6.6 Fluids and electrolytes

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Key points

- Water is essential for survival and has many functions in the body.
- Regulation of body fluid is under tight homeostatic control; maintenance of fluid balance is an important aspect of dietetic management.
- Disorders of electrolyte and water balance are common in clinical practice, particularly as a result of surgery, trauma, disease and drug therapy.
- Managing fluids and electrolytes is complex and can be challenging; it requires extensive knowledge and experience, usually from a lead clinician.

Humans can survive for several weeks without food, but cannot withstand water deprivation for more than a few days. Water has many vital functions in the body, including:

- As a solvent for ions and molecules.
- As a transport medium, especially for the excretion of osmotically active solutes such as urea and salts.
- As a lubricant.
- In temperature regulation.

Body fluids

Water is the most abundant body fluid and accounts for approximately 60% total body weight in men and 50% in women. Lean body tissue has a high water content of 75%, in contrast to 10% in adipose tissue. In obese patients, lean body weight should be used to determine total body water (TBW).

Body fluid compartments

Total body water has two main compartments: intracellular fluid (ICF, 67%) within the cells, and extracellular fluid (ECF, 33%) outside the cells. Extracellular fluid is further subdivided into interstitial fluid, which includes the fluid surrounding the cells and the fluid of the lymphatic system, and intravascular fluid, the fluid portion of the blood (plasma volume) (see Figure 6.6.1).

Movement and regulation of fluids

A number of processes determine the movement of water and other substances between body fluid compartments. Cell membranes can be permeable, semi-permeable or impermeable to certain molecules, and act as an effective barrier between the cell and interstitial fluid by controlling the exchange of solutes and water. The movement of water across semi-permeable membranes is known as osmosis; water moves into an area of higher solute concentration to achieve equilibrium.

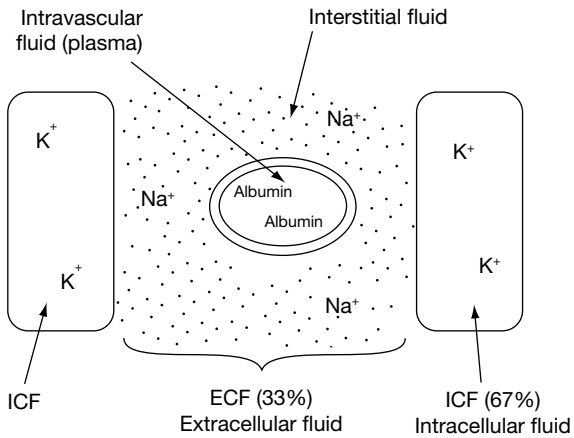

Figure 6.6.1 Body fluid compartments

SECTION 6

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Osmotic pressure of a solution is the pressure by which water is drawn into it through the semi-permeable membrane, and is often used to express the concentration of the solution (the more solutes, the greater its osmotic pressure). Each fluid compartment contains one principle solute that determines the osmotic pressure. The effective osmotic pressure of a solution is also known as tonicity, and is maintained by the following factors:

- Potassium retains water in the intracellular space.
- Sodium retains water in the extracellular space.
- Plasma proteins retain water in the intravascular space; albumin is the most important plasma protein in maintaining oncotic pressure. Oncotic pressure is the osmotic pressure of a solution with colloids (proteins) as the main solute.

Regulation of extracellular fluid compartment

The volume of the ECF is controlled by the sodium content, and homeostatic mechanisms are directed at controlling the retention or excretion of sodium. Sodium homeostasis depends on renal excretion. An increased intake in sodium leads to a higher ECF osmolarity, which triggers thirst and the release of antidiuretic hormone (ADH) (vasopressin). The presence of ADH leads to the passive reabsorption of water by the kidneys and allows osmolarity to return to normal by increasing the ECF volume. This in turn triggers a different pathway to stimulate sodium and water loss, and the ECF will return back to normal. Altered ECF (changes in blood volume and subsequently blood pressure) can be detected by volume receptors in the large veins and atrium of the heart. The volume receptors trigger a pathway that affects ADH release and regulates the kidneys' production of urine. The kidneys also play a significant role in controlling the ECF volume. A reduction in blood pressure reduces renal blood flow and increases the secretion of renin from the juxtaglomerular apparatus, a structure within the kidney that is important in regulating blood pressure, body fluid, and electrolytes. This results in the production of angiotensin II, which in turn stimulates the adrenal cortex to release aldosterone, causing sodium and water retention (renin–angiotensin–aldosterone system).

Regulation of intracellular fluid compartment

The cell membrane is permeable to water and large macromolecules, but impermeable to electrolytes (with the exception of the electrical gradient formed by pumping sodium (Na^+) and potassium (K^+) across the membrane through active transport). This means that the ICF volume is sensitive to changes in the sodium concentration of the ECF. A high ECF sodium concentration will result in water moving out of the cells by osmosis, causing cells to shrink; with low ECF sodium concentration, water will move into the cells, and they swell. Cell function can be impaired as a result of the change in cell volume, and the brain in particular can be affected by swelling. Maintaining extracellular fluid osmolarity is therefore paramount.

Fluid balance

Water homeostasis is dependent on the control of water intake and water output, and is regulated on three levels:

- Gastrointestinal tract – fluids and electrolytes are produced and mostly reabsorbed along the GI tract.
- Kidneys – sodium and water excretion is largely regulated via ADH.
- Renin–angiotensin–aldosterone system – this regulates sodium excretion and blood pressure.

If any of these systems fail or begin to fail, fluid and electrolyte imbalances may occur.

Disorders of sodium and water balance

Disorders of sodium (and other electrolytes) and water balance are a common occurrence in clinical practice, particularly as a result of surgery, trauma, disease and drug therapy. Appropriate treatment to correct any disorder needs to be based on a careful physical examination and interpretation of both serum and urine biochemistry. Any disorders of sodium and water balance will be reflected in the serum sodium concentration.

Sodium deficit

Sodium cannot be lost from the body without water. A sodium deficit may occur as a result of gastrointestinal losses, e.g. diarrhoea, diuretic therapy, Addison's disease, diabetic ketoacidosis, ascites and chronic kidney disease. The result is a decrease in the ECF volume, with associated hypertension and tachycardia. If the sodium deficit is severe, there is a risk of circulatory failure and renal failure, although ICF levels are unaffected. In the case of a sodium deficit, it is the total amount of ECF sodium that is important. There may be little change in the serum sodium concentration as water loss may increase as a compensatory effect. Sodium deficiency is normally treated with intravenous infusion of 0.9% sodium chloride.

Sodium excess

This can be the result of reduced sodium excretion, e.g. renal sodium retention secondary to kidney disease, primary or secondary aldosteronism; another cause can be the intravenous administration of sodium bicarbonate to correct metabolic acidosis in the clinical setting; or large volumes of 0.9% saline where there are hypotonic losses such as in diabetes mellitus. Sodium retention leads to expansion of the ECF volume where oedema and hypertension may be present. Increased serum sodium may stimulate thirst.

Water deficit

Water deficit usually results from an inadequate intake, often due to the inability to drink, inadequate intravenous fluid or excessive loss. Thirst and oliguria with highly concentrated urine will normally be present.

There is less effect on the ECF volume than from the loss of a similar volume of isotonic fluid; hypernatraemia is usually present.

Water excess

This is usually caused by either impaired water excretion, e.g. inappropriate (increased ADH secretion or renal failure) or excessive water intake, usually in association with impaired excretion. If severe, cerebral overhydration and oedema can occur; hyponatraemia is usually present.

Sodium

Sodium (Na^+) is the principal extracellular cation and controls the volume of the extracellular fluid in the body. The average dietary sodium intake in the UK is 8.1 g/day (138 mmol/day). A small amount of sodium is lost via sweat and faeces; the majority is excreted via the kidneys. Urinary sodium levels usually reflect dietary sodium intake, unless there are significant extrarenal losses such as diarrhoea or vomiting.

Hyponatraemia

Hyponatraemia is defined as a serum sodium level of <135 mmol/L. Risk factors include increasing age, lower body weight, thiazide and thiazide-like diuretics, hypotonic intravenous fluids and surgery.

Symptoms

Clinical manifestations of moderate hyponatraemia (serum sodium 125–129 mmol/L) can be nausea, headache and confusion. Severe hyponatraemia (serum sodium level <125 mmol/L) is associated with vomiting, agitation, psychosis and seizures.

Diagnosis and management

The main cause of hyponatraemia is an imbalance between extracellular water and sodium, where water is in excess as opposed to sodium. In order to treat this condition successfully, it is helpful to understand the aetiology of hyponatraemia. Serum osmolality (serum tonicity) describes the amount of chemicals dissolved in the liquid component (serum) of the blood, including sodium, chloride, bicarbonate, protein and glucose, and is used as a first step to categorise hyponatraemia. If a measurement is not available, serum osmolality can be estimated as $2 \times (Na^+ + K^+) + \text{urea} + \text{glucose}$ (mmol/L).

For example $2 \times (Na^+\ 136 + K^+\ 4.2) + \text{urea}\ 5.0 + \text{glucose}\ 4.1 = 287$ mmol/kg H_2O.

Normal serum osmolality is 275–290 mmol/kg H_2O, but reference ranges vary slightly.

Hyponatraemia can be classified as:

- Hypertonic hyponatraemia: serum osmolality >290 mmol/kg H_2O.
  - High serum tonicity, e.g. hyperglycaemia.
- Isotonic hyponatraemia: serum osmolality 275–290 mmol/kg H_2O.
  - Normal serum tonicity, caused by hyperlipidaemia, hyperproteinaemia.
- Hypotonic hyponatraemia: serum osmolality <275 mmol/kg H_2O.
  - Low serum tonicity.

Hypotonic hyponatraemia can occur with decreased, normal or increased existing sodium stores (i.e. hypovolaemic, euvolaemic and hypervolaemic hyponatraemia, respectively) (see Table 6.6.1).

Management of non-hypotonic hyponatraemia

This focuses on the underlying disorder rather than the hyponatraemia itself.

Management of hypotonic hyponatraemia

Treating patients with euvolaemic and hypervolaemic hyponatraemia successfully means eliminating the underlying cause as well as restricting water. In symptomatic hyponatraemia, the use of hypertonic saline

Table 6.6.1 Hypotonic hyponatraemia

States of hypotonic hyponatraemia	Changes in water and/or sodium	Underlying cause
Hypovolaemia	Loss of water and sodium	Renal: urinary sodium >20 mmol/L • Thiazide diuretics, salt-wasting nephropathy • Ketonuria, adrenal insufficiency Extrarenal: urinary sodium <20 mmol/L • Gastrointestinal losses • Excessive sweating, blood loss
Euvolaemia	Increase in water	Hypothyroidism, polydipsia SIADH, post-operative state
Hypervolaemia	Increase in sodium and water	Urinary sodium >20 mmol/L • Renal failure Urinary sodium <20 mmol/L • Disorders associated with oedema (e.g. congestive cardiac failure, liver cirrhosis, nephrotic syndrome)

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

(e.g. 3% NaCl) may be necessary to achieve a satisfactory increase in sodium, and furosemide is often used in combination to limit treatment-induced expansion of extracellular fluid volume. Most patients with hypovolaemic hyponatraemia can be treated successfully with isotonic saline (0.9% NaCl). Correction of serum sodium levels should not exceed 8–10 mmol/L per 24 hours to prevent irreversible brain damage.

Hypernatraemia

Hypernatraemia is defined as a serum sodium level of >145 mmol/L. Patients at risk of developing an elevated serum sodium level are those with a decreased ability to recognise thirst, or those with reduced access to water. This includes infants, the elderly and patients with altered cognitive function or mental status.

Symptoms

Clinical manifestations of moderate hypernatraemia (serum sodium of 151–160 mmol/L) include excessive thirst, anorexia, insomnia and muscle twitching, while severe hypernatraemia (serum sodium level >160 mmol/L) is associated with altered mental status, irritability, seizures and coma.

Diagnosis and management

The main cause of hypernatraemia is an imbalance between extracellular water and sodium, with an excess of sodium. Hypernatraemia can occur with decreased, normal or increased total body sodium (i.e. hypovolaemic, euvolaemic and hypervolaemic hypernatraemia, respectively). In order to treat this condition successfully, it is helpful to understand the aetiology of hypernatraemia (see Table 6.6.2). Treating hypernatraemia successfully means eliminating the underlying cause as well as correcting the lack of water.

When replacing water, fluids should ideally be given orally or enterally via a feeding tube. If there is no enteral access available, fluids should be administered intravenously. Infusates should be hypotonic (e.g. 5% glucose and 0.45% NaCl), and serum sodium levels should not be corrected by >10 mmol/L per 24 hours to avoid cerebral oedema and convulsions.

Potassium

Potassium (K^+) is the principal intracellular cation in contrast to sodium, which is the major extracellular cation. The sodium–potassium ATPase pump in the cell membrane maintains the difference in distribution of the two cations by pumping three sodium ions out of cells in exchange for two potassium ions. The ratio of the potassium concentrations in the extracellular fluids and in the cells is the main determinant of the resting membrane potential, which is essential for normal muscle and neural function. Both hypo- and hyperkalaemia can therefore cause muscle paralysis and potentially fatal cardiac arrhythmias.

Hypokalaemia

A range of clinical conditions can result in hypokalaemia, which may occur with or without potassium loss. It is generally defined as a serum potassium level of <3.5 mmol/L. In case of potassium depletion, the kidney can significantly reduce potassium excretion; insufficient intake is therefore rarely the sole cause for hypokalaemia. Its causes include:

- Hypokalaemia without potassium loss:
  - Alkalosis (results in the movement of K^+ into cells in exchange for an equimolar number of H^+).
  - Insulin excess (drives K^+ into cells, may be more noticeable during the treatment of diabetic ketoacidosis (DKA) or nonketotic hyperglycaemia).
  - Increased cellular uptake (e.g. treatment of megaloblastic anaemia).
  - Refeeding syndrome.
  - Elevated beta2-adrenergic activity (catecholamines regulate potassium entry into cells by increasing the activity of the sodium–potassium ATPase pump).
- Hypokalaemia with potassium loss:
  - Gastrointestinal loss – vomiting, diarrhoea, laxatives.
  - Excess alcohol.

Table 6.6.2 Identifying cause and management of hypernatraemia

States of hypernatraemia	Changes in water and/or sodium	Underlying cause
Hypovolaemia	Loss of water and sodium	Renal: >20 mmol/L urinary sodium • Renal failure • Diuretics Extrarenal: <20 mmol/L urinary sodium • Gastrointestinal losses • Excessive sweating, fever • Burns
Euvolaemia	Loss of water	Diabetes insipidus
Hypervolaemia	Increase in sodium	Cushing's syndrome Primary hyperaldosteronism Excess administration of sodium-containing IV fluids

- Urinary loss – primary aldosteronism, type 1 and 2 renal tubular acidosis, diuretics, corticosteroids, leukaemia, hypomagnesaemia, polyuria, excess intake of liquorice.

Management

The immediate goal of treatment is to raise serum potassium to a safe level and for the underlying cause to be identified and treated. The amount of potassium required depends on the severity of hypokalaemia, clinical situation, renal function and if the cause of hypokalaemia has been addressed. In mild to moderate hypokalaemia, potassium can often be given orally, but may result in gastrointestinal side effects, e.g. nausea, vomiting and diarrhoea. Potassium is often administered intravenously as potassium chloride (KCl) in a controlled manner to reduce the risk of hyperkalaemia.

Hyperkalaemia

Acute, severe hyperkalaemia requires urgent treatment. The threshold for emergency treatment varies, but most guidelines recommend that emergency treatment be given if the serum potassium is ≥6.5 mmol/L with or without ECG changes. Hyperkalaemia occurs in a variety of clinical settings, but is usually a result of renal failure. Dietary-induced hyperkalaemia generally involves concurrent renal insufficiency. Causes of hyperkalaemia include:

- Increased potassium release from cells:
  - Insulin deficiency – DKA, hyperosmolar / hyperglycaemic state.
  - Metabolic acidosis.
  - Pseudohyperkalaemia, e.g. release of intracellular K^+ during phlebotomy.
  - Catabolic states, e.g. tumour lysis syndrome and rhabdomyolysis (recent history of muscle damage relating to seizures, ischaemia, exercise, trauma or medications such as statins, etc.).
  - Drug related (e.g. beta blockers, digoxin and suxamethonium).
  - Hyperkalaemic periodic paralysis.
- Reduced urinary potassium excretion:
  - Acute and chronic kidney disease.
  - Hypoaldosteronism.
  - Addison's disease (primary adrenal insufficiency).
  - Certain drugs, e.g. angiotensin inhibitors, non-steroidal anti-inflammatory drugs, heparin and potassium-sparing diuretics (e.g. Spironolactone).

Management

In acute hyperkalaemia, the aim is to protect the myocardium and increase intracellular potassium. There is limited evidence to guide treatment, and practice varies. However, treatment generally includes:

- Intravenous calcium salt (gluconate or chloride) to temporarily protect against myocardial excitability.
- Intravenous insulin–glucose infusion to reduce serum potassium concentrations.

Any prescribed drugs exacerbating hyperkalaemia should be discontinued if possible. Chronic hyperkalaemia is usually managed by using cation-binding resins, diuretics (where appropriate) and dietary restriction of potassium. Renal replacement therapy, such as haemodialysis, peritoneal dialysis and kidney transplantation, may be necessary.

Calcium

Calcium (Ca^{2+}) is the body's most abundant divalent cation and has vital roles in regulating neuromuscular function, hormone release, myocardial contractibility and enzyme activity. The most significant effect of altered plasma calcium concentrations is related to the excitability of the nervous system. Serum calcium is under tight homeostatic control; hence, even when calcium intake is inadequate, blood calcium remains normal, but at the expense of bone loss. About half of the total serum calcium is bound to protein, and the remaining free ionised calcium is physiologically active. Therefore, before making a diagnosis of hypercalcaemia or hypocalcaemia, serum calcium levels must be corrected for albumin levels. Fibre, in general, and the binders phytate and oxalate inhibit calcium absorption, but unless consumed in excess they are not a significant contributor to calcium loss. Severe hypocalcaemia and hypercalcaemia are both potentially life threatening, requiring urgent treatment.

Hypocalcaemia

Causes of hypocalcaemia include:

- Low parathyroid hormone (PTH).
  - Hypoparathyroidism.
  - Hypomagnesaemia.
- Hungry bone syndrome (post parathyroidectomy).
- Acute pancreatitis.
- Vitamin D deficiency.
- Hyperphosphataemia.
- Large-volume blood transfusions.
- Critical illness.
- Drugs (e.g. bisphosphonates).
- Rhabdomyolysis.
- Refeeding syndrome.

Management

Acute hypocalcaemia is normally treated with intravenous calcium gluconate, but it is also essential to determine the underlying cause and commence specific treatment as early as possible. Magnesium deficiency (which reduces parathyroid hormone secretion) or alkalosis should be corrected if present. In chronic hypocalcaemia, treatment is designed to increase intestinal calcium absorption through calcium and vitamin D supplementation.

Hypercalcaemia

The most common causes of hypercalcaemia are malignancy and primary hyperparathyroidism. Other causes include:

- Prolonged immobilisation.
- Drug related (e.g. lithium; calcium co-prescribed with antacid, milk-alkali syndrome, or vitamin D intoxication; thiazide diuretics; hypervitaminosis A).
- Granulomatous disease including tuberculosis and sarcoidosis.
- Adrenal insufficiency.
- Chronic kidney disease.

Management

Severe hypercalcaemia often occurs in conjunction with ECF depletion, and expansion of the ECF compartment with intravenous fluids may be effective in slowly reducing the serum calcium levels; however, it is usually not the only treatment, and it may lead to fluid overload. The use of loop diuretics is controversial, but they are sometimes used to treat hypercalcaemia once hypovolaemia has been corrected. Intravenous infusion of bisphosphonates may be required for long-term control in symptomatic or more severe hypercalcaemia. Any prescribed drugs exacerbating hypercalcaemia should be discontinued if possible.

Mild hypercalcaemia may not require immediate therapy, but drugs contributing to hypercalcaemia should be stopped or reduced if appropriate, and serum levels of calcium repeated. Treatment of chronic hypercalcaemia depends on the primary cause, and a referral should be made to the relevant specialist.

Phosphate

Phosphate (PO_4^{3-}) is the body's most abundant trivalent anion and is essential for all intracellular processes and for the structural integrity of cell membranes. It regulates the affinity of haemoglobin for oxygen and thus regulates oxygen delivery to tissues. It is also important in the renal acid–base buffer system.

Hypophosphataemia

A range of clinical conditions can result in hypophosphataemia, including:

- Redistribution
  - Respiratory alkalosis.
  - Glucose/insulin therapy.
  - Sepsis.
  - Catecholamines.
  - Rapid cell uptake (e.g. hungry bone syndrome, acute leukaemia).
  - Refeeding syndrome.
  - Recovery from DKA.
- Increased renal excretion
  - Metabolic acidosis.
  - Volume expansion.
  - Diuretics.
  - Corticosteroids.
  - Tubular disorders.
  - Hyperparathyroidism.
- Decreased intestinal absorption:
  - Malabsorption.
  - Phosphate-binding agents.
  - Vitamin D deficiency.
  - Secretory diarrhoea and steatorrhoea.
  - Vomiting.
  - Antacid abuse.

Management

Acute management is usually only necessary with moderate to severe hypophosphataemia. Intravenous administration of phosphate can lead to extraskeletal calcification, and oral supplementation is therefore often safer; however, absorption can be unpredictable.

Hyperphosphataemia

Causes of hyperphosphataemia include:

- Renal insufficiency.
- Hypoparathyroidism.
- Hypovolaemia.
- Cell breakdown (release of phosphorus into ECF), e.g. rhabdomyolysis, haemolysis, chemotherapy, tumour lysis syndrome, profound catabolic stress.
- Increased intake:
  - Phosphate enemas and laxatives.
  - Vitamin D intoxication.

Management

The treatment of acute hyperphosphataemia includes volume expansion, oral phosphate binders and dialysis; nevertheless, in normal or mild to moderate kidney disease, it is usually self-resolving, owing to the continued ability of the kidney to excrete phosphate loads. Chronic hyperphosphataemia is usually due to chronic kidney disease, and is treated with dietary phosphate restriction and oral phosphate binders.

Magnesium

Magnesium (Mg^{2+}) is the second most abundant intracellular cation. It is a co-factor in more than 300 enzyme reactions and is important for the synthesis of proteins, RNA and DNA. It is essential for muscle contractions and relaxation, heart rhythm, nerve function, vascular tone and bone formation. Circulating magnesium is under close homeostatic regulation, primarily through renal reabsorption and excretion.

Hypomagnesaemia

Serum magnesium is a poor predictor of total body magnesium content, because only 0.3% is found in serum. Only 30–50% of total dietary magnesium is absorbed, and other nutrients such as fibre, phytates, oxalates, and phosphates can bind the cation and decrease its absorption. Causes of hypomagnesaemia include:

- Reduced intake (e.g. malnutrition, alcoholism).
- Gastrointestinal losses:

  - Vomiting, diarrhoea, malabsorption (e.g. IBD/coeliac disease), short bowel syndrome, intestinal fistulae, excessive use of laxatives, long-term use of proton pump inhibitors.
- Renal losses.
- Renal tubular disorders.
- Drugs (loop and thiazide diuretics, tacrolimus, nephrotoxins e.g. cyclosporine, cisplatin, pentamidine, amphotericin and aminoglycosides).
- Endocrine.
- Diabetes mellitus/DKA.
- Hyperthyroidism.
- Hyperaldosteronism.
- Hungry bone syndrome.
- Others
  - Acute pancreatitis.
  - Refeeding syndrome.
  - ECF expansion.

Management

There are no universal guidelines for repletion of magnesium, and varying practices exist. Magnesium sulphate ($MgSO_4$) is most commonly used for intravenous administration. Intravenous repletion should be given slowly, over a period of hours. A slow rate of infusion is essential as the renal reabsorption threshold is affected by plasma magnesium concentrations; abrupt elevation above the normal range will reduce retention, and up to 50% of the infused magnesium will be excreted in the urine. The absorption of magnesium from the gastrointestinal tract is poor, and magnesium salts can cause diarrhoea, which leads to further electrolyte losses. Mild hypomagnesaemia is often treated by giving oral magnesium supplements in divided doses three to four times per day to reduce their laxative side effects. It should be noted that sufficient renal function is required prior to providing magnesium supplementation.

Hypermagnesaemia

Causes of hypermagnesaemia include:

- Kidney disease – acute or chronic.
- Administration of magnesium-containing drugs or salts (e.g. antacids, laxatives and enemas).
- Iatrogenic (e.g. high doses of magnesium supplementation given in error).
- Tissue breakdown – rhabdomyolysis, burns, DKA.

Management

Treatment is initially by removing the underlying cause and then by removing excess magnesium. If this is associated with renal disease, dialysis may be necessary. In severe hypermagnesaemia, intravenous calcium may be given to counteract the cardiac effects of magnesium.

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Further reading

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