid, physiological saline or blood transfusion (if necessary). At least two animal studies have indicated that the amount of sodium infused does not adversely affect intracranial pressure (Ramming et al., 1994). In one of the studies, infusion of a dextrose solution in amounts similar to the infused sodium load significantly decreased serum sodium, increased brain edema and decreased neurological outcome (Shapira et al., 1995).

16.11 References


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