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CONTENTS 21.2.1 Disorders of water and sodium homeostasis 4729 Michael L. Moritz and Juan Carlos Ayus 21.2.2 Disorders of potassium homeostasis 4748 John D. Firth 21.2.1 Disorders of water and sodium homeostasis Michael L. Moritz and Juan Carlos Ayus ESSENTIALS Regulation of water balance and sodium disorders Water intake and the excretion of water are tightly regulated processes that are able to maintain a near-constant serum osmolality. Sodium disorders (dysnatraemias—hyponatraemia or hypernatraemia) are almost always due to an imbalance between water intake and water excretion. Understanding the aetiology of sodium disorders depends on under- standing the concept of electrolyte-free water clearance—this is a con- ceptual amount of water that represents the volume that would need to be subtracted (if electrolyte-free water clearance is positive) or added (if negative) to the measured urinary volume to make the electrolytes contained within the urine have the same tonicity as the plasma electrolytes. It is the concentration of the electrolytes in the urine, not the osmolality of the urine, which ultimately determines the net excretion of water. Hyponatraemia Hyponatraemia, defined as a serum sodium concentration of less than 135 mmol/litre, is a common electrolyte disorder. It is al- most invariably due to impaired water excretion, often in states where antidiuretic hormone release is (1) a normal response to a physiological stimulus such as pain, nausea, volume depletion, postoperative state, or congestive heart failure; or (2) a patho- physiological response as occurs with thiazide diuretics, other types of medications, or in the syndrome of inappropriate diuresis; with both often exacerbated in hospital by (3) inappropriate iatrogenic administration of hypotonic fluids. Clinical features—these can range from the patient who is en- tirely asymptomatic at one end of the spectrum to hyponatraemic encephalopathy—most commonly manifesting with nausea, vomiting,

and headache—at the other. Cerebral demyelination is a serious complication associated with hyponatraemia and its treat- ment, at its worst manifesting as pseudocoma with a ‘locked in’ state. Children and premenopausal women are at particular risk of poor outcomes, as are those who are hypoxic at presentation. It is now recognized that even mild chronic hyponatraemia is as- sociated with subtle neurological impairment, leading to falls and associated bone fractures in the elderly, and is an independent risk factor for mortality in both ambulatory and hospital settings. Management approach—the first priority is to exclude a hyperosmolar state and verify whether the patient is hypotonic, by (when possible) measuring the serum osmolality. The diagnostic approach is further based on the history, clinical assessment of the patient’s volume status, and estimation of urinary electrolytes. Key issues are to recognize that (1) hyponatraemic encephalopathy is a medical emergency that should be diagnosed and treated promptly with hypertonic saline to prevent death or devastating neurological complications; but also (2) that patients who are asymptomatic do not require immediate treatment with hypertonic saline, whatever their level of serum sodium. Precipitating causes (e.g. thiazide diur- etics) should be withdrawn when possible. Practical management—algorithms, even if complex, cannot ac- curately predict a patient’s response to treatment of hyponatraemia: close monitoring of serum sodium is essential. Patients with sus- pected hyponatraemic encephalopathy, with either mild or advanced symptoms, children or adults, should receive a 2 ml/kg bolus of 3% NaCl with a maximum volume of 100 ml. A single bolus would result in at most a 2 mmol/litre acute rise in serum sodium, which would quickly reduce brain oedema. The bolus could be repeated one or two times if symptoms persist. The advantage of this approach over a continuous infusion of 3% NaCl is that there is a controlled and immediate rise in serum sodium and there is little or no risk of inad- vertent overcorrection, as can occur if a 3% NaCl infusion runs at an excessive rate or for too long. Cerebral demyelination—this is a serious complication that has been associated with the correction of severe and chronic hyponatraemia, hence all patients receiving an infusion of 3% saline

 should have their serum sodium measured at least every 2 h until they are clinically stable and the serum sodium values are stable, with appropriate modification of treatment in response to the measure- ments. Failure to do so, and reliance on a calculated infusion rate, can lead to significant patient injury from an excessive increase in serum sodium. Prevention—hyponatraemia is usually iatrogenic and can be avoided or detected as follows: (1) hypotonic fluids should never be administered following surgery unless used to correct a free-water deficit—0.9% (normal) saline (NaCl) should be given postoperatively if parenteral fluids are indicated; (2) all hospitalized patients should be considered at risk for the development of hyponatraemia and should not be given hypotonic fluids unless a free-water deficit is present or if ongoing free-water losses are being replaced; and (3) patients taking thiazide diuretics, especially older people, should be weighed before and after starting therapy and serum electrolytes monitored to detect water retention and the development of hyponatraemia. Hypernatraemia Hypernatraemia, defined as a serum sodium concentration greater than 145 mmol/litre, is a common electrolyte disorder that occurs when water intake is inadequate to keep up with water losses. Since the thirst mechanism is such a powerful stimulus, hypernatraemia almost invariably occurs in the context of an illness and care that re- stricts the patient’s access to water. Clinical features—these are mainly related to central nervous system dysfunction caused by cerebral dehydration and cell shrinkage. Management approach—the first step in evaluation is to take a de- tailed history focusing on fluid intake and losses. To assess urinary water losses, it is

necessary to measure the urinary cationic electro- lytes (sodium and potassium) and the urinary osmolality, remem- bering that the urinary osmolality alone cannot always determine the presence or absence of electrolyte-free water losses in the urine, the reason being that water can be excreted with nonelectrolyte osmoles or with electrolyte osmoles. Practical management—needs to be guided by the following principles: (1) correction of underlying deficits in circulatory blood volume by infusion of 0.9% saline; (2) correction of chronic hypernatraemia at a pace that avoids therapy-induced cerebral oe- dema, which requires an understanding of both the initial water deficit and of ongoing water losses if the patient is polyuric; (3) ad- ministration of water by drinking or feeding tube is preferable to treatment with intravenous fluids if possible; (4) glucose-containing solutions should be avoided if possible; (5) as for the treatment of hyponatraemia, algorithms cannot accurately predict the response to treatment of hypernatraemia, hence regular monitoring of serum sodium with appropriate adjustment of treatment in response to the values obtained is mandatory; (6) patient should be corrected to high normal or mildly hypernatraemic values to prevent cerebral oedema from overcorrection. Prevention—(1) patients with impaired access to water (e.g. infants, elderly, and hospitalized patients) should be considered at risk for the development of hypernatraemia, and their serum sodium should be monitored; (2) urinary electrolytes should be measured in conjunc- tion with urinary osmolality in patients with polyuria to assess water losses in the urine and urinary concentrating ability; and (3) adequate free water should be provided to prevent hypernatraemia. Disorders of water metabolism Hyponatraemia and hypernatraemia occur when there is a break- down of the normal homeostatic mechanisms that keep water in- take and excretion precisely balanced to prevent the development of disturbances in the serum sodium. There are numerous causes of impairment in this homeostatic function, such as renal failure, use of diuretics, and nonosmotic release of antidiuretic hormone (ADH) due to nausea, pain, or other stimuli. Poor outcomes are still common among patients with hypernatraemia and hyponatraemia, in many cases due to failure to promptly recognize a life-threatening condition and initiate appropriate treatment. In this chapter, the pathophysiology of sodium disturbances is addressed, with a focus on understanding clinical presentations of the diseases. Regulation of water balance Dysnatraemias (hyponatraemia or hypernatraemia) occur when there is an imbalance between water intake and water excretion. Extracellular fluid tonicity is reflected by the concentration of the serum sodium. Nearly all cell membranes are permeable to water, hence water will equilibrate between the intracellular space and the extracellular space to maintain the same osmolality in both compartments, and intra- cellular electrolyte concentrations will approximate the extracellular electrolyte concentrations. This means that the serum sodium concen- tration (Nase) is proportional to the total body exchangeable sodium (Nae) plus the total body exchangeable potassium (Ke): Na + K / total body water Na e e se ( ) ∝

(Equation 21.2.1.1) Water intake and the excretion of water are tightly regulated pro- cesses and therefore a near-constant serum osmolality is maintained (Fig. 21.2.1.1). Because of this tight regulation, disturbances in serum sodium are nearly always caused by perturbations in water balance, not of electrolytes. Renal water handling It is through the actions of ADH (also known as arginine vaso- pressin) that the kidney regulates water excretion. The normal kidney has the ability to vary urinary concentration significantly, from as low as 50 mOsm/kg to as high as 1200 mOsm/kg when ADH activity is maximal, although when there is renal insufficiency (especially tubulointerstitial disease) this range is much more re- stricted. This means that the kidney can either excrete a large water load in very dilute urine or conserve water significantly. A math-ematical illustration can make this clear. If a daily solute load is taken to be 800 mOsm (mainly

electrolytes and urea, the latter due to protein catabolism), then this amount must be excreted in 24 h in order to maintain solute balance. Under conditions of maximal urinary concentration, this could be excreted in approximately 667 ml of urine ([800 mOsm/1200 mOsm] × kg−1), which would be the expected response to a hypernatraemic state. Conversely, under conditions of maximal urinary dilution, this osmolar load would be excreted in 16 litres of urine ([800 mOsm/50 mOsm] × kg−1), which would be an expected response to water intoxication or could occur in the setting of diabetes insipidus. Therefore, the body has the ability, under normal conditions, to achieve water balance across a very wide range of water intake. Disorders in water balance usually

21.2.1 Disorders of water and sodium homeostasis 4731 occur when there is a disruption in these processes that allow water intake and water excretion to be exquisitely matched. The concept of electrolyte-free water The concept of electrolyte-free water is a good approach to under- standing patients with disturbances in water balance. The electrolyte- free water clearance is a conceptual amount of a fluid that represents the volume that would need to be subtracted (if electrolyte-free water clearance is positive) or added (if negative) to the measured urinary volume to make the electrolytes contained within the urine have the same tonicity as the serum electrolytes (Fig. 21.2.1.2): [1 ([Na] [K] / Na [K] volume of urine ml
) ([ ])] ( ) u u se se − + + × + + + + = electrolyte free water clearance −

(Equation 21.2.1.2) where [Na+]u is urinary sodium concentration, [K+]u is urinary po- tassium concentration, [Na+]se is serum sodium concentration, and [K+]se is serum potassium concentration. The electrolyte-free water represents the amount of water lost in excess of electrolytes and which would therefore—if not replaced— have an effect on serum osmolality. A few key points must be made about the electrolyte-free water. First, it is truly a conceptual volume because, as can be seen in Equation 21.2.1.2, it can take on a negative value, which occurs when the electrolyte concentration in the urine exceeds that in the serum: when the electrolyte-free water clearance is negative, there is net retention of electrolyte-free water. Second, the concept of electrolyte-free water clearance highlights the fact that it is the concentration of the electrolytes in the urine, not the osmolality of the urine, which ultimately determines the net excre- tion of water. In other words, the urine osmolality may be high but, if the urine contains mainly urea and very few electrolytes, there will still be a net loss of water. Electrolyte-free water clearance can there- fore be calculated as shown in Equation 21.2.1.2 as a convenient clin- ical tool for assessing water need in a patient. Clinical utility of electrolyte-free water clearance A critical point to understand is that the urine electrolytes and not the urine osmolality determine the amount of free water excreted in the urine. Typically, if the relationship between the serum elec- trolytes and the urine electrolytes is understood, it is not necessary to calculate a value for the electrolyte-free water clearance. In the case where the concentration of electrolytes in the urine exceeds the concentration of electrolytes in the serum, then free water is not being excreted in the urine. Conversely, when the concentra- tion of electrolytes in the urine is less than that in the serum, then free water is being excreted in the urine. Figure 21.2.1.3 illustrates this relationship: much can be learned regarding water excretion by simply examining the concentration of the electrolytes in the urine. Hyponatraemia Hyponatraemia is defined as a serum sodium concentration lower than 135 mmol/litre, which is a common condition in hospital set- tings and increasingly recognized in outpatients. Hyponatraemia can be asymptomatic, although careful neurological evaluation has de- tected subtle abnormalities in patients with chronic hyponatraemia ADH suppressed Dilute urine (free-water excretion) ADH release stimulated Concentrated urine

(free-water retention) Thirst stimulated Increased water intake Free-water retention Free-water excretion Free-water intake = free-water excretion Hyponatraemia Hypernatraemia Normonatraemia Fig. 21.2.1.1 Regulation of water intake and excretion to maintain normonatraemia. Reproduced with permission from Achinger SG, Ayus JC. Fluid and Electrolytes. In Civetta, Taylor, and Kirby's Critical Care, 4th edition. Volume of electrolytes isotonic to serum Volume of electrolyte-free water (urea, glucose, and ketones) Volume of urine containing electrolytes and nonelectrolytes (urea, glucose, and ketones) Fig. 21.2.1.2 Resolution of urinary volume into a proportion of electrolytes isotonic to serum, with the remainder as 'electrolyte-free water'.

section 21 Disorders of the kidney and urinary tract 4732 and serum sodium as high as 132 mmol/litre, which can lead to falls and fractures in the elderly. There is increasing evidence that hyponatraemia is an independent risk factor for mortality, particu- larly in patients with endstage liver disease, congestive heart failure, pneumonia, and endstage renal disease. Hyponatraemia is a signifi- cant healthcare burden, resulting in increased medical costs and length of hospital stay. The most serious complication of hyponatraemia is hyponatraemic encephalopathy (central nervous system symptoms secondary to cerebral oedema), which is a medical emergency that must be diag- nosed promptly and treated quickly, or death or devastating neuro- logical complications can result. It is critical to differentiate between symptomatic and asymptomatic hyponatraemia as the management is much different. It is recognized that risk factors for hyponatraemic encephalopathy play a critical role in determining whether or not patients are likely to develop this condition as a consequence of hyponatraemia: those of young age, premenopausal women, and those with hypoxia are at increased risk of a poor outcome. Prevention Most cases of hospital-acquired hyponatraemia can be prevented by avoiding hypotonic intravenous fluids and administering 0.9% NaCl when indicated. Significant morbidity and mortality from hyponatraemic encephalopathy has occurred in hospital- ized patients receiving hypotonic intravenous fluids, in particular postoperative patients. In 2003, we proposed that 0.9% NaCl (Na 154 mmol/litre) be administered for the prevention of hospital- acquired hyponatraemia in patients at risk for ADH excess, and that the routine practice of administration of hypotonic and near isotonic intravenous fluids (Na ≤130 mmol/litre) be aban- doned. Hospitalized patients are at high risk for hospital-acquired hyponatraemia from numerous physiological stimuli for ADH production, such as nausea, vomiting, pain, stress, volume deple- tion, and disease states associated with high ADH production such as respiratory illnesses, central nervous system disease, and the postoperative state. There have been numerous prospective studies demonstrating that hypotonic fluids result in a high incidence of hospital-acquired hyponatraemia, whereas 0.9% NaCl effectively prevents the development of hyponatraemia without resulting in fluid-related complications such as hypernatraemia or fluid over- load. We recommended that hypotonic fluids be restricted in their use to patients with either hypernatraemia (Na >145 mmol/litre), or ongoing urinary or extrarenal free water losses. Isotonic fluids are incapable of producing hypernatraemia in the absence of a renal concentrating defect or large extrarenal free water losses, as a normal functioning kidney can generate free water by excreting hypertonic urine. Pathogenesis The main defence against the development of hyponatraemia is the ability of the kidney to dilute the urine and excrete free water. The typical adult (assuming normal renal function) can excrete ap- proximately 15 litres of free water per day in the urine, hence ex- cess ingestion of water as the sole cause of hyponatraemia is rare outside of the setting of mental illness. There are numerous haemo- dynamic and nonhaemodynamic stimuli for ADH production which place virtually all acutely ill patients at risk for the develop- ment

of hyponatraemia (Fig. 21.2.1.4). An underlying condition that impairs free-water excretion is typically necessary in conjunc- tion with free-water intake for the development of hyponatraemia. States of impaired water excretion are often states where ADH re- lease is a normal response to a physiological stimulus such as pain, nausea, volume depletion, postoperative state, or congestive heart failure. ADH release may also be pathophysiological such as occurs with thiazide diuretics or with other types of medications such as antiepileptic drugs, or in the syndrome of inappropriate diuresis. Brain defences against cerebral oedema Hyponatraemia leads to an osmotic gradient favouring water move- ment intracellularly, which—if allowed to act unopposed—could lead to cerebral oedema and severe neurological injury. The first- line defence against this is the blood–brain barrier, which impedes the entry of water. This starts with tight junctions between vascular endothelial cells of the brain capillaries and their interface with the foot processes of astrocytes, the latter being a highly specialized subtype of glial cell that performs many supporting functions in maintenance of the fluid environment and electrolyte milieu of the extracellular space of the brain. The astrocytes are the main regulator of brain water content: they swell during hypotonic stress, whereas neurons do not, with this cap- acity largely due to the presence of a water channel specific to astro- cytes, aquaporin 4. Mice with targeted deletion of aquaporin 4 are protected from cytotoxic cerebral oedema caused by water intoxica- tion, brain ischaemia, or meningitis, but are particularly vulnerable to vasogenic cerebral oedema caused by, for example, cerebral abscess or tumour, or hydrocephalus. The response of the astrocyte is critical in determining the degree of cerebral oedema in response to hypo- osmolar stress, and modulation of aquaporin 4 production or function may prove useful in the management of a variety of cerebral disorders, including those associated with hyponatraemia, in the future. However, progressive and increasing swelling of astrocytes in the face of hyponatraemia would not protect the brain against ad- verse consequences, and there are several other protective mech- anisms. There is shunting of cerebrospinal fluid from within the brain: this is a rapid response, but its capacity to buffer significant volume change is limited. Ultimately, cell volume regulatory mech- anisms in the cerebral astrocytes must be active to decrease the brain size. This is accomplished by reduction in cellular osmolyte content (mainly electrolytes) using an ATP-dependent mechanism that re- quires Na+,K+-ATPase to extrude ions (electrolytes) from within, with water obligatorily following to reduce brain volume. In animal Nau + Ku < Nase + Kse Nau + Ku > Nase + Kse Measure Nau, Ku, Nase, Kse Retaining electrolyte- free water Excreting electrolyte- free water Fig. 21.2.1.3 Measurement of serum and urinary electrolytes can determine whether the patient is retaining or excreting electrolyte-free water. Kse, serum potassium; Ku, urine potassium (spot); Nase, serum sodium; Nau, urine sodium (spot).

 models of acute hyponatraemia, brain water content is returned to near the baseline value 6 h after induction of acute hyponatraemia. As will be discussed later, several clinical factors have been shown to impair these glial cell adaptive responses, and these are the chief risk factors for poor patient outcome. Clinical manifestations Advanced symptoms of hyponatraemic encephalopathy include seizures, respiratory arrest, and noncardiogenic pulmonary oedema. The symptoms of hyponatraemia are attributable to osmotic swelling of the brain, with pressure on the brain parenchyma arising because of the rigid structures encasing the central ner- vous system. The manifestations can be varied and not necessarily related to the degree of decrease in serum sodium concentration, which is frequently less than 120 or 115 mmol/litre in congestive heart failure and in cirrhosis with very few—if any—overt symp- toms (Fig. 21.2.1.5). Conversely, life-threatening cerebral oedema can be the presentation of a

patient with a serum sodium as high as 128 mmol/litre. Hyponatraemic encephalopathy is defined as symptomatic cerebral oedema secondary to hyponatraemia: the early signs are usually nonspecific—nausea, vomiting, headache— and can often go unrecognized, with advanced symptoms being signs of brainstem herniation—including seizures, respiratory ar- rest, noncardiogenic pulmonary oedema, dilated pupils, and decor- ticate posture—which can lead to death if left untreated. Hyponatraemic encephalopathy Risk factors Not all patients are equal in terms of risk of morbidity and mortality following the development of hyponatraemia. Hyponatraemic en- cephalopathy is primarily encountered when there is an acute fall in serum sodium (<48 h), but can occur in chronic hyponatraemia in high-risk patients (see Box 21.2.1.1 later in this chapter). Children are at particular risk for poor outcome following the development of hyponatraemia due to their high ratio of brain size to skull size, the skull not reaching its full size until age 16 years, whereas the brain reaches its adult size at approximately age 6 years. This means that children cannot accommodate as much increase in brain size as adults: there is less capacity for brain expansion before pressure is exerted on the brain parenchyma. For this reason, the long-standing practice of administering hypotonic fluids to children is being chal- lenged: normal (0.9%) saline is the most appropriate fluid to use to prevent the development of iatrogenic hyponatraemic encephalop- athy in children. Hemodynamic stimuli Pain and stress Nausea and vomiting Hypoxemia and hypercapnia Hypoglycemia Medications Perioperative state Cancer Inflammation Pulmonary disease CNS disease Hypotension Volume depletion Cirrhosis Nephrotic syndrome Adrenal insufficiency Congestive heart failure Nonhemodynamic stimuli Fig. 21.2.1.4 Nonosmotic states of ADH excess. From Moritz ML, Ayus JC (2015). Maintenance Intravenous Fluids in Acutely Ill Patients. N Engl J Med, 373, 1350–60. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission.

section 21 Disorders of the kidney and urinary tract 4734 Premenopausal women are another significant risk group in terms of neurological outcomes following hyponatraemia, being 25 times more likely to die following hyponatraemic encephalopathy than other groups of patients. This striking difference is not accounted for by differences in clinical presentation, and anatomical factors in terms of the brain size—cranial vault size ratio (as is seen with children)—cannot explain the disparity in outcomes. Differences in adaptive responses to hyponatraemia must exist. As previously de- scribed, it is known that ATP-dependent mechanisms are important for the response to hypo-osmolar stress in the brain. Oestrogens have a similar steroidal structure to ouabain and other cardiac glycosides (such as digoxin), which are known to inhibit the Na+,K+-ATPase, and female sex hormones have been shown to inhibit the activity of this pump in diverse tissues such as mammalian heart, diaphragm, red blood cells, and liver. Sex steroids and gender also play a signifi- cant role in brain adaptation and in animal models of hyponatraemia. There is increased morbidity from hyponatraemia in female rats, and isolated synaptosomes from female hyponatraemic rats have an in- creased uptake of sodium compared with male hyponatraemic rats, suggesting impairment in sodium extrusion. Regulatory volume de- crease is also inhibited by the presence of oestrogen/progesterone in rat astrocytes treated in vitro. These studies support the notion that the presence of female sex hormones can impair the critical energy- dependent astrocyte cell volume regulatory processes, with this im- pairment leading to more severe cerebral oedema. Finally, female rats have more intense vasoconstriction than male rats in response to ADH, which may lead to tissue hypoxia, which is another possible factor in producing poor outcomes. Role of hypoxia Animal studies have demonstrated that survival is severely im- paired and brain adaptation is significantly impaired following hyponatraemia and simultaneous brain

hypoxia. Epidemiological studies have shown that patients with hypoxia at presentation of hyponatraemic encephalopathy have a poor outcome compared with those who are not hypoxic, even after adjustment for comorbid Box 21.2.1.1 Treatment of symptomatic hyponatraemia 1 A 2-ml/kg bolus of 3% NaCl, given IV over 10 min to maximum volume of 100 ml. 2 Repeat bolus one or two times as needed until symptoms improve, with goal being to produce a 5- to 6-mmol/litre increase in serum sodium in first 1 to 2 h. 3 Recheck serum sodium following second bolus or at 2 h. 4 Hyponatraemic encephalopathy is unlikely if there is no clinical improvement following an acute rise in serum sodium of 5 to 6 mmol/litre 5 Stop further therapy with 3% NaCl boluses when patient is either:

— symptom free: awake, alert, responding to commands, resolution of headache and nausea

— there is an acute rise in sodium of 10 mmol/litre in first 5 h 6 Correction in first 48 h should:

— not exceed 15–20 mmol/litre

— avoid normo- or hypernatraemia If 3% NaCl is not available, then an equivalent amount of 8.4% sodium bicarbonate (1 mEq/ml) can be administered as a 1 ml/kg bolus (max- imum 50 ml). Reproduced with permission from Moritz ML, Ayus JC (2010). New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephal- opathy in children. Pediatr Nephrol, 25(7), 1225–38. Age <16 Female sex steroids Hypoxia Post-operative state Underlying CNS dis. Headache, nausea vomiting lethargy, confusion somnolence Blurred vision , dilated pupils Decorticate and decerebrate posturing Seizure Cerebral edema Intracranial hypertension Tentorial herniation Release of excitatory amino acids Exercise-associated hyponatremia Acute mountain sickness Ecstasy [3,4-MDMA] Post-operative state Neurogenic pulmonary edema Hypercapnic respiratory failure

- Risk factors for the development of symptomatic hyponatremia Elderly Females Thiazide diuretics Ant-depressant (SSRI) ↓ bone mineralization ↑ osteoclastic activity *CNS symptoms CNS symptoms CNS Impairment (Anatomic) Bone Disease *Bone disease *Pulmonary Involvement Pulmonary Involvement Falls Fractures HYPONATREMIA (Na <135 mEq/L) Fig. 21.2.1.5 Risk factors and clinical manifestation of hyponatraemia. Reproduced with permission from Ayus JC et al. (2012). Nephrol Dial Transplant, 27(10), 3725–31. Copyright © 2012 Oxford University Press.

21.2.1 Disorders of water and sodium homeostasis 4735 conditions. Since impairment of astrocyte adaptive mechanisms can explain poor outcome in premenopausal females, it has been pro- posed that hypoxia may similarly have an effect on astrocyte volume regulation. Impairment of energy utilization in the brain—a common phenomenon following asphyxiation or cardiac arrest—can lead to diffuse cerebral oedema, termed ‘cytotoxic’ cerebral oedema, related to the impairment of cell-volume regulatory mechanisms. Hence, if hyponatraemia—which will by itself induce cerebral oedema—is compounded with impairment in volume regulatory mechanisms through hypoxia, then this is likely to lead to more severe cerebral oedema than if hypoxia were not present and a poor outcome. Hypoxia develops in patients with hyponatraemic encephalop- athy through two mechanisms: hypercapnic respiratory failure and neurogenic pulmonary oedema. Hypercapnic respiratory failure is secondary to central respiratory depression and is a first sign of impending

brainstem herniation, with the hypoxaemia that then develops being due to the central respiratory depression further worsening astrocyte cell-volume regulatory mechanisms and leading to worsening of brain oedema. Neurogenic pulmonary oedema, caused by increased vascular permeability and increased catechol- amine release that occurs secondary to elevated intracranial pressure, is a complication of cerebral oedema and can occur in the setting of hyponatraemic encephalopathy as well (Fig. 21.2.1.6). This form of noncardiogenic pulmonary oedema is known as the Ayus–Arieff syndrome, and is secondary to increased intracranial pressure due to cerebral oedema. Hypoxaemia is therefore both a risk factor and a pathogenic mechanism in severe cerebral oedema, as once hyp- oxaemia is established, the underlying cerebral oedema will worsen because the hypoxia will initiate a vicious cycle that—unless broken— results in worsening of the underlying cerebral oedema. Diagnostic approach to hyponatraemic patients With a patient with hyponatraemia, the first priority is to exclude a hyperosmolar state and verify that a hypotonic state exists by (when possible) measuring the serum osmolality. An osmotically active substance confined to the extracellular fluid—most typically glucose, mannitol, or glycine—leads to translocation of water from the intracellular space and to a decreased serum sodium concen- tration despite a net increase in serum osmolality. In assessing for a disturbance of sodium when hyperglycaemia is present, the serum sodium must be ‘corrected’ for the presence of hyperglycaemia by adding 1.4 mmol/litre for every 5 mmol/litre increase of the serum glucose above 5 mmol/litre (or 1.6 mmol/litre for every 100 mg/dl above 100 mg/dl). The possibility of pseudohyponatraemia should also be kept in mind. Hyperproteinaemia and hyperlipidaemia can lead to spuri- ously low serum sodium measurements despite a normal plasma osmolality by the displacement of plasma water. Serum sodium levels can be measured by direct or indirect-reading ion-selective electrode potentiometry. The direct method will not indicate pseudohyponatraemia because it measures the activity of sodium in the aqueous phase of plasma only. By contrast, the indirect method may indicate pseudohyponatraemia because the specimen is diluted with a reagent prior to measurement. Whole blood sodium concen- tration measurement using a blood gas or i-Stat point-of-care ana- lyser is not subject to pseudohyponatraemia. The diagnostic approach is further based on the history, urinary electrolytes, and clinical assessment of the patient’s volume status (Fig. 21.2.1.7), which will be further demonstrated in the case dis- cussions to follow. Serum and urine biochemistries can be par- ticularly helpful in diagnosing the syndrome of inappropriate antidiuresis/syndrome of inappropriate antidiuretic hormone se- cretion (SIADH), which occurs when hyponatraemia is due to nonhaemodynamic stimuli for ADH production. SIADH In SIADH, subclinical volume expansion triggers a haemodynamic regulatory mechanism that results in a natriuresis, with increased so- dium excretion in the urine in order to maintain plasma volume at the expense of serum sodium concentration. SIADH is a heteroge- neous condition with different patterns of ADH secretion, hence the urine osmolality and urinary sodium excretion are similarly variable. SIADH is essentially a diagnosis of exclusion: other conditions such as renal dysfunction, adrenal insufficiency, hypothyroidism, and disease states associated with haemodynamic stimuli for ADH production must be excluded. In addition to standard blood and urine chemical analysis, evaluation of plasma and urine uric acid can be helpful in confirming the diagnosis. SIADH is usually as- sociated with a combination of hypouricaemia (uric acid <240 μmol/litre (4 mg/dl)) and an elevated fractional excretion of urate (FEUrate >11%). This can be particularly helpful in distinguishing SIADH from other hyponatraemic states where the urinary sodium may be elevated, such as adrenal insufficiency or renal tubular dys- function, or if loop diuretics have been used. Urate excretion can also be helpful in distinguishing SIADH from a similar condition called cerebral salt wasting. Cerebral salt wasting Cerebral salt wasting is a rare

condition that is primarily but not ex- clusively associated with central nervous system disease. It is best considered as a syndrome of inappropriate natriuresis that leads to volume depletion. The pathophysiology of SIADH and cerebral salt wasting are fundamentally different. In SIADH, the primary disorder Hyponatraemia Cytotoxia cerebral oedema Increased intracranial pressure Centrally mediated increased vascular permeability Catecholamine release Pulmonary vasoconstriction Elevated capillary hydrostatic pressure Capillary wall injury Noncardiogenic pulmonary oedema Fig. 21.2.1.6 Mechanism of noncardiogenic pulmonary oedema in hyponatraemic encephalopathy.

section 21 Disorders of the kidney and urinary tract 4736 is the inappropriate (with regard to serum osmolality) release ADH. In cerebral salt wasting, there is inappropriate and excessive release of natriuretic peptides that leads to a primary natriuresis and volume depletion, with a secondary neurohormonal response of increased renin–angiotensin system activation and ADH production. One might think that the two conditions could be easily distinguished on physical examination and by different serum and urinary biochemistries, but in fact they can be nearly indistinguishable at presentation. Signs of volume depletion are not always apparent, and there are no biochem- ical findings that reliably separate the two disorders at the time of pres- entation, although there is some data to suggest that urate excretion differs in SIADH and cerebral salt wasting following the correction of hyponatraemia. Urate excretion is said to normalize following the correction of hyponatraemia in SIADH, whereas hypouricaemia and an elevated FEUrate are said to persist in cerebral salt wasting, but additional data are needed to confirm these findings. Treatment of hyponatraemic encephalopathy A 100-ml 3% NaCl bolus is the preferred treatment for symptomatic hyponatraemia. Hyponatraemic encephalopathy is a life-threatening medical emergency that must be treated appropriately and in a timely manner to avoid death or severe neurological impairment. As previously de- scribed, early symptoms are headache, nausea, and vomiting, with seizures commonly seen if cerebral oedema worsens. The final stages, if not corrected, are coma, respiratory arrest, and death. The aims of treatment of hyponatraemic encephalopathy are to (1) remove patients with severe manifestations of cerebral oedema from immediate danger, (2) correct serum sodium to a mildly hyponatraemic level, and (3) maintain this level of serum sodium to allow for the brain to adapt to the change in serum osmolality. Prompt treatment is essential in all patients with hyponatraemic encephalopathy, with the definitive therapy being administra- tion of hypertonic saline (3% NaCl, 513 mmol/litre). Most of the morbidity associated with this condition results from insufficient therapy rather than overcorrection. Fluid restriction alone is inad- equate therapy for symptomatic hyponatraemia, and 0.9% NaCl, 1.8% NaCl, and V2 receptor antagonists are also inappropriate for the treatment of patients who are encephalopathic. Concentrations of 0.9% and 1.8% NaCl are not sufficiently hypertonic to consist- ently induce the rapid rise in plasma osmolality necessary for the reduction in cerebral oedema central to the management of this condition. The only consistent way of acutely increasing the plasma sodium and to most effectively treat hyponatraemic encephalopathy is to administer 3% NaCl, which has a sodium concentration that exceeds the kidney’s ability to generate free water. There are two pri- mary misconceptions related to the use of hypertonic saline in the treatment of hyponatremic encephalopathy which are barriers to its appropriate use; (1) the mistaken believe that the risks of developing cerebral demyelination associated with using hypertonic saline ex- ceeds the benefits and (2) that hypertonic saline must be adminis- tered through a central line in the intensive care unit. Studies have demonstrated that incidence of cerebral demyelination associated with correction of severe hyponatremia is very small and

primarily in patients with multiple other risk factors. Short term infusions of hypertonic saline can also be given safely through a peripheral IV in a non-ICU setting and is not associated with phlebitis. We recommend that any patient with suspected hyponatraemic encephalopathy, with either mild or advanced symptoms, child or adult, should receive a 2 ml/kg bolus of 3% NaCl to a maximum volume of 100 ml (Box 21.2.1.1). A single bolus results in at most a 2-mEq/litre acute rise in serum sodium, which would quickly re- duce brain oedema, and the bolus can be repeated one or two times if symptoms persist. The advantage of this approach over a continuous infusion of 3% NaCl is that there is a controlled and immediate rise in serum sodium and little or no risk of inadvertent overcorrection, as can occur if a 3% NaCl infusion runs for too long. At times the diagnosis of hyponatraemic encephalopathy can be difficult to establish, such as in patients with either (a) hepatic en- cephalopathy, (b) central nervous system infections, tumours, or trauma, or c) postoperative nausea and vomiting with associated hyponatraemia. Bolus therapy with 3% NaCl can serve as a diag- nostic manoeuvre, as a patient who does not show some clinical im- provement after two to three boluses is most likely is not suffering from hyponatraemic encephalopathy. As long as it does not lead to a significant delay in pursuing other diagnostic possibilities, no harm could come from using this approach in a patient with suspected hyponatraemic encephalopathy, even if they subsequently prove not to have this condition, and a therapeutic trial of a bolus of 3% NaCl should precede radiological investigations because (a) neurological deterioration could occur if there is a delay in therapy, and (b) a CT scan cannot exclude the possibility of hyponatraemic encephalopathy. Serum Na < 135 mEq/L Plasma Osmolality

> 280 mOsm/kg H2O • Hyperglycemia • Mannitol • IV contrast • Pseudohyponatremia • Hyperlipidemia • Hyperproteinemia <200 mOsm/kg H2O, FE Urate < 11% • Psychogenic polydypsia • Water intoxication in infants • Reset Osmostat Urine Na < 30 mEq/L, FENa < 0.5% • Extrarenal losses • Edematous states Urine Na > 30 mEq/L, FENa > 0.5% • FE Urate <11% • Salt wasting nephropathy • Mineralocorticoid deficiency • Diuretics • Osmotic diuresis • FE Urate >11% • Cerebral/Renal salt wasting (CSW) Normonatremia • FE Urate < 11% ° SIAD • FE Urate > 11% ° CSW Urine Osmolality <280 mOsm/kg H2O 200 mOsm/kg H2O Effective Circulatory Volume Depletion No No Renal Insufficiency Hypothyroid Glucocorticoid deficiency Mineralocorticoid deficiency Diuretics Urine Na > 30 mEq/L, FENa > 0.5% • FE Urate > 11%

• SIAD

• CSW Yes Fig. 21.2.1.7 Diagnostic approach to hyponatraemia. DDAVP, deamino-d-arginine vasopressin; GI, gastrointestinal. Reproduced from Moritz ML. Syndrome of Inappropriate Antidiuresis. Pediatr Clin North Am 2019; 66(1): 209–226 with permission from Elsevier.

21.2.1 Disorders of water and sodium homeostasis 4737 Recommended safe limits for the correction of hyponatraemia vary among experts depending on the setting of hyponatraemia, including 6–8 mEq/litre in 24 h or 20 mEq/litre in 48 h, as do re- commendations for using hypertonic saline. Our recommenda- tion to use bolus therapy is an approach that would stay well

within widely recommended limits of correction and can be used safely in any setting—for children or adults, in chronic or acute symptom- atic hyponatraemia, and in the outpatient or inpatient setting. The approach is simple: it does not rely on formulas or complicated cal- culations, and it can be administered quickly in the emergency de- partment or at the bedside, prior to transfer to a monitored setting. A few precautionary points must be understood to prevent therapy-induced brain injury: (1) the serum sodium should not be corrected to a normonatraemic or hypernatraemic level in a patient treated for hyponatraemic encephalopathy; (2) following correc- tion, patients should be maintained at mildly hyponatraemic levels for a few days following hyponatraemic encephalopathy (this main- tenance period will allow the patient to adjust to the new serum tonicity); and (3) if the patient has decreased cardiac output and pulmonary oedema may develop with vigorous saline volume ex- pansion, then furosemide should be given in addition to hypertonic saline—this should prevent volume overload and pulmonary oe- dema, but such a patient requires very close monitoring. Early recognition of hyponatraemic encephalopathy and institu- tion of prompt treatment are the factors most associated with good neurological outcomes. Appropriate treatment with hypertonic sa- line is safe and effective, but improper therapy can have severe con- sequences. Some authors describe formulas of varying complexity to guide treatment of hyponatraemia: these should not be used at all when determining the amount of hypertonic saline to give because they are fundamentally flawed. Ongoing water losses are unpredict- able, and formulas are not able to take these into account because they are based on a closed system assumption (i.e. no ongoing water losses). Significant overcorrection can occur if saline is prescribed according to formula when a patient undergoes a spontaneous water diuresis, which can easily occur when the stimulus for water reten- tion is removed and the body begins to respond appropriately to hypotonicity by suppressing ADH release and excreting dilute urine, hence the recommendations made in Box 21.2.1.1. Risk factors for the development of cerebral demyelination Cerebral demyelination is a potential complication of the over correction of chronic hyponatraemia. Cerebral demyelination is a serious complication that has been associated with the overcorrection of severe (serum sodium <115 mEq/litre) chronic hyponatraemia (>48 h) and is rarely seen in acute hyponatraemia. The symptoms often become apparent days to weeks following correction of hyponatraemia, and can vary from being minimal or none to as severe as a pseudocoma with a ‘locked- in stare’. A key point is that the hourly rate of correction of serum sodium by itself is not predictive of cerebral demyelination, whereas the absolute change in serum sodium over 48 h is predictive. This is important because it is not appropriate to treat a patient with re- spiratory arrest due to hyponatraemic encephalopathy with a ‘slow’ infusion of hypertonic saline to increase the serum sodium by 0.5 to 1 mmol/litre per hour. This type of patient—with impending brain- stem herniation—should be treated with a bolus of hypertonic sa- line to quickly reduce brain volume, after which the hourly rate of correction can be more modest as long as the total change in serum sodium does not exceed 15 to 20 mmol/litre over 48 h and the pa- tient is not corrected to normonatraemic levels. There are numerous risk factors that increase the likelihood of cerebral demyelination independent of the degree of hyponatraemia or rate of its correction. These include hypokalaemia, thia- zide diuretic use, severe liver disease, alcoholism, malnutrition, hypophosphataemia, and hypoxia. These conditions can all con- tribute to intracellular solute depletion, which aggravates osmotic stress following correction. Most patients reported with demye- lination have had one of these risk factors, and some high-risk patients—particularly those with alcoholism or liver disease—have had demyelination despite careful correction of hyponatraemia and, in some cases, in the absence of hyponatraemia. Preventing overcorrection of hyponatraemia Preventing an extreme rise in serum sodium

(>25 mmol/litre in 48 h) can be difficult, particularly in the severely hyponatraemic patient (serum sodium ≤115 mmol/litre). The overall rate of cor- rection of hyponatraemia is primarily a determinant of the renal response to fluid therapy, more so than the composition of fluids administered. Hyponatraemia almost invariably develops due to a state of high ADH production. Once the stimulus for ADH produc- tion abates, there will be brisk urinary excretion of free water and hyponatraemia will correct rapidly. The main conditions in which correction by fluid therapy will induce a brisk free water diuresis are (1) thiazide-induced hyponatraemia, (2) water intoxication, (3) gastroenteritis, (4) adrenal insufficiency following replacement therapy, and (5) 1-deamino-8-d-arginine vasopressin (DDAVP)- induced hyponatraemia following DDAVP withdrawal. Even in pa- tients who are not typically at high risk for overcorrection, such as those with SIADH and postoperative hyponatraemia, a free water diuresis will ensue when the stimuli for ADH production abates. In general, if the serum sodium is greater than 115 mmol/litre, then even if there is a brisk free water diuresis, the absolute rise in serum sodium will not be likely to exceed 25 mmol/litre, and the risk of brain injury is small. Box 21.2.1.2 outlines the measures that should be taken to prevent overcorrection of hyponatraemia. Under certain circumstances, the administration of DDAVP will be indicated to prevent an overcorrection, and this can also be used to therapeutic- ally relower the serum sodium following overcorrection of chronic hyponatraemia. In cases of DDAVP-induced hyponatraemia, it may be safer to continue the DDAVP and administer 3% NaCl in order to achieve a controlled correction of hyponatraemia. This is particu- larly so if there is severe hyponatraemia (Na <115 mmol/litre) or if there is a disorder in the thirst mechanism or restricted access to water as can occur in central diabetes insipidus. Asymptomatic hyponatraemia Asymptomatic hyponatraemia is an independent risk factor for falls and fractures in the elderly and for increased hospital mortality. It has become increasingly clear that any degree of hyponatraemia can have dangerous consequences and is associated with increased morbidity and mortality. Mild chronic hyponatraemia (sodium <130 mmol/litre) can produce subtle neurological impairment af- fecting both gait and attention, similar to that of moderate alcohol intake. This may explain why hyponatraemia has been increasingly associated with falls and bone fractures in the elderly, in which regard

 there is additional evidence in both animals and humans that chronic hyponatraemia contributes to osteopenia. Hyponatraemia appears to induce bone loss by stimulating osteoclastogenesis and bone re- sorptive activity as a means of preserving sodium homeostasis (Fig. 21.2.1.8). It is now well established in adults that hospital- associated hyponatraemia is an independent risk factor for all-cause mortality, with studies documenting an association in the ambula- tory setting and general medical wards, as well as in patients with community-acquired pneumonia, congestive heart failure, and endstage liver disease. Hyponatraemia is also recognized as an inde- pendent predictor of increased medical costs in hospitalized patients. Treatment of asymptomatic chronic hyponatraemia Hyponatremia is a multifactorial condition that can result from numerous causes and management will vary depending on the underlying disease and etiology of hyponatremia. There are various therapies available, most of which have not been for- mally studied in great detail. Fluid restriction is the corner- stone in the management of hyponatremia, as hyponatremia is unlikely to occur in the absence fluid intake. Fluid restriction is primarily indicated as part of the management of euvolemic and hypervolemic hyponatremia, as is seen in SIADH and con- gestive heart failure. For fluid restriction to be successful, fluid intake from all sources will have to be less than the total daily urine output, and generally less then 600–1000 ml/day in an adult. It is generally a slow

means of correcting hyponatremia and frequently ineffective. Isotonic saline is primarily indicated for the management of hypovolemic hyponatremia as can occur with gastrointestinal losses, diuretics or mineralocorticoid de- ficiency. Administering isotonic (0.9%) saline can also be useful in distinguishing hypovolemic hyponatremia from SIADH: it is generally ineffective in increasing the serum sodium in SIADH, whereas an appreciable rise in serum sodium is consistent with volume depletion. Saline should be avoided in patients with hypervolemic hyponatremia as it can worsen fluid overload. Studies are beginning to support the use of oral urea as practical therapy to correct asymptomatic chronic hyponatremia from SIADH. Urea primarily works as an osmotic diuretic by increasing the renal solute load. A commercially available lemon-flavored urea powder drink (Ure-Na by Nephcentric LLC) is now avail- able in the United States. In the US it is a medical food, Generally Regarded as Safe (GRAS) ingredient by the FDA, which can be purchased over the counter to be used under medical supervi- sion. It comes in 15 gm single serve packets to be mixed in 3–4 ounces of water or juice. It can be used in conjunction with other therapies such as sodium chloride tablets. It is generally well tol- erated and allows for a more liberal fluid restriction. Hypertonic saline is primarily indicated for the management of symptomatic hyponatremia, though in highly selected cases it may be used to correct asymptomatic hyponatremia unresponsive to conven- tional therapies in patients with SIADH, cerebral salt wasting and in conjunction with loop diuretics in congestive heart failure. A new class of drugs which hold a promising but as yet un-defined role in the management of asymptomatic euvolaemic or hypervolaemic hyponatraemia are nonpeptide vasopressin V2 re- ceptor antagonists (vaptans) that selectively antagonize the anti-diuretic effect of ADH and result in a urinary free water diuresis (aquaresis) without increasing losses of electrolytes. There have been numerous placebo-controlled trials that have demonstrated the safety and efficacy of these drugs for the treatment of hyponatraemia associ- ated with congestive heart failure, cirrhosis, and SIADH. The vaptans produce an aquaresis within 1 to 2 h of administration that abates within 12 to 24 h. When used to treat hyponatraemia they result in an approximately 5 to 7 mEq/litre increase in serum sodium within the first 24 h of administration, but the effect is highly variable. The most common side effects are increased thirst, polyuria, and dry mouth. There are currently two vaptans that are FDA approved in the United Chronic hyponatremia (SNa < 135 mmol/L) CNS impairment • Unsteady gait • Decrease bone mineralization • Increase osteoclastic activity Fragile bones Fall Bone fracture • Confusion • Lethargy Osteoporosis
Fig. 21.2.1.8 Mechanism of bone injury from chronic hyponatraemia in the elderly. SNa, serum sodium. Reprinted with permission from Ayus JC, Moritz ML. Bone disease as a new complication of hyponatremia: moving beyond brain injury. Clin J Am Soc Nephrol 2010; 5: 167–8. Copyright 2010 American Society of Nephrology. Box 21.2.1.2 Preventing overcorrection of hyponatraemia 1 Overcorrection is defined as an increase in serum sodium (SNa) of greater than 25 mmol/litre in 48 h 2 Identify patients at high risk for overcorrection

— Patients with SNa less than or equal to 115 mmol/litre

— Patients at risk for a spontaneous free water diuresis: • Thiazide diuretics • Gastroenteritis • Water intoxication • DDAVP-associated hyponatraemia • Adrenal insufficiency 3 Avoid excessive administration of 0.9% NaCl or 3% NaCl 4 Monitor for a spontaneous free water diuresis following the initial correction in SNa

— Check SNa every 4 h

— Monitor urine output carefully

— Check urine specific gravity or urine osmolality with each void 5 Evidence of a free water diuresis is as follows:

— Increase in SNa greater than 1 mmol/litre per h

— Urine flow greater than 1–2 ml/kg per h

— Urine specific gravity less than 1.010

— Urine osmolality less than 250 mOsm/kg 6 Treating patients with free water diuresis

— Restrict sodium containing fluids

— Encourage oral fluid intake

— Consider DDAVP

21.2.1 Disorders of water and sodium homeostasis 4739 States of America: tolvaptan, which is available in an oral formulation, and conivaptan, which is available in an intravenous preparation. While vaptans have proved to be effective in the management of hyponatraemia, there are no data to suggest that their use re- sults in decreased mortality, and safety concerns are beginning to arise. Tolvaptan was found to cause an elevation of serum alanine aminotransferase and hepatotoxicity with long-term use in patients with autosomal dominant polycystic kidney disease. They can also result in overcorrection in hyponatraemia from excessive free water diuresis, and this effect is refractory to DDAVP until the vaptan wears off. Such overcorrection is of particular concern in the elderly, critic- ally ill, or moribund patient with restricted free access to water, and in patients with severe hyponatraemia (Na <120 mEq/litre), and there are reports of demyelination associated with vaptan use. For these reasons, the most recent European guidelines have advised against their use in the management of hyponatraemia. If they are to be used, they should be initiated or reinitiated in the hospital. Furthermore, some patients have been reported to have a marked response to standard doses of tolvaptan, and it may need to be compounded in smaller doses. Vaptans are not appropriate for the treatment of symp- tomatic hyponatraemia as the onset of action and rate of correction are not sufficiently rapid, and nor is the response sufficiently predictable. Vaptans should not be used in hypovolaemic hyponatraemia, or in conjunction with saline-containing intravenous fluids. These agents are inhibitors of cytochrome P450 and should not be used in conjunc- tion with other drugs known to be metabolized by this pathway. In summary, at the present time vaptans cannot be recommended as a first-line agent in the management of hyponatraemia. They may be suitable as second-line agents for short-term use in pa- tients with mild to moderate chronic asymptomatic euvolaemic or hypervolaemic hyponatraemia, but it is not clear that their effect in raising serum sodium concentration leads to any substantial clinical benefit that can justify their considerable cost. Case discussions Case 1: postoperative hyponatraemia A 29-year-old woman without significant medical history undergoes an elective laparoscopic cholecystectomy. During the procedure, 5% dextrose in quarter-strength normal saline (0.22% NaCl) is started and maintained at 125 ml/h. There was some bleeding during the procedure, but blood transfusion was not required. The patient is kept in

the hos- pital for observation because of the bleeding. She does not tolerate oral intake, and the intravenous fluids are continued at the current rate. At 4 a.m. the following day, the woman complains of headache and she is given paracetamol by the on-call physician. At 10.30 a.m. the attending doctor is notified that the serum sodium is 128 mmol/litre: no new or- ders are received. The woman is found to be lethargic by the nursing staff and an order is received to withhold pain medications. That after- noon the woman has a seizure and goes into respiratory failure. She is placed on mechanical ventilation and transferred to the intensive care unit. At the time of transfer, the serum sodium is 124 mmol/litre. Discussion The patient has several nonosmotic stimuli for ADH secretion (postoperative, volume depletion, pain, nausea) and the admin- istration of a hypotonic fluid was not appropriate. Postoperative hyponatraemia can be prevented by the administration of 0.9% sa- line when parenteral fluids are indicated, with avoidance of the use of hypotonic fluids in a postsurgical patient. The induction of hyponatraemic encephalopathy is iatrogenic in this case and therapy needs to be instituted immediately, with a 100-ml 3% NaCl bolus as described in Box 21.2.1.1 to try to prevent death or severe neuro- logical impairment. Case 2: exercise-associated hyponatraemia A 24-year-old woman collapses 20 min after completing a mara- thon and is brought to the emergency department for evaluation. She has a decreased level of consciousness and is very short of breath. Cardiological examination is normal, but there are crackles in all lung fields. Neurological examination reveals a depressed mental status with no focal signs. The chest radiograph is consistent with pulmonary oedema. Serum electrolytes include sodium of 125 mmol/litre and potassium of 3.3 mmol/litre. Discussion Exercise-associated hyponatraemia has been reported in mara- thon runners, with those at risk for this problem consuming large amounts of water throughout the course of the race. It is thought that significant amounts of this water remain unabsorbed, sequestered in the gut because blood flow is directed away from the splanchnic circulation while exercising vigorously. At the end of the race the sequestered water is absorbed and hyponatraemia develops rapidly, with water excretion being inhibited by high levels of ADH release secondary to extreme physical exertion. As with Case 1, treatment needs to be started immediately with a 100-ml 3% NaCl bolus. This condition can be prevented by limiting fluid intake during endurance running: salt consumption or the use of hypotonic electrolyte sports drinks do not appear to be effective in prevention. Case 3: DDAVP withdrawal A 39-year-old man with a history of central diabetes insipidus following resection of a pituitary tumour is brought into the emergency department after a generalized seizure. He has previ- ously been taking DDAVP 10 µg intranasally twice a day for his condition. In the emergency department he is found to be leth- argic and unresponsive, with a pulse of 80 beats/min and blood pressure of 135/80 mmHg, and his serum sodium is 119 mmol/ litre and serum potassium 4.0 mmol/litre. It is not clear when the patient was last given a dose of DDAVP. Urine sodium is 125 mmol/litre and urine potassium 20 mmol/litre, with urine osmolality 585 mOsm/kg. The man is given 2 litres of 0.9% saline in the emergency de- partment. Six hours after presentation, the serum sodium is 127 mmol/litre and the man is admitted for management of hyponatraemia. The admitting physician continues to withhold the DDAVP and stops the intravenous fluids. The urine output increases significantly over the ensuing night, and the following morning the serum sodium is 158 mmol/litre, urine sodium 17 mmol/litre, urine potassium 10 mmol/litre, and urine osmo- lality 70 mOsm/kg. Discussion DDAVP by itself is not a cause of hyponatraemia. DDAVP will cause retention of free water and therefore dosing must be titrated in con- junction with the patient’s fluid intake. The patient must be closely

section 21 Disorders of the kidney and urinary tract 4740 monitored and the serum electrolytes closely followed. If DDAVP is withheld following DDAVP-associated hyponatraemia, then a free water diuresis will ensue and dangerous overcorrection of the serum sodium hypernatraemia may occur, as observed here. This is espe- cially a concern in a patient such as this who has central diabetes insipidus and can rapidly excrete a large volume of dilute urine. An appropriate approach to this patient with diabetes insipidus and hyponatraemic encephalopathy due to DDAVP-associated hyponatraemia would have been to continue DDAVP and restrict all enteral fluid intake. To correct the patient to the desired serum sodium level, 3% saline could have been used, and then discontinued. During this time, absolutely no hypotonic fluids would be given, and the patient would be monitored closely to restrict all enteral intake. A slow infu- sion of 0.9% saline could have been continued after the 3% saline was stopped if necessary to support volume status. This approach, coupled with frequent monitoring of the serum sodium, would have prevented overcorrection secondary to water diuresis as happened in this case. Case 4: hyponatraemia due to syndrome of inappropriate diuresis A 28-year-old man with HIV and a CD4 count of 75 is seen in follow-up 3 days after being discharged from the hospital where he had been diag- nosed with pneumonia, suspected to be due to Pneumocystis jirovecii. His serum sodium had been decreased throughout the hospitalization, which was managed with fluid restriction. Current medications include a taper of prednisone and co-trimoxazole. He is significantly improved since hospital discharge, with physical examination revealing that he is afebrile, with a pulse of 84 beats/min, blood pressure of 104/55 mmHg, and no abnormalities in the cardiac or respiratory systems—the lungs are clear and there is no peripheral oedema. Laboratory values from the morning of the clinic visit reveal the following: • Serum—sodium 113 mmol/litre, potassium 3.9 mmol/litre, blood urea nitrogen 19.6 mmol/litre (7 mg/dl), creatinine 64 µmol/litre (0.7 mg/dl), glucose 6.2 mmol/litre (112 mg/dl), uric acid 120 µmol/litre (2.0 mg/dl), and osmolality 248 mOsm/kg • Urine—sodium 105 mmol/litre, potassium 18 mmol/litre, and osmolality 590 mOsm/kg Discussion This presentation is consistent with the syndrome of inappropriate diuresis, which is defined as hypotonic hyponatraemia, with a urine osmolality above 100 mOsm/kg, in the absence of volume depletion, adrenal insufficiency, congestive heart failure, hypothyroidism, cir- rhosis, and/or renal impairment. The laboratory values support the syndrome of inappropriate diuresis as the serum osmolality is de- creased, which rules out hyperosmolar hyponatraemia (also known as dilutional hyponatraemia) and pseudohyponatraemia, the urine osmolality is high, and there is hypouricaemia. If this patient was responding normally to the hypotonicity of the serum, the urine should be dilute. The fact that the urine is concen- trated is abnormal, but it is important to be sure that the patient does not have another cause of a water-retentive state that is a physio- logical response. These are most commonly congestive heart failure, cirrhosis, and volume depletion. In these conditions, the low effective circulating blood volume initiates both sodium and water-retentive mechanisms. Hence a similar set of laboratory values may be seen in these conditions, with the exception that the urine sodium should not be 105 mmol/litre. When the kidney is conserving sodium, the urinary sodium is typically less than 20 mmol/litre, but many patients with cirrhosis and congestive heart failure receive diuretics and inter- pretation of the urinary sodium must be done cautiously in this set- ting. The presence of severe congestive heart failure and cirrhosis is typically obvious based on history and physical examination. Volume depletion (not due to diuretic use) can be distinguished from the syn- drome of inappropriate diuresis based on the urine sodium, which should be less than 20 mmol/litre. In addition, the low blood urea ni- trogen and hypouricaemia are more suggestive of a volume expanded state then a prerenal or volume-depleted state. Other conditions leading to ADH release should also be con- sidered and ruled out

before the syndrome of inappropriate diur- esis is diagnosed: these include postoperative stress, medications, trauma, pain, and nausea. Pulmonary disease, especially pneumonia, is a common cause of the syndrome of inappropriate diuresis, as seen in this case: other causes are given in Table 21.2.1.1. The diagnosis of the syndrome of inappropriate diuresis is often made incorrectly: the syndrome is a diagnosis of exclusion and it is essential that the diagnostic approach is rigorously applied to pre- vent the wrong diagnosis and treatment. Despite the profound hyponatraemia, this man is clinically well and thus he does not require treatment with hypertonic saline. Fluid restriction should be advised, with regular monitoring of the serum sodium, which should increase as the syndrome of inappropriate diuresis resolves with recovery from pneumonia. If hyponatraemia is persistent and refractory to fluid restriction, then a V2 receptor blocker should be considered. Case 5: hyponatraemic encephalopathy in an elderly woman presenting with a fall A 77-year-old woman is brought to the emergency department after falling at home. Her past medical history is significant only with re- gard to osteoporosis, but the patient's daughter states that 2 weeks ago she was started by her primary care physician on a blood pressure medication and that she has been slightly confused over the last few days. Physical examination reveals that she is afebrile, with a pulse of 70 beats/min and blood pressure of 120/60 mmHg. She is confused and not answering questions appropriately, but cardiac examination is normal, the lungs are clear, and she does not have any pedal oedema. Laboratory investigation reveals the following: • Serum—sodium 110 mmol/litre, potassium 2.7 mmol/litre, cre- atinine 118 µmol/litre (1.3 mg/dl), urea 7.9 mmol/litre (22 mg/dl), glucose 6.2 mmol/litre (108 mg/dl), chloride 78 mmol/litre, and bicarbonate 20 mmol/litre Discussion Hydrochlorothiazide can lead to significant hyponatraemia and is one of the more common causes of hyponatraemia in an outpatient setting. Thiazide diuretics (but not loop diuretics) act at the level of the distal convoluted tubule and impair urinary concentrating cap- acity. ADH secretion is stimulated by a state of relative volume de- pletion, and the result is increased urinary concentration and water retention. Loop diuretics, by contrast, act in the ascending limb of the loop of Henle on the Na+/K+/2Cl− cotransporter and lead to im- pairment of both urinary concentrating and diluting capacity and are less likely to lead to hyponatraemia.

 Depending on the degree of this woman's confusion, her immediate management could either be with the administration of 0.9% NaCl or with the administration of a 100 ml 3% NaCl bolus as described in Box 21.2.1.1. Her thiazide should be stopped. Intravenous fluids should not be continued following the administration of volume expansion, as this patient is at high risk for overcorrection of hyponatraemia from a spon- taneous free water diuresis and for the development of demyelination. She has many of the relevant risk factors, including chronic (>48 h) and severe hyponatraemia (115 mEq/litre), thiazide diuretic use, hypokal- aemia, malnutrition, and the potential for overcorrection in the serum sodium by greater than 25 mEq/litre in 48 h. Preventing overcorrection of severe hyponatraemia when a free water diuresis is occurring can be difficult (Box 21.2.1.2). In this situation, the safest and most effective approach is to administer desmopressin. Desmopressin is a synthetic replacement for human arginine vasopressin which increases renal water reabsorption. The administration of desmopressin will stop the free water diuresis, allowing the serum sodium to be corrected slowly with fluid restriction, with care taken to ensure that the serum sodium is not inadvertently lowered. Depending on definition, about 10% of patients develop hyponatraemia when given a thiazide, and older people are particu- larly susceptible. A proposed measure to detect those who might be retaining water and thereby becoming hyponatraemic is to have the patient weigh themselves

before and 48 h after starting the medica- tion. If they fail to lose weight, or they actually gain weight, then the medication should be stopped and serum electrolytes checked. All patients given thiazide diuretics should have their electrolytes meas- ured after the onset of therapy or dose adjustments. Hypernatraemia Hypernatraemia, defined as a serum sodium concentration of greater than 145 mmol/litre, is a commonly encountered problem. It occurs when water intake is inadequate to keep up with water losses, and, since the thirst mechanism is such a powerful stimulus, restricted ac- cess to water is nearly always necessary for its development. This oc- curs in a variety of settings, usually in the very young or very old, or in patients whose illness inhibits their access to water. Several other clinical factors typically seen in the hospital setting can contribute to hypernatraemia, including water losses due to solute diuresis (typically urea or glucose), loop diuretics, gastrointestinal fluid losses, and ex- cessive hypertonic sodium bicarbonate administration. Most patients who develop hypernatraemia have some combination of factors that lead to both impaired access to water and ongoing free-water losses. Hypernatraemia is common in the hospital setting and is frequently iatrogenic during critical illness, typically involving the failure to rec- ognize significant water losses in the urine and to provide the appro- priate amount of replacement in either parenteral or enteral solutions. Pathogenesis When water intake falls below the level of ongoing water losses, the relative amount of exchangeable electrolytes in the body compared with water increases, and this leads to hypernatraemia. The thirst mechanism and the kidney’s ability to concentrate the urine are the defences against this. However, in patients with normal mental status it is rare for hypernatraemia to develop, irrespective of the degree of Table 21.2.1.1 Causes of the syndrome of inappropriate antidiuresis Neoplastic disease Carcinoma (bronchus, pancreas, bladder, prostate, duodenum) Thymoma Mesothelioma Lymphoma, leukaemia Ewing’s sarcoma Carcinoid Bronchial adenoma Neurological disorders Head injury, neurosurgery Brain abscess Brain tumour Meningitis, encephalitis Guillain–Barré syndrome Cerebral haemorrhage Cavernous sinus thrombosis Hydrocephalus Cerebellar and cerebral atrophy Shy–Drager syndrome Peripheral neuropathy Seizures Subdural haematoma Alcohol withdrawal Chest disorders Pneumonia Tuberculosis Emphysema Cystic fibrosis Pneumothorax Aspergillosis Drugs Chlorpropamide Opiates Vincristine, cis-platinum Vinblastine Thiazides Dopamine antagonists Tricyclic antidepressants MAOIs SSRIs ‘Ecstasy’ (3,4-MDMA) Anticonvulsants Miscellaneous Genetic—loss of function of the osmoregulatory TRPV4 gene Idiopathic Psychosis Porphyria Abdominal surgery 3,4-MDMA, 3,4-methylenedioxymetamphetamnine; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

 ongoing water losses, if access to water is not limited because the thirst mechanism will lead to increased water intake to match ongoing losses. The common causes of hypernatraemia are shown in Table 21.2.1.2. Hypernatraemia leads to osmolar forces that cause movement of water out of cells, which in particular subjects the brain to stress that can lead to significant damage. The brain attempts to counteract the osmolar stress during hypernatraemia through a series of adaptations, the principal among these being accumulation of osmotically active ions and de novo generation of osmotically active idiogenic osmoles. The earliest response involves accumulation of the osmotically active cations sodium and potassium. Idiogenic osmoles are a heterogeneous group of substances—including glycerophosphocholine, choline, myoinositol, and sorbitol—that are generated intracellularly to exert an osmotic effect and counteract osmotic forces favouring water re- moval from the cells. These responses are seen very quickly, and after 1 week of hypernatraemia no further changes in

brain osmolality are observed. They serve to maintain brain volume during elevations in serum osmolality and prevent a significant decrease in brain size due to osmotic water losses. During correction of chronic hypernatraemia it must noted that idiogenic osmoles are not rapidly dissipated, and correction of chronic hypernatraemia over 24 h can lead to cerebral oedema. For this reason, chronic hypernatraemia should be treated cautiously to prevent the development of cerebral oedema. Clinical manifestations Clinical manifestations are mainly related to central nervous system dysfunction as cerebral dehydration and cell shrinkage occurs. Hypernatraemia, perhaps due to the underlying conditions that lead to its development, is associated with an overall mortality between 40 and 70%. Groups at particular risk for complications and poor outcomes from hypernatraemia are older people and patients with endstage liver disease. In the latter case, the use of lactulose in the treatment of hepatic encephalopathy frequently leads to an osmotic diarrhoea and significant water losses in the stool: if this is not ap- preciated and free water is not given (many encephalopathic patients are obtunded and unable to drink), then hypernatraemia can de- velop quickly and lead to severe morbidity. It is therefore mandatory to monitor the serum electrolytes closely in this setting, particularly given that patients with liver disease are at increased risk for cerebral demyelination during changes in the serum sodium. Diagnostic approach to hypernatraemic patients The first step in evaluating a patient with hypernatraemia is to take a detailed history focusing on fluid intake and losses. Various potential sources of water loss need to be assessed. This is generally straightfor- ward in the outpatient setting, where these are mainly in the urine, but in the patient in hospital, many sources of water losses may need to be considered: from the gastrointestinal tract (diarrhoea, nasogastric suction, and bowel fistulae), from the urine, and from insensible losses (fever, sepsis, massive diaphoresis, and burns). Whenever practical, these losses should be calculated or estimated. To assess urinary water losses it is necessary to measure the urinary cationic electrolytes (so- dium and potassium) and the urinary osmolality, these pieces of in- formation giving complementary but different information. However, a word of caution is necessary in the interpretation of urinary osmo- lality as errors are frequent in this area. The urinary osmolality alone cannot always determine the presence or absence of electrolyte-free water losses in the urine, the reason for this being that water can be ex- creted with nonelectrolyte osmoles or with electrolyte osmoles. Both of these contribute to the osmolality of the urine, but their excretion will have different effects on water balance. Recall the relationship that the serum sodium is proportional to total body electrolytes relative to total body water (Equation 21.2.1.1). Therefore, when water is excreted with very few electrolytes, the loss of water is in excess of the loss of electro- lytes and hypernatraemia can develop if this water is not adequately replaced. This situation of a high urine osmolality, but very few elec- trolytes in the urine, most typically occurs when there is a significant amount of urea or glucose (e.g. with poorly controlled diabetes) in the urine. By contrast, when water is excreted with a significant amount of electrolyte osmoles, this will tend not to affect the serum sodium, as long as the concentration of electrolytes in the urine and serum are similar, because loss of water is proportional to the loss of electrolytes and therefore the value of the serum sodium does not change. When there is a high urea or glucose load, tremendous quantities of water can be lost in the urine despite maximal urinary concentra- tion. This is what occurs during a solute diuresis and such a patient is typically polyuric. However, if there is a failure to concentrate the urine during a time of hypernatraemia when the patient does not have a solute diuresis, then this should raise suspicion of a urinary concentrating defect. The most common causes of such urinary con- centrating defects are renal failure, loop diuretics, tubulointerstitial renal disease, and diabetes insipidus. Treatment of hypernatraemia Patients with hypernatraemia typically have significant intravascular volume

depletion, hence the initial goal of treatment is to restore this, which is best accomplished with 0.9% saline or colloid. Focus then switches to correction of the serum sodium with free-water replace- ment (Box 21.2.1.3). The rate of fluid administration required by the patient will depend significantly on the degree of ongoing water losses, so that the appropriate amount of replacement water can be given for these in addition to that required for correction of the hypernatraemic state. If there are extrarenal fluid losses, these will need to be estimated because accurate monitoring is typically not possible, and it is ne- cessary to assess any ongoing water losses in the urine to determine whether the kidneys are appropriately conserving water, or whether they are inappropriately continuing to excrete it. As described previ- ously, electrolyte-free water losses in the urine can be calculated with the formula from Equation 21.2.1.2: [1 − ([Na+]u + [K+]u) / ([Na+]se + [K+]se)] × urinary output rate (ml) = rate of urinary water loss. Table 21.2.1.2 Common causes of hypernatraemia Lack of water intake • Decreased thirst (e.g. dementia, neurological impairment) • Bowel rest/nasogastric suction • Dependent on others (e.g. mechanical ventilation, infants) Increased water losses • Solute diuresis (e.g. hyperglycaemia, urea loading from tube feeds, or hyperalimentation) • Loop diuretics • Gastrointestinal water losses • Diabetes insipidus

 Patients with hypernatraemia may be insulin resistant such that hyperglycaemia can result if dextrose-containing solutions are given. For this reason, glucose-containing solutions are potentially harmful and should be avoided if possible, but if they must be used (e.g. 5% dextrose in water), then plasma glucose should be moni- tored closely. When possible, the enteral route should be used before use of parenteral fluid administration. As with the treatment of patients with symptomatic hyponatraemia, patients with neurological impairment due to hypernatraemia re- quire serial measurement of electrolytes, every 2 h, until they are neurologically stable. In patients without evidence of encephalopathy, the serum sodium should not be corrected more quickly than 0.5 to 1 mmol/litre per hour or 15 mmol/litre over 24 h, and, in severe cases (serum sodium >170 mmol/litre), sodium should not be corrected to below 150 mmol/litre in the first 48 to 72 h. If the patient is at high risk for developing cerebral oedema, such as with head trauma or encephalitis, the rate of correction of hypernatraemia should be even slower. Case discussions The evaluation of a polyuric patient and differentiation of pri- mary polydipsia, central diabetes insipidus, nephrogenic diabetes insipidus (Table 21.2.1.3), and hypernatraemia due to a solute di- uresis can be complex and daunting to the general physician, but should be approached as described in the following case studies. Case 6: central diabetes insipidus A 45-year-old man weighing about 70 kg is involved in a motor vehicle accident and suffers a closed head injury, following which he is admitted to the intensive care unit. He is administered large amounts of 0.9% NaCl for fluid resuscitation and then prescribed continued 0.9% NaCl as maintenance fluid. He develops raised intra- cranial pressure with evidence of cerebral oedema, which is treated by placement of an extraventricular device and infusion of 3% NaCl. He then develops polyuria with urine output exceeding 500 ml/h. His serum sodium increases to 184 mEq/litre, with a spot urinary osmolality being 120 mOsm/kg of H2O and the combined urinary sodium plus urinary potassium concentrations being 50 mEq/litre. A continuous DDAVP infusion is started and the urine osmolality increases to 800 mOsm/kg of H2O. Discussion This patient’s hypernatraemia is multifactorial. There is a brisk free water diuresis, and the patient is receiving both 0.9% saline and hypertonic saline, which in combination with urinary reten- tion of sodium has resulted in severe hypernatraemia. The initi- ation of DDAVP has stopped the free water diuresis and so the hypernatraemia should not worsen, indeed—because the patient has a

fixed inability to excrete free water while on DDAVP—even 0.9% saline could in theory lead to a fall in serum sodium concen- tration, and this should be administered at a restricted rate of 50 ml/ h to maintain water and sodium homeostasis. The optimum rate of correction of hypernatraemia is difficult to determine. A serum sodium of greater than 180 mmol/litre could lead to brain injury, but a fall in the serum sodium could aggravate cerebral oedema. In this situation, the rate of sodium correction should probably not exceed 10 mmol/litre per 24 h, and 5 mmol/24 h should be initially attempted. If intracranial pressures increase with correction of hypernatraemia, a 100-ml bolus of 3% NaCl should be administered to acutely raise the serum sodium and decrease the cerebral oedema. The free water required to correct the serum so- dium by 5 mEq is 1.25 litres (Box 21.2.1.3: [5/140] × 35) or about 50 ml/h over 24 h. An appropriate management strategy would there- fore be (in addition to giving the 0.9% saline described earlier) to administer 50 ml/h of 5% dextrose in water, checking the serum so- dium every 2 h. If the serum sodium were to fall faster than antici- pated or the intracranial pressure to rise, the rate of the free water infusion would be adjusted accordingly. The rate of correction may end up being greater than predicted if a natriuresis were to ensue. Case 7: diarrhoeal dehydration A 77-year-old woman who is a nursing home resident develops vomiting and diarrhoea for 3 days, presenting to the emergency department with intravascular volume depletion and dehydration. Box 21.2.1.3 Treatment of hypernatraemia 1 Correct extracellular volume depletion with an isotonic fluid such as 0.9% saline until the patient is haemodynamically stable with good peripheral perfusion. 2 Estimate the free water deficit—because of the many variables that can affect the serum sodium in clinical practice, making a very precise es- timate of the patient's water deficit is not necessary. An approxima- tion of the free water deficit can be made by assuming that 4 ml/ kg of free water will decrease the serum sodium by 1 mmol/litre or that it is equal to [(serum sodium concentration −140)/140] × total body water. For total body water, 0.5 × body weight is a close enough working approximation. Hence an 80-kg man with serum sodium of 160 mmol/litre has a water deficit of [(160 − 140)/140] × 40 = 5.7 litres. 3 Replacement of ongoing water losses, estimated as described in the text, will be required in addition to that required to correct the deficit. 4 Aim of treatment—to decrease serum sodium concentration by 0.5 mmol/litre per hour and by no more than 15 mmol/litre in the first 24 h. In severe hypernatraemia (>170 mmol/litre), serum sodium should not be corrected to below 150 mmol/litre in the first 48 to 72 h. 5 Give hypotonic fluid:

— Route and fluid: preferably water by mouth or nasogastric tube (or other feeding tube), but if parenteral treatment is required, the usual replacement fluid is 0.45% saline (77 mmol/litre NaCl); a lower sodium concentration may be needed if there is a renal concentrating defect or sodium overload. Glucose-containing so- lutions should be avoided.

— Volume: using the incorrect assumption of a closed system (see dis- cussion of treatment for hyponatraemia), and using the example described earlier in this box, to reduce the patient's serum sodium by 10 mmol/litre in the first 24 h would require administration of (10/140) × 40 = 2.85 litres of water in addition to fluids required to accommodate ongoing loses. This could be administered as water by drinking or by feeding tube, or by intravenous infusion of twice the volume of 0.45% saline (given 77 mmol/litre NaCl, half of the volume of a bag of 0.45% saline can be regarded as 'free water'). In practice, if the patient cannot drink freely, does not have a feeding tube, and it is not possible or desirable to place one, then it is rea- sonable to give 0.45% saline at 250 ml/h, adjusting the rate appro- priately in response to repeated monitoring. If 5% dextrose is used (125 ml/h, all of which can be regarded as 'free water'), then it is essential to monitor blood glucose

regularly. 6 Monitoring—serum electrolytes should be measured every 2 h until the patient is neurologically stable, and every 4 h while they remain on an intravenous infusion of hypotonic saline or 5% dextrose.

section 21 Disorders of the kidney and urinary tract 4744 On presentation her weight is 46 kg, down from 50 kg just 2 weeks earlier. Her blood pressure is 90/40 mmHg with a pulse of 126/min. Biochemical testing reveals a serum sodium concentration of 156 mEq/litre, potassium 5.6 mEq/litre, blood urea nitrogen 18 mmol/ l (50 mg/dl), and creatinine 130 µ mol/l (1.4 mg/dl). Urinary tests reveal a sodium concentration less than 5 mEq/litre, potassium 20 mEq/litre, and osmolality 800 mOsm/kg of H_2O. Discussion This woman has an estimated volume deficit of approximately 4 litres, based on her recent weight loss, which would have a composition of approximately 0.9% NaCl (154 mEq/litre). To correct her serum so- dium by 10 mmol/litre in 24 h, approximately 1.8 litres of free water would have to be administered (Box 21.2.1.3: [10/140] × 25). She should initially be given 2 litres of 0.9% saline to acutely correct her intravascular volume depletion and restore circulatory perfusion. This would leave the remaining deficit of approximately 2 litres of isotonic fluid to be corrected over 24 h. Her typical maintenance fluid requirement would otherwise be about 2 litres for the next 24 h, which with the addition of 2 litres of deficit therapy would result in a total volume of 4 litres or 166 ml/h. A total of 4 litres of 0.45% NaCl with 2.5% dextrose in water would provide the equivalent of 2 litres of free water and 2 litres of 0.9% saline and would be adequate therapy to correct both the remaining volume deficit and free-water deficit and to provide for urinary losses. Polyuria and polydipsia The evaluation of a polyuric patient and differentiation of pri- mary polydipsia, central diabetes insipidus, nephrogenic diabetes insipidus (Table 21.2.1.3), and hypernatraemia due to a solute di- uresis can be complex and daunting to the general physician, but should be approached as described in the following case studies. Case 8: primary polydipsia A 27-year-old man with schizophrenia is being evaluated prior to admission to a psychiatric hospital. His only complaint is of frequent Table 21.2.1.3 Causes of polyuria–polydipsia syndromes Cranial diabetes insipidus Familial Autosomal dominant inheritance—mutation of the arginine vasopressin gene (AVP) Autosomal recessive inheritance—DIDMOADa (Wolfram’s) syndrome type 1, caused by mutation in the gene wolframin (WFS1) that encodes a membrane glycoprotein of uncertain function which localizes primarily to the endoplasmic reticulum Acquired Idiopathic Inflammatory (lymphocytic infiltration, sarcoidosis, histiocytosis X autoimmunity, Guillain–Barré syndrome) Trauma (neurosurgery, head injury) Neoplasms (craniopharyngioma, germinoma, pinealoma, hypothalamic metastasis, large pituitary tumour) Infection (meningitis, encephalitis) Vascular (sickle cell anaemia, aneurysms of anterior communicating artery, Sheehan’s syndrome) Pregnancy (associated with vasopressinase) Nephrogenic diabetes insipidus Familial X-linked inheritance—mutation of the arginine vasopressin receptor-2 gene (AVPR2) Autosomal inheritance—mutation of the aquaporin-2 gene (AQP2) can cause autosomal recessive or autosomal dominant disease Acquired Idiopathic Metabolic (hypercalcaemia, hypokalaemia) Vascular (sickle cell disease) Osmotic diuresis (glycosuria, postobstructive uropathy) Chronic renal disease (renal failure, amyloid, myeloma, sarcoidosis, pyelonephritis) Drugs (lithium, demeclocycline, amphotericin, glibenclamide, methoflurane) Primary polydipsia Unknown aetiology Psychogenic (compulsive water drinking) Psychotic (schizophrenia, mania) Idiopathic Secondary Granuloma (sarcoidosis) Vasculitis TB meningitis Multiple sclerosis Drugs (phenothiazines, tricyclic antidepressants) a DIDMOAD, diabetes insipidus, diabetes mellitus, optic atrophy, deafness (Wolfram syndrome).

21.2.1 Disorders of water and sodium homeostasis 4745 urination, approximately 15 times per day according to his family, and that he is always thirsty. He has had no recent seizures and his level of consciousness is normal. Routine physical examination is unremarkable. Laboratory values are as follows: • Serum—sodium 131 mmol/litre, potassium 4.0 mmol/litre, chloride 96 mmol/litre, bicarbonate 24 mmol/litre, urea 5.7 mmol/ litre (16 mg/dl), creatinine 118 µmol/litre (1.3 mg/dl), and glucose 5.4 mmol/litre (98 mg/dl) • Urine—sodium 10 mmol/litre, potassium 8 mmol/litre, and osmolality 65 mOsm/kg Discussion This patient is very likely to be polyuric, given the history. Blood tests reveal mild hyponatraemia and near-normal renal function (chronic kidney disease stage 3). Urinary parameters are consistent with a water diuresis. Calculation of the electrolyte-free water clearance shows that he is losing significant amounts of water in the urine (Equation 21.2.1.2): ([Na+]u + [K+]u)/([Na+]se + [K+]se) = (10 + 8)/(131 + 4) = 0.13. This means that 87% of the patient's urine output is electrolyte-free water. The low urinary osmolality signifies that this is a water diuresis, rather than being driven by the presence of nonelectrolyte solute (e.g. glucose). The question now becomes whether the water diuresis is an appropriate response to excessive water intake or whether it is pathological, leading to excessive water losses that must then be re- placed. In this case, the most likely answer is excessive water intake because of the hyponatraemia and decreased serum osmolality. If a urine concentrating defect was the primary cause of the polyuria, then the patient should not be hyponatraemic unless they had both a urinary concentrating defect and excessive water intake. Case 9: primary polydipsia vs diabetes insipidus A 39-year-old mother is concerned because her 12-year-old daughter has noted frequent urination and says that she is always thirsty. The patient is a well-adjusted adolescent with no past med- ical history and normal development up to this point. Her physical examination is normal. She also has had no recent seizures and her level of consciousness is normal. Serum electrolytes and the results of a 24-h urinary collection are as follows: • Serum—sodium 140 mmol/litre, potassium 4.5 mmol/litre, chloride 103 mmol/litre, bicarbonate 25 mmol/litre, urea 5.4 mmol/litre (15 mg/dl), creatinine 109 µmol/litre (1.2 mg/dl), and glucose 5.7 mmol/litre (103 mg/dl) • Uurine (24 h)—total volume 9 litres, sodium 15 mmol/litre, potas- sium 8 mmol/litre, and osmolality 70 mOsm/kg Discussion The 24-h urinary collection volume clearly demonstrates that this girl is polyuric, and the urinary studies—similar to Case 8—are consistent with a water diuresis. However, the patient is normonatraemic and thus the serum electrolytes are not helpful in reaching a diagnosis: based on the information that we currently have, it is impossible to tell whether her polyuria is due to excessive water intake or to a urinary concen- trating defect, which is an important determination to make in this seemingly healthy adolescent. In order to distinguish between these two possibilities, a water deprivation test can be performed. This is usually done in a hospital setting because a patient with diabetes insipidus can rapidly develop hypernatraemia if water intake is restricted. The details of different protocols for water deprivation tests are beyond the scope of this chapter, but a typical test and its interpretation are shown in Box 21.2.1.4, the basic principle being that if a patient with diabetes insipidus is deprived of water and allowed to become mildly hypernatraemic, then such a patient will not have concentrated urine at that time. By contrast, a patient with primary polydipsia will begin to concentrate the urine if allowed to become mildly hypernatraemic. Case 10: nephrogenic diabetes insipidus A 41-year-old man presents for a routine physical examination. His past medical history is significant only for bipolar disorder, for which he has taken lithium carbonate for the last 15 years. This in- formation leads to further questioning, and he admits to frequent urination and excessive thirst, but denies any symptoms of hesitancy or dysuria. His physical examination is normal. Serum chemistry profile and urine studies are as follows: • Serum—sodium 147 mmol/litre, potassium 3.8 mmol/litre, chloride 110 mmol/litre,

bicarbonate 26 mmol/litre, urea 5.4 mmol/litre (15 mg/dl), creatinine 73 µmol/litre (0.8 mg/dl), and glucose 6.9 mmol/litre (124 mg/dl) • Urine—sodium 25 mmol/litre, potassium 22 mmol/litre, and osmolality 160 mOsm/kg Box 21.2.1.4 Procedure and interpretation of a water deprivation test Procedure 1 The patient is encouraged to drink normally in the evening/night be- fore the test. 2 In the morning, at the beginning of the test, the patient is weighed and baseline measurements made of urinary volume, and urinary and serum osmolality. 3 All fluid intake is withheld for 8 h, with the patient weighed and urine and blood samples taken and analysed every 1–2 h. The test is stopped if the patient loses more than 5% of their initial body weight, or if urinary osmolality above 750 mOsm/kg is achieved. 4 DDAVP (2 µg) is given by intramuscular injection, and the patient is allowed to drink (sensibly) and eat. 5 Urinary samples are collected for the next 16 h. Interpretation Urine osmolality (mOsm/kg) Diagnosis After dehydration After DDAVP

> 750 750 Normala <300 750 Cranial diabetes insipidus <300 <300 Nephrogenic diabetes insipidus 300–750 <750 Partial cranial diabetes insipidus, partial nephrogenic diabetes insipidus, or primary polydipsiab, c a Assuming that serum osmolality remains in the normal reference range of 285–295 mOsm/kg. b The distinction of cranial or nephrogenic partial diabetes insipidus from each other and from primary polydipsia is difficult; measurement of plasma ADH may help in this circumstance. c Assuming significant urinary output, if the patient does not lose weight over 8 h and serum osmolality does not rise, then they must be drinking. The period of ‘water deprivation’ can be extended, but this is unlikely to be helpful if the patient has not abstained from drinking from the beginning of the test. In this situation, a hypertonic saline infusion test may be helpful. The diagnosis is likely to be primary polydipsia, but it may be difficult, if not impossible, to exclude mixed pathology.

section 21 Disorders of the kidney and urinary tract 4746 Discussion The laboratory data in this case are most consistent with diabetes insipidus. The history suggests polyuria, and, as nephrogenic diabetes insipidus is a complication of lithium therapy, it is appropriate to rule out this diagnosis in a patient such as this. In contrast with Case 9, we have a definite differentiation between primary polydipsia and dia- betes insipidus because the serum sodium is mildly elevated and the urinary osmolality is simultaneously low, which confirms the diag- nosis of diabetes insipidus. In a sense, by demonstrating the failure to concentrate the urine despite having hypernatraemia, we have the results of a water deprivation test. However, it is important to note that—based solely on the information given here—it is not known whether the patient has central or nephrogenic diabetes insipidus, although the latter would clearly be anticipated in a patient taking lithium. To make this distinction would require formalized testing to assess the response to exogenously administered DDAVP: if the patient fails to concentrate the urine following administration of DDAVP, then they have nephrogenic diabetes insipidus. Case 11: central diabetes insipidus A 28-year-old man is brought to the emergency department by am- bulance following a car accident during which he sustained severe head trauma. His past medical history is significant only for asthma as a child and a previous appendicectomy. He is taken immediately to surgery for evacuation of an acute epidural haematoma. During the course of surgery, his urinary output increases from 35 ml/h to over 300 ml/h. Blood tests taken immediately on admission to

hospital reveal a serum sodium concentration of 141 mmol/litre; the findings on serum chemistry profile and urine studies taken just after surgery when he arrives on the intensive care unit are as follows: • Serum—sodium 148 mmol/litre, potassium 4.5 mmol/litre, chloride 112 mmol/litre, bicarbonate 26 mmol/litre, urea 6.8 mmol/litre (19 mg/dl), creatinine 127 µmol/litre (1.4 mg/dl), and glucose 6.4 mmol/litre (115 mg/dl) • Urine—sodium 17 mmol/litre, potassium 13 mmol/litre, and osmolality 120 mOsm/kg Discussion The history is highly suggestive of central diabetes insipidus due to head trauma as the cause of polyuria. The urinary studies, as in the three previous cases, show a water diuresis, and, as in Case 10, we have a definite diagnosis of diabetes insipidus because the patient is simultaneously hypernatraemic and undergoing a water diuresis. Again, based solely on the information given, it is not possible to say whether the patient has central or nephrogenic diabetes insipidus, but since the history is so suggestive of a central cause it is prudent to simply administer DDAVP and assess the response. If the patient fails to concentrate the urine following administration of DDAVP, then he has nephrogenic diabetes insipidus, whereas if the urine becomes concentrated—as would be anticipated in this case—then the diagnosis is central diabetes insipidus. When DDAVP is ad- ministered, water intake should be adjusted appropriately to avoid precipitation of significant hyponatraemia, and serum electrolytes should be monitored closely during dose titration. Central diabetes insipidus should always be suspected when the urine is not concentrated in the setting of hypernatraemia. Severe hypernatraemia can develop rapidly in an individual who has restricted access to fluids, such as a patient in an intensive care unit, and hence early recognition is vital. Case 12: solute diuresis from excess urea load A 58-year-old man with a long history of alcohol abuse and chronic liver disease is admitted with necrotizing pancreatitis. Among other manoeuvres, a urinary catheter is inserted, which demonstrates that his urinary output is 30 ml/h. Admission laboratory test results are as follows: • Serum—sodium 138 mmol/litre, potassium 3.9 mmol/litre, chloride 103 mmol/litre, bicarbonate 21 mmol/litre, urea 11.8 mmol/litre (33 mg/dl), and creatinine 136 µmol/litre (1.5 mg/dl) The patient is ordered to have no enteral intake overnight, and he re- ceives 5 litres of 0.9% (normal) saline volume expansion. His abdom- inal pain worsens 24 h after admission and he is continued without enteral intake. Repeat laboratory tests show that his serum sodium has risen to 146 mmol/litre. Over the following 24 h his urinary output increases and infusion of 0.9% saline is continued at 100 ml/h. Total parenteral nutrition is initiated with a daily regimen that com- prises a total volume of 1.5 litres, including 120 mmol of sodium and high amino acid content. Repeat laboratory tests are as follows: • Serum—sodium 151 mmol/litre, potassium 3.2 mmol/litre, chloride 117 mmol/litre, bicarbonate 26 mmol/litre, urea 22.5 mmol/litre (63 mg/dl), creatinine 100 µmol/litre (1.1 mg/dl), and glucose 7.0 mmol/litre (126 mg/dl) • Urine—volume 150 ml/hour; sodium 50 mmol/litre, potassium 13 mmol/litre, and osmolality 650 mOsm/kg Discussion What has occurred in this case is very typical of a solute diuresis leading to hypernatraemia in the critical care setting. The patient is significantly polyuric and has become progressively more and more hypernatraemic. It is important to recognize that, in contrast to pre- vious cases discussed, the urinary osmolality is high, meaning that ADH activity is present and it must be concluded that the patient is losing ‘free water’ (which has to be the situation because the serum so- dium is increasing in the absence of administration of any hypertonic sodium solution). The loss of free water occurring at the same time that the urine is highly concentrated may appear paradoxical, but the answer is evi- dent when the electrolyte-free water is calculated. The ratio of the (sodium + potassium) in the urine to the (sodium + potassium) in the serum is 63/159 = 0.39, hence at his current urinary output he is losing water at a rate of (0.61 × 150) or 91.5 ml/h. Water replace- ment must be given at least equal to this rate to replace the ongoing urinary water losses. The low

urinary sodium and potassium at a time when the urine osmolality is high signifies that there must be a nonelectrolyte osmole in the urine that is ‘obligating’ water loss. The patient is undergoing an osmotic diuresis secondary to a high urea load, this probably being secondary both to the hypercatabolic state of critical illness/stress (protein breakdown is increased, leading to significant urea generation) and to the high amino acid content of the total parenteral nutrition. This scenario is commonly seen in critical illness and is easily preventable if the responsible clinician appreciates the possibility of free-water loss in a patient who be- comes polyuric.

21.2.1 Disorders of water and sodium homeostasis 4747 FURTHER READING Achinger SG, Moritz ML, Ayus JC (2006). Dysnatremias: why are pa- tients still dying? South Med J, 99, 1–12. Achinger SG, et al. (2014). Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series. Nephrol Dial Transplant, 29, 2310–15. Agre P, et al. (1993). Aquaporin CHIP: the archetypal molecular water channel. Am J Physiol, 265, F463–76. Arieff AI, Ayus JC (1993). Endometrial ablation complicated by fatal hyponatremic encephalopathy. JAMA, 270, 1230–2. Arieff AI, Ayus JC, Fraser CL (1992). Hyponatraemia and death or per- manent brain damage in healthy children. BMJ, 304, 1218–22. Ayus JC, Achinger SG, Arieff AI (2008). Brain cell volume regulation in hyponatremia: role of sex age, vasopressin, and hypoxia. Am J Renal Physiol, 295, F619–24. Ayus JC, Arieff AI (1995). Pulmonary complications of hyponatremic encephalopathy. Noncardiogenic pulmonary edema and hypercapnic respiratory failure. Chest, 107, 517–21. Ayus JC, Arieff AI (1999). Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA, 281, 2299–304. Ayus JC, Arieff AI, Moritz ML (2005). Hyponatremia in marathon runners. N Engl J Med, 353, 427–8. Ayus JC, Krothapalli RK, Arieff AI (1987). Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. N Engl J Med, 317, 1190–5. Ayus JC, Moritz ML (2010). Bone disease as a new complication of hyponatremia: moving beyond brain injury. Clin J Am Soc Nephrol, 5, 167–8. Ayus JC, Moritz ML (2019). Misconceptions and barriers to the use of hypertonic saline to treat hyponatremic encephalopathy. Front Med (Lausanne), 6, 47. Ayus JC, Wheeler JM, Arieff AI (1992). Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med, 117, 891–7. Ayus JC, et al. (2012). Is chronic hyponatremia a novel risk factor for hip fracture in the elderly? Nephrol Dial Transplant, 27, 3725–31. Ayus JC, et al. (2015). Treatment of hyponatremic encephalopathy with a 3% sodium chloride protocol: a case series. Am J Kidney Dis, 65, 435–42. Ayus JC, et al. (2016). Mild prolonged chronic hyponatremia and risk of hip fracture in the elderly. Nephrol Dial Transplant. 31(10), 1662–9. Danziger J, Zeidel ML (2015). Osmotic homeostasis. Clin J Am Soc Nephrol, 10, 852–62. Fenske W, et al. (2008). Value of fractional uric acid excretion in dif- ferential diagnosis of hyponatremic patients on diuretics. J Clin Endocrino Metab, 93, 2991–7. George JC, Zafar W, Bucaloiu ID, Chang AR (2018). Risk factors and outcomes of rapid correction of severe hyponatremia. Clin J Am Soc Nephrol, 13, 984–92. Greenberg A, et al. (2015). Current treatment practice and outcomes. Report of the hyponatremia registry. Kidney Int, 88, 167–77. Heilig CW, et al. (1989). Characterization of the major brain osmolytes that accumulate in salt-loaded rats. Am J Physiol, 257, F1108–16. Hew-Butler T, et al. (2005). Consensus statement of the 1st International Exercise-Associated Hyponatremia Consensus Development Conference, Cape Town, South Africa 2005. Clin J Sport Med, 15, 208–13. Hoorn EJ, Zietse R (2013). Hyponatremia and mortality: moving be- yond associations. Am J Kidney Dis, 62, 139–49. Knepper MA, Kwon TH, Nielsen S (2015). Molecular physiology of water balance. N Engl J Med, 372, 1349–58. Maesaka JK, Imbriano LJ, Miyawaki N (2018). Determining fractional urate excretion rates in hyponatremic conditions and - improved methods to distinguish cerebral/renal salt wasting from the syn- drome of inappropriate

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section 21 Disorders of the kidney and urinary tract 4748 21.2.2 Disorders of potassium homeostasis John D. Firth ESSENTIALS The normal range of potassium concentration in serum is 3.5 to 5.0 mmol/litre and within cells it is 150 to 160 mmol/litre, the ratio of intracellular to extracellular potassium concentration being a critical determinant of cellular resting membrane potential and thereby of the function of excitable tissues. Hypokalaemia Hypokalaemia is defined as a serum potassium concentration lower than 3.5 mmol/litre and is the most common electrolyte ab- normality seen in clinical practice, found in about 20% of hospital inpatients. Clinical features and investigation—mild hypokalaemia is asymp- tomatic, but nonspecific symptoms develop with more severe dis- turbance, and serious neuromuscular problems sometimes arise at serum potassium concentrations lower than 2.5 mmol/litre. Extensive testing of patients with mild hypokalaemia is almost cer- tainly inappropriate and likely to be fruitless if pursued. Emergency management—this is rarely required, but intravenous infusion of potassium should be given in the rare circumstances of life-threatening cardiac arrhythmia or muscular paralysis. Aetiology—there are a very large number of possible causes of hypokalaemia, but in most instances the diagnosis is immediately apparent, the most common causes being diuretics (particularly thiazides), vomiting, and diarrhoea. The differential diagnosis of patients with unexplained severe hypokalaemia usually

comprises various abnormalities (usually genetic) of tubular potassium trans- port, concealed vomiting and/or usage of purgatives, and concealed ingestion of diuretics. Renal tubular causes of hypokalaemia—the most common genetic cause is Gitelman's syndrome, an autosomal reces- sive condition caused by mutations in the Na–Cl cotransporter
(NCCT) in the distal convoluted tubule that can cause nonspecific symptoms and is associated with hypotension, alkalosis, hypo- magnesaemia, hypocalciuria, and hypermagnesuria. Management is with potassium and magnesium supplements. Other causes of tubular wasting of potassium include Bartter's syndrome (due to mutations in different tubular cotransporters, channels, or asso- ciated proteins—NKCC2, ROMK, ClCN-Ka, ClCN-Kb, and barttin), and mineralocorticoid excess (real or apparent, each of various types). Altered internal balance causing hypokalaemia—there are several rare conditions in which hypokalaemia is associated with episodes of extreme weakness/paralysis, including thyrotoxic periodic paralysis and familial hypokalaemic periodic paralysis. Hyperkalaemia Hyperkalaemia, defined as a serum potassium concentration of greater than 5.0 mmol/litre, is asymptomatic, and severe hyperkalaemia (>7 mmol/litre) is the most serious of all electrolyte disorders because it can cause cardiac arrest. Clinical assessment—the electrocardiogram (ECG) is the best guide to the significance of hyperkalaemia in any particular individual. As the serum potassium rises, the following changes are seen: (1) tenting of the T wave; (2) P-wave flattening, prolongation of the P–R interval, and widening of the QRS complex; and (3) a 'sine wave' pattern as a prelude to ventricular fibrillation and death. Emergency management—patients with ECG manifestations more severe than tenting of the T waves should be given intravenous cal- cium gluconate (10 ml of 10%) followed by intravenous insulin and glucose, or nebulized salbutamol. Aetiology—there are many causes of hyperkalaemia, but by far the most common are renal failure (acute kidney injury or chronic kidney disease) and/or drugs, in particular, potassium supplements, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers. Other causes of hyperkalaemia—these include hyporeninaemic hypoaldosteronism, other drugs (nonsteroidal anti-inflammatory agents, heparin, calcineurin inhibitors, and trimethoprim– sulfamethoxazole), and renal transport abnormalities (type IV renal tubular acidosis and pseudohypoaldosteronism types 1 and 2 (Gordon's syndrome)). Altered internal balance causing hyperkalaemia—causes include exhaustive exercise, acidosis, drugs (e.g. digoxin and depolarizing muscle relaxants), and hyperkalaemic periodic paralysis (very rare). Potassium homeostasis Potassium is the most abundant cation in the body. Total body po- tassium ranges between 37 and 52 mmol/kg of body weight, and of this 98% is found within cells, where its concentration is 150 to 160 mmol/litre. By contrast, the normal range of potassium concen- tration in serum is 3.5 to 5.0 mmol/litre. The ratio of intracellular to extracellular potassium concentration is a critical determinant of cellular resting membrane potential and thereby of the function of excitable tissues, particularly the nerves and muscles. Potassium tends to leak out of cells through a variety of ion-selective potassium channels found in all cell membranes. The maintenance of the intra- cellular to extracellular gradient is largely dependent on the ubiqui- tous enzyme Na+,K+-ATPase, which pumps two potassium ions into the cell for every three sodium ions extruded. The mechanisms of potassium homeostasis can be considered in terms of internal balance (the relationship between intracellular and extracellular potassium concentration) and external balance (which determines total body potassium). Internal balance A wide variety of factors modulate the distribution of potassium be- tween the intracellular and extracellular fluid compartments. These factors either alter the function of the Na+,K+-ATPase or the rate of efflux of potassium from cells, which together dictate intracellular po- tassium concentration. In view of the importance of the ratio of in- ternal to external potassium concentration for critical neuromuscular functions, some of

these mechanisms serve as essential acute defence

21.2.2 Disorders of potassium homeostasis 4749 mechanisms to counteract life-threatening hyperkalaemia. Factors modulating internal potassium balance are shown in Box 21.2.2.1. External balance Dietary potassium intake in people in Western societies typically varies between 50 and 150 mmol/day, but balance can be attained with an intake of up to 500 mmol/day if homeostatic mechanisms are intact. In normal circumstances, potassium excretion in the stool is not regulated, but amounts to only 5 to 15 mmol/day. When renal function is compromised, the absolute magnitude as well as the proportion of potassium in the faeces is increased, but variation in renal excretion of potassium is usually the only means by which the body achieves external potassium balance by ensuring that ex- cretion equals intake. With a normal intake of potassium, 10 to 20% of the potassium filtered at the glomerulus is excreted, but fractional excretion of po- tassium can vary from 1% when intake is restricted to over 100% when intake is excessive. Micropuncture studies have shown that the amount of potassium reaching the distal convoluted tubule does not vary in these circumstances, indicating that modulation of renal potassium excretion is normally a property of the distal nephron. Factors that modify potassium excretion by the distal nephron are shown in Box 21.2.2.2. These factors are clearly interrelated: it is rare that one is modified in isolation and the overall effect on potassium excretion is almost invariably the aggregate result of several comple- mentary or competing stimuli. Hypokalaemia A low serum potassium concentration (≤3.5 mmol/litre) is the most common electrolyte abnormality seen in clinical practice, found in up to 20% of patients in hospital. Most have mild hypokalaemia, with serum potassium in the range 3.0 to 3.5 mmol/litre, but 5% have a level lower than 3.0 mmol/litre, and 0.03% (more in some series) have very severe hypokalaemia with serum potassium concentra- tion less than 2.5 mmol/litre. Clinical features Patients with mild hypokalaemia often have no symptoms attrib- utable to their low serum potassium concentration. A variety of nonspecific symptoms develop with more severe hypokalaemia, including lassitude, generalized weakness, and constipation. At a Box 21.2.2.1 Factors modulating internal potassium balance Acid–base status Acidosis (excepting renal tubular acidosis) tends to diminish potas- sium uptake by cells and to cause hyperkalaemia; alkalosis has the op- posite effect. The relationship between pH and serum potassium is not simple, but in metabolic acidosis the serum potassium can rise by up to 0.7 mmol/litre for each 0.1 unit fall in blood pH, and alkalosis reduces serum potassium by up to 0.3 mmol/litre per 0.1 pH unit rise. Pancreatic hormones Insulin release is stimulated by hyperkalaemia and inhibited by hypokal- aemia. It induces cellular uptake of potassium by activating the Na +,K+- ATPase directly. Glucagon can increase serum potassium concentration. Catecholamines β2- Adrenergic agonists promote cellular potassium uptake by activating the Na+,K+-ATPase via a cAMP-dependent mechanism. α-Adrenergic agonists have the opposite effect. Exercise Exercise results in loss of potassium from muscle cells, which causes local vasodilatation and increases regional blood flow. Serum potassium can increase by as much as 50% after 10 to 15 min of vigorous exercise, falling precipitately in the recovery period. Aldosterone The most important actions of aldosterone are on external balance, but there is also evidence of effect on internal balance. Osmolality Hyperosmolality increases the serum potassium concentration. Total body potassium The distribution of potassium between intracellular and extracellular compartments is influenced by the total amount of potassium in the body. Changes in the extracellular compartment are always proportion- ately greater than those in the intracellular compartment. The mechan- isms are not known. Box 21.2.2.2 Factors that modify potassium excretion by the distal nephron Aldosterone Aldosterone is the dominant hormone regulating

potassium homeo- stasis. An increase in serum potassium directly stimulates aldosterone secretion by the adrenal glands. In the principal cells of the collecting ducts, aldosterone binds to its intracellular mineralocorticoid receptor, is translocated to the nucleus, and induces production of basolateral Na+,K+-ATPase and the apical sodium channel. The effect is to increase intracellular potassium concentration and the electrochemical potential favouring potassium secretion into the tubular fluid and hence its excre- tion from the body. Under normal conditions, changes in sodium intake lead to changes in plasma aldosterone (an increase leading to decreased secretion) such that potassium homeostasis is preserved despite alter- ation in sodium and fluid delivery to the distal nephron. Intravascular volume Reduction of intravascular volume leads to a 'contraction alkalosis', stimu- lated largely by aldosterone, and which is associated with hypokalaemia. Dietary potassium intake Chronic alterations in dietary potassium intake induce profound modifications in the renal capacity to excrete or conserve potassium. A low-potassium diet leads to an enhanced renal capacity to conserve potassium and a high-potassium diet enhances the ability to excrete a potassium load. The mechanisms involved in these adaptations are poorly understood, although aldosterone is involved. Serum potassium concentration The potassium concentration gradient across the basolateral membrane modulates potassium uptake by the cell and/or passive back-leakage, hence hyperkalaemia leads to enhanced potassium excretion. Acid–base status Systemic pH modulates potassium uptake across the basolateral membrane and conductance of the luminal membrane, with acidosis inhibiting excretion. Chronic metabolic alkalosis is almost invariably as- sociated with potassium depletion. Urine flow rate Increased flow of tubular fluid lowers potassium concentration in that fluid and favours secretion across the luminal membrane. Sodium Reduced delivery of sodium (<30 mmol/litre) to the distal nephron im- pairs potassium secretion by the cortical collecting duct. Other factors ADH, poorly reabsorbable anions (such as sulphates), glucocorticoids, and α-adrenergic agonists stimulate potassium secretion.

 serum potassium level of less than 2.5 mmol/litre, serious neuromus- cular problems sometimes arise. Muscle cramps, rhabdomyolysis, and myoglobinuria (see Chapter 21.5) can occur, and increases in serum creatine kinase activity indicative of muscle injury are fre- quently detectable in those with a serum potassium concentration below 3.0 mmol/litre. Respiratory failure due to muscle weakness has been reported, and hypokalaemia can cause intestinal ileus, par- ticularly in the postoperative period when other factors also conspire to prevent normal gut motility. Paralysis of skeletal muscle has been reported, most dramatically in cases of hypokalaemic quadraparesis, which appears to be more common in India than elsewhere. A wide variety of cardiac arrhythmias can be seen. Paraesthesias and tetany have rarely been described. Hypokalaemia can cause impaired urinary concentrating ability with polyuria and polydipsia, as well as inducing increased produc- tion of ammonia by renal tubular cells and increased bicarbonate reabsorption by the renal tubule, leading to a metabolic alkalosis. Severe prolonged potassium depletion is associated with chronic interstitial nephritis, the presence of renal cysts (most prominent in the medulla), and the development of chronic renal failure. It is not always clear, however, whether hypokalaemia is the cause or effect of this condition. Hypokalaemia may be suspected from the clinical context (e.g. the patient taking diuretics or vomiting copiously), but there are no specific physical signs. Alterations induced in the ECG include flattening of the T wave, depression of the ST segment, and the de- velopment of prominent U waves, which can give the impression of a prolonged QT interval. These changes, typically observed with a serum potassium concentration lower than 3.0 mmol/litre, provide a diagnostic clue to the presence of hypokalaemia, but do not have any serious clinical implications in a patient

with a normal heart. However, hypokalaemia can cause problems in those whose heart is abnormal. There is a correlation between hypokalaemia and the de- velopment of ventricular tachycardia or fibrillation during the acute phase of myocardial infarction; hypokalaemia can provoke life- threatening arrhythmias in those receiving digoxin; patients whose serum potassium falls to less than 3 mmol/litre on treatment with a thiazide diuretic are twice as likely to have ventricular arrhyth- mias on 24-h cardiac monitoring as those whose potassium remains above this level, but whether this constitutes a risk factor for sudden cardiac death remains uncertain. Hypokalaemia may be associated with hypomagnesaemia, which can be caused by gastrointestinal losses (diarrhoea) or urinary losses (loop and thiazide diuretics, alcohol, some nephrotoxic drugs, proton pump inhibitors (PPIs), various renal magnesium wasting syndromes). Patients with this combination may not respond to potassium replacement alone, hence in refractory cases of hypokal- aemia the serum magnesium should be checked and magnesium given if hypomagnesaemia is present. Oral replacement is appro- priate for patients with no or minor symptoms; intravenous therapy (e.g. 50 mmol of magnesium over 8 h) should be reserved for those with pressing clinical indications (e.g. ventricular arrhythmias). Management In emergencies Emergency treatment of hypokalaemia is rarely required. In the rare circumstances of life-threatening cardiac arrhythmia or muscular paralysis, intravenous infusion of potassium (usually potassium chloride) should be given immediately. This must be administered into a central vein (internal jugular, subclavian, femoral, or periph- erally inserted central catheter (PICC line)) since solutions con- taining the necessary high concentration of potassium cause pain and phlebitis if given peripherally, and can cause chemical burns if they extravasate. There is no good evidence on which to base a recommendation regarding dose and rate, but the maximum rate of infusion usually employed is 1 mmol/min, which should be con- trolled with a volumetric pump. The main danger of giving potas- sium with such rapidity is the development of hyperkalaemia, hence the patient and their ECG should be observed continuously and the serum potassium checked frequently, and infusion should be slowed as soon as the life-threatening problem has resolved (arrhythmia settled, muscular power improved). In one study, administration of 40 mmol of potassium over 1 h was found to increase serum potas- sium concentration by an average of 1.1 mmol/litre in hypokalaemic patients with both normal and impaired renal function. In cases that are not emergencies In most circumstances, the management of a patient with hypokal- aemia requires a methodical approach to establishing the diagnosis, which is often readily apparent (but not always so), rectification (if possible) of the underlying cause, and administration of potassium at a less hurried rate than that described previously. In most cases of hypokalaemia, the fall in the serum potassium concentration rep- resents the tip of an iceberg, a reduction of 0.3 mmol/litre typically reflecting a 100 mmol deficit in body stores. This relationship is vari- able, but it is important to remember that patients with even modest hypokalaemia may have a very considerable deficit of total body po- tassium that needs to be replaced. Potassium can be given orally or intravenously. Foods with high po- tassium content are listed later in this chapter, but it should be noted that the potassium which they contain is almost entirely coupled with phosphate. In the absence of adequate chloride intake they are therefore ineffective in replenishing body potassium in the many and common causes of hypokalaemia associated with chloride depletion, such as use of diuretics or vomiting (see later for further discussion). Potassium chloride can be given in either liquid or tablet form, typ- ically 2 to 4 g (c.25–50 mmol) daily in divided doses. Both are well absorbed, but the liquid preparations are unpalatable to many pa- tients and slow-release tablets have been associated with gastrointes- tinal ulceration, bleeding, and stricture, such that they must be taken with fluid while sitting or standing and not just before retiring to bed for the

night. If intravenous administration of potassium is required, infusions containing a concentration of 20 mmol/litre can usually be tolerated through a good peripheral line. If a higher concentration than this is required, central venous access will be necessary. Care must always be taken to monitor serum levels closely. Common causes There are a very large number of possible causes of hypokalaemia (Box 21.2.2.3), but in most instances the diagnosis is immedi- ately apparent. Whenever this is not so, it is wise to remember that common things are the most likely, and it is also important to rec- ognize that concealment of the cause is not infrequent, with diuretic abuse or covert vomiting more likely than the many more exotic and rare causes of hypokalaemia.

21.2.2 Disorders of potassium homeostasis 4751 Hypokalaemia is not a prominent feature of many of the dis- orders listed in Box 21.2.2.3: discussion in this chapter is limited to those conditions that are common, or where hypokalaemia is an important manifestation. A pragmatic approach is first to consider the most frequent causes of hypokalaemia—diuretic ingestion and gastrointestinal fluid loss—and then proceed to a systematic analysis if these are not evidently the cause of the problem. Diuretics The most common cause of hypokalaemia is diuretic therapy. All diuretics other than those acting directly on the collecting duct (amiloride, triamterene, spironolactone) block some form of chloride-associated sodium transport. As a result, they increase the delivery of sodium to the collecting duct, where its reabsorp- tion creates a favourable electrochemical gradient for and obligates potassium secretion. Hypokalaemia frequently occurs together with metabolic alkalosis (serum bicarbonate concentration 28–36 mmol/ litre). In general, the hypokalaemia is mild, with serum potassium in the range 3 to 3.5 mmol/litre, the average fall after initiation of the usual doses of loop diuretics (furosemide, bumetanide, torasemide) being about 0.3 mmol/litre, somewhat more with the usual doses of thiazides (bendroflumethiazide, chlorothiazide, chlorthalidone) at about 0.6 mmol/litre. In one analysis of publications on hypokal- aemia and diuretics, it was found that the fall in serum potassium was little influenced by the reason for prescription (hypertension or heart failure), or by the dose or duration of treatment. The question of whether or not patients receiving diuretics prone to induce hypokalaemia should be prescribed potassium supple- ments or potassium-retaining diuretics has been much debated. There is no strong evidence on which to base recommendations. It seems common sense to monitor for and intervene to prevent hypo- kalaemia in those considered at particular risk of hypokalaemic complications, including those with a history of cardiac arrhythmia, those on digoxin, and those with liver disease in whom electrolyte imbalance might precipitate encephalopathy. Most patients do not fall into any of these categories, and here the balance is between an attempt to prevent a hypothetical but unproven hazard and the re- quirement for medication that is unpalatable to many and in rare in- stances can have significant side effects. As in many other aspects of medicine, the behaviour of the physician will say as much about them as about the condition that they are dealing with. Those that like all test results to be in the ‘normal range’ will prescribe, but short of stop- ping diuretic therapy, correcting diuretic-induced hypokalaemia is not easy. In one study that monitored adverse drug reactions in 5047 consecutive inpatients, 2439 were taking potassium-losing diuretics, in whom serum potassium was less than 3.5 mmol/litre in 21%, and below 3.0 mmol/litre in 3.8%. When the group taking potassium- losing diuretics was broken down into those taking them without any attempt to prevent hypokalaemia, those taking them in conjunction with potassium supplements, and those taking them together with a potassium-sparing diuretic, then serum potassium below 3.5 mmol/ litre was found in 24.9%, 19.7%, and 15.2%, respectively. Box 21.2.2.3 Causes of hypokalaemia Altered internal balance (redistribution of potassium from extracellular to intracellular compartment) • Alkalosis • Insulin (high doses) • β2-Adrenergic

stimulants • Vitamin B12 therapy of deficiency anaemia • Intoxications:

— Theophylline

— Toluene (paint/glue sniffing)

— Barium • Periodic paralysis:

— Thyrotoxic periodic paralysis

— Sporadic periodic paralysis

— Familial hypokalaemic periodic paralysis • ?Aldosterone Altered external balance (low total body potassium) Renal losses (inappropriately high urinary potassium excretion, see text for further information) • Appropriate renal response to alkalosis:

— Vomitinga • Mineralocorticoid excess:

— Primary hyperaldosteronism (Conn’s syndrome)

— Fludrocortisone

— Congenital adrenal hyperplasia

— 11β-Hydroxylase deficiency

— 17α-Hydroxylase deficiency

— Renin-secreting tumours

— Ectopic ACTH production

— Cushing’s syndrome

— Glucocorticoid-responsive aldosteronism

— Renovascular hypertension

— Accelerated (malignant)-phase hypertension

— Vasculitis • Apparent mineralocorticoid excess:

— Liddle’s syndrome

— Syndrome of apparent mineralocorticoid excess (hereditary 11β- hydroxysteroid dehydrogenase deficiency)

— Acquired 11β-hydroxysteroid dehydrogenase deficiency: liquorice, chewing tobacco, carbenoxolone • Impaired renal tubular ion transport:

— Diureticsa

— Bartter’s syndrome

— Gitelman’s syndrome

— Renal tubular acidosis (distal)

— High-dose penicillins

— Magnesium depletion, including PPIs Extrarenal losses (appropriately low urinary potassium excretion, see text for further information) • Gastrointestinal losses:

— Biliary loss

— Lower gastrointestinal loss: diarrhoea,a laxative abuse, villous adenoma

— Fistula

— Ureterosigmoidostomy • Skin losses a The most common causes are diuretics, vomiting, and diarrhoea—these should be excluded before rare conditions are pursued.

section 21 Disorders of the kidney and urinary tract 4752 Loss of gastrointestinal fluid In one study of severe hypokalaemia (serum potassium <2.5 mmol/ litre), gastrointestinal fluid loss was the main cause in 22% of cases. Vomiting The concentration of potassium in gastric and upper intestinal secre- tions is between 3 and 12 mmol/litre. Reduced intake and direct loss of potassium in vomit are not, therefore, the cause of hypokalaemia, which is due to increased renal excretion of potassium. This arises as a result of the kidney’s response to metabolic alkalosis, which is the dominant metabolic problem. Aside from modest quantities of potassium, gastric juices contain sodium ions (30–90 mmol/litre), protons (90 mmol/litre), and chloride (50–125 mmol/litre). Loss of gastric acid (HCl) pulls the buffer equation $H_2CO_3 + Na^+ + Cl^- \Leftrightarrow Na^+ + HCO_3^- + H^+ + Cl^-$ to the right, hence the main effect is meta- bolic alkalosis. Depletion of extracellular fluid volume also occurs, activating the renin–angiotensin–aldosterone system. As the bi- carbonate concentration in the blood rises, more is filtered at the glomerulus and some is excreted in the urine, partly in conjunction with potassium, whose distal excretion is stimulated by high levels of aldosterone. Considerations of acid–base balance have taken pre- cedence over those of potassium homeostasis, and hypokalaemia results. An important point to note is that the combination of direct chloride loss in vomit and contraction of extracellular fluid volume lead to a situation where the kidney avidly retains chloride and the urinary concentration of chloride falls to a very low level (<10 mmol/ litre, sometimes as low as 1–2 mmol/litre, when the normal range is 30–120 mmol/litre). This is of critical clinical significance be- cause reabsorption of filtered sodium and potassium ions by the renal tubule can only be achieved in combination with an anion, usually chloride, hence if urinary chloride concentration is already close to zero there is no way in which sodium and potassium can be reabsorbed efficiently, meaning that sodium and potassium that are

administered can only be retained if provided in conjunction with chloride, and not if given as other salts. The renal response of chloride retention also means that measurement of urinary chloride concentration can be helpful in making the diagnosis of surrepti- tious vomiting (see later). Resuscitation of a patient with hypokalaemia due to vomiting re- quires the intravenous infusion of 0.9% sodium chloride, together with potassium supplementation as described previously. In severe cases, the total body deficit of fluid may be in excess of 5 litres, and of potassium of many hundreds of millimoles. Diarrhoea The concentration of potassium in stool is 80 to 90 mmol/litre, hence—given normal stool weight of 100 to 200 g/day—faecal loss of potassium is usually in the range 5 to 15 mmol/day. The potassium concentration in the stool decreases as stool volume increases, but volume can increase massively, such that substantial potassium loss and profound hypokalaemia can complicate any severe diarrhoeal illness. Potassium loss in diarrhoeal states is usually associated with loss of bicarbonate, resulting in a coexisting metabolic acidosis, such that serum levels of potassium may not reflect the true body deficit. In this circumstance, the renal excretion of potassium is broadly appropriate, and potassium deficiency is not due to a renal leak. However, in some situations, potassium in stool is lost in conjunc- tion with chloride, resulting in a metabolic alkalosis and a picture similar to that seen with vomiting. A villous adenoma of the colon or rectum can rarely result in pro- found hypokalaemia. The mechanism seems to involve secretion of cAMP and prostaglandin E2 by the tumour, leading to disturb- ance of ion transport in the normal colonic mucosa. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can significantly reduce stool volume and help to correct both volume depletion and hypokalaemia. Similar disturbances probably underlie the hypokal- aemia of patients with the watery diarrhoea, hypokalaemia, achlor- hydria syndrome, caused by excess vasoactive intestinal peptide secreted by certain tumours. In addition to treatment directed at the tumour itself, somatostatin or somatostatin analogues are effective in controlling symptoms. Hypomagnesaemia and proton pump inhibitors PPIs (e.g. omeprazole, esomeprazole, lansoprazole, and pantopra zole) are widely prescribed for the treatment of upper gastro- intestinal symptoms. In 2006, it was recognized that they could, by a generic effect, and particularly when taken in combination with diuretics, cause hypomagnesaemia associated with hypocal- caemia and relative hypoparathyroidism. The presumed mech- anism is by PPI-induced inhibition of transient receptor potential melastatin-6 (TRPM6) and TRPM7 channels in intestinal epi- thelial cells, which are responsible for absorption of magnesium from the gut. Hypokalaemia is thought to arise by the following mechanism: intracellular magnesium inhibits potassium secretion through luminal potassium channels (ROMK) in the connecting and cortical tubules, hence hypomagnesaemia and a reduction in intracellular magnesium concentration can induce kaliuresis and hypokalaemia by releasing this inhibitory effect. This provides an explanation for the clinical observation that treatment of hypo- kalaemia in the context of PPI use, or with other causes of hypo- magnesaemia, requires correction of magnesium depletion: it is refractory to potassium supplementation alone. Diagnosing the cause of hypokalaemia in difficult cases The diagnosis of the cause of hypokalaemia is usually straightfor- ward and explained by diuretic therapy or gastrointestinal fluid loss, as described earlier. In other patients, the abnormality is mild, with the occasional serum potassium concentration measured at just below the lower limit of the normal range, such that extensive inves- tigation is almost certainly inappropriate (and likely to be fruitless if pursued). However, some patients present with unexplained se- vere hypokalaemia, and these represent a considerable challenge for both diagnosis and management. The differential diagnosis in these cases usually lies between various abnormalities of tubular potas- sium transport, concealed vomiting and/or usage of purgatives, and concealed ingestion of diuretics. It is important to ask directly for a history of vomiting or diar-

rhoea, and about present or past use of any medications, particularly diuretics or purgatives. It is also worthwhile to ask about consump- tion of liquorice or chewing tobacco (see ‘Apparent mineralocor- ticoid excess’). Examination is likely to be unremarkable in cases of unexplained hypokalaemia, but pay particular attention to body

21.2.2 Disorders of potassium homeostasis 4753 weight, height, and body mass index, and to any other features that might support the diagnosis of an eating disorder such as anorexia nervosa or bulimia nervosa (see Chapter 26.5.10). A logical investigative approach to the patient with unexplained hypokalaemia begins with trying to establish whether or not the urinary potassium excretion is appropriate (Box 21.2.2.3). If potas- sium depletion is not due to urinary losses, then the normal renal response is to reduce urinary potassium concentration to less than 15 mmol/litre or less than 30 mmol/day. Values higher than these suggest that renal potassium loss is at least partly responsible for the hypokalaemia. However, the measurement of a ‘spot’ urinary potas- sium concentration may be misleading if the patient is polyuric, and 24-h urinary collections are cumbersome at best, and cannot be reli- ably obtained from some patients. The effects of urinary dilution can be compensated for by esti- mation of the urinary potassium-to-creatinine ratio. In a study of 43 patients with severe hypokalaemia, estimation of the ratio of potassium excretion to creatinine excretion proved helpful in differentiating those with renal potassium wasting (ratio >2.5 mmol potassium/mmol creatinine, >22 mmol potassium/g creatinine)) from those with a nonrenal condition (ratio lower). A further re- finement is to calculate the transtubular potassium concentration gradient (TTKG), which estimates the potassium concentration at the end of the cortical collecting tubule (the site responsible for most potassium excretion) according to the formula: TTKG = urinary K plasma osmolality / plasma[K] urin ([ ]) (× × ary osmolality) In a normal subject on a normal Western diet, the TTKG is 8 to 9. In a patient with hypokalaemia, a value below 3 suggests that the kidneys are trying to conserve potassium appropriately and a value above 3 that they are wasting potassium. A careful study reported the findings of extensive investigation of 27 adult patients (17 women) who presented with chronic hypo- kalaemia (serum potassium concentration <3.4 mmol/litre) that was sustained for over 5 years and which had previously eluded diagnosis. The following diagnoses were established: diuretic abuse (in 5 patients), surreptitious vomiting (8), laxative abuse (1), renal tubular acidosis (1), and Gitelman’s syndrome (12). Medical work- up that had sought to make the diagnoses by measurement of plasma renin activity, plasma aldosterone concentration, and urinary potas- sium concentration failed to discriminate between these conditions. Investigations that were diagnostically helpful are given in Table 21.2.2.1, the most useful being the plasma pH and chloride concen- tration, urinary chloride concentration and screen for diuretics, and (in one case) stool weight. A report of 99 patients with chronic normotensive hypokalaemia (mean serum potassium 2.8 mmol/L of 4 years’ duration) described similar diagnoses: Gitelman’s syndrome (33 cases), Bartter’s syn- drome (10), distal renal tubular acidosis (12), anorexia/bulimia nervosa (21), and surreptitious use of laxatives (11) or diuretics (12). An Indian study of 50 cases of hypokalaemic flaccid paralysis found underlying diagnoses of potassium loss due to excessive sweating, diarrhoea and vomiting, thyroid disorders (11 cases thyrotoxic, 3 cases hypothyroid), and renal tubular dysfunction (5 cases distal renal tubular acidosis, 4 cases Gitelman’s syndrome). The finding of a low plasma chloride concentration with the vir- tual absence of chloride from the urine supports the diagnosis of surreptitious vomiting. Screening the urine for diuretics is appro- priate if the urinary chloride concentration is above 20 mmol/litre, and if no diuretics are found in samples with a chloride concen- tration of above 50 mmol/litre then Gitelman’s syndrome is likely. Vomiting, diuretics, and

Gitelman’s syndrome all cause alkalosis, whereas laxative abuse is associated with acidosis, as is renal tubular acidosis. The diagnosis of renal tubular acidosis can be established Table 21.2.2.1 Diagnostic clues in 27 cases of hypokalaemia that were hard to diagnose Investigation Normal range Diagnosis Diuretic consumption Vomiting Laxative consumption Renal tubular acidosis Gitelman’s syndrome Number of cases 5 8 1 1 12 Plasma/serum Chloride 97–108 mmol/litre Low normal or low Low Low Normal Low normal or low Bicarbonate 22–28 mmol/litre High normal or high High Low Low High normal or high Magnesium 0.8–1.1 mmol/litre NR NR NR NR Low Urinary Sodium 40–130 mmol/litre Normal Normal Low Normal High normal or high Potassium 30–110 mmol/litre Normal Normal Normal Variable Normal Chloride 30–120 mmol/litre Normal Very low (<10 mmol/litre) Low Normal High Calcium 2.5–8.0 mmol per 24 h NR NR NR NR Low Magnesium 2.5–7.5 mmol/litre NR NR NR NR High Diuretic screen Positive Negative Negative Negative Negative Stool Weight 100–200 g/day Normal Normal High Normal Normal NR, not reported. Reproduced with permission from Gladziwa et al. (1995). Nephrology, Dialysis, Transplantation 10, 1607.

section 21 Disorders of the kidney and urinary tract 4754 by demonstrating an inability to produce acid urine in the presence of systemic acidosis (see Chapter 21.15 for further discussion). The management of cases of surreptitious vomiting, or diuretic or purgative abuse is difficult. Many patients will fulfil diagnostic criteria for anorexia nervosa or bulimia nervosa, and issues other than those simply and directly related to potassium homeostasis will clearly need to be considered. The physician may well need to seek expert psychiatric help. See Chapter 26.5.10 for further discussion. Rare causes of hypokalaemia due to altered external potassium balance Mineralocorticoid excess Hypokalaemia can be caused by a large number of causes of min- eralocorticoid excess, as shown in Box 21.2.2.3. Primary aldoster- onism is discussed in Chapters 13.5.1 and 16.17.3, congenital adrenal hyperplasia in Chapter 13.5.2, and glucocorticoid-remediable aldos- teronism in Chapter 16.17.4. Hypokalaemia is rarely a prominent feature of the other conditions of mineralocorticoid excess listed, which are discussed elsewhere in this book. Apparent mineralocorticoid excess Activating mutations in the β- or γ-subunits of the epithelial so- dium channel in the collecting duct causes Liddle’s syndrome. Disabling mutations in the type 2 11β-hydroxysteroid dehydro- genase gene cause a deficiency of the enzyme, allowing cortisol access to the mineralocorticoid receptor and the syndrome of ap- parent mineralocorticoid excess. Acquired inhibition of the action of 11β-hydroxysteroid dehydrogenase can be caused by liquorice, carbenoxolone, and chewing tobacco. Hypokalaemia with low plasma concentrations of renin and aldosterone are features of all of these conditions, which are discussed in Chapter 16.17.4. Renal tubular abnormalities of potassium transport Patients with ‘classic’ distal renal tubular acidosis are prone to hypo- kalaemia, as are most patients with proximal renal tubular acid- osis: these conditions are discussed in Chapter 21.15. In 1962, Bartter described ‘hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis: a new syndrome’. Well over 100 papers were subsequently written to describe features of what was believed to be the same eponym- ously named condition. The picture became immensely confused, but since 1995 has been clarified by the recognition of distinct phenotypes within the group of patients previously thought to have ‘Bartter’s syndrome’ and the application of powerful molecular gen- etic methods to their study. These revealed that most adults previ- ously thought to have Bartter’s syndrome in fact have Gitelman’s syndrome. Gitelman’s syndrome Gitelman’s syndrome is the most common genetic cause of hypo- kalaemia. It is an autosomal recessive condition typically caused by biallelic inactivating mutations in the SLC12A3 gene that codes for the thiazide-sensitive Na–Cl cotransporter (NCCT; Fig. 21.2.2.1), which explains why the clinical phenotype is mimicked

by con- sumption of such diuretics. However, some patients with a Gitelman phenotype will have an inactivating mutation in a single SLC12A3 allele combined with other abnormalities in the other allele, and mutations in CLCNKB (the cause of Bartter's syndrome type III) are sometimes found. There are no dramatic clinical symptoms or signs, hence sus- picion of the diagnosis of Gitelman's syndrome often arises only when hypokalaemia is found (or in screening of family members of a known case) (Table 21.2.2.1). However, when surveyed dir- ectly, most patients with Gitelman's syndrome are found to be sig- nificantly symptomatic, reporting salt craving, musculoskeletal symptoms (cramps, muscle weakness, and aches), constitutional symptoms (fatigue, generalized weakness, and dizziness), nocturia, thirst and polydipsia, paraesthesia and numbness, and palpitations, with many patients considering their symptoms to be a moderate problem or worse. Whereas blood pressure is typically normal or low in young adults with the condition, hypertension can develop in later life for reasons that remain obscure. Arthralgia and/or chondrocalcinosis are common, the latter possibly related to chronic hypomagnesaemia. The diagnosis of Gitelman's syndrome can be confirmed by gen- etic testing and recent guidance (KDIGO Controversies Conference) suggested that this should be offered to all suspected of having the condition. However, this is not straightforward: the genes involved are large, with multiple mutations and lack of 'hot spots'. Patients should be encouraged to indulge their tendency to consume salt (sodium chloride) ad libitum. Otherwise, lifelong oral magnesium and/or potassium supplementation is required, with the intention of achieving a serum potassium concentration greater than 3.0 mmol/ L and a serum magnesium concentration greater than 0.6 mmol/L. It is noteworthy that magnesium deficiency aggravates hypokalaemia and renders this refractory to treatment with potassium. All types of magnesium salts are effective, but they are often poorly tolerated because of their propensity to cause diarrhoea. Organic salts (aspar- tate, citrate, lactate) have higher bioavailability than inorganic (oxide, Na 2Cl Distal convoluted tubule Medullary thick ascending limb Blood Cl ATP K ClC-Kb (Bartter's III) Na Cl K Na K ATP Lumen K Na Blood Lumen NKCC2 (Bartter's I) ROMK (Bartter's II) NCCT (Gitelman's) Fig. 21.2.2.1 Some genetic disorders of the renal tubule that cause hypokalaemia. ClC-Kb, kidney-specific chloride channel; NCCT, Na–Cl cotransporter; NKCC2, Na–K–2Cl cotransporter; ROMK, ATP-regulated potassium channel.

 hydroxide). Magnesium chloride will also compensate for urinary chloride loss, with a typical recommended starting dose being 300 mg/day (magnesium component), best taken as slow-release tablets in divided doses with meals. Potassium supplements should be given as chloride, initially 40 mmol/day in divided doses, titrated up as needed. Intravenous potassium chloride and/or magnesium chloride/sulphate may be needed in extreme circumstances, for example, serious cardiac arrhythmia or muscular paralysis. Options to be considered in patients with persistent symptomatic hypokalaemia that is refractory to magnesium and/or potassium supplements, or who cannot adhere to these, include potassium-sparing diuretics, renin–angiotensin system blockers and (by sup- pressing an elevated level of renal prostaglandin E2 secretion) NSAIDs. Heterozygote carriers of Gitelman mutations have increased urinary sodium excretion (due to a self-selected higher salt in- take), modestly lowered blood pressure and reduced chance of developing hypertension, a serum potassium concentration to- wards the lower limit of the normal range, and increased sus- ceptibility to hypokalaemia induced by diuretics. They also have increased bone density. See Chapter 21.16 for further discussion, in particular of genetic aspects and matters related to hypomagnesaemia.

Bartter's syndrome Bartter's syndrome (types I–IV) is caused by autosomal recessive mutations of ion transporters or ion channels in cells of the thick ascending limb of the nephron (Fig. 21.2.2.1). It

generally presents in childhood with features including growth failure and mental re- tardation, polyuria, and polydipsia, associated with hypokalaemia and metabolic alkalosis. Type I and type II Type I is caused by mutations in the SLC12A1 gene encoding the Na–K–2Cl cotransporter (NKCC2). Type II is caused by mutations in the KCNJ1 gene, which encodes the apical ATP-sensitive potassium channel (ROMK) that recycles potassium back into the lumen and is critical for continued activity of the NKCC2 cotransporter. Both cause polyhydramnios in pregnancy and premature birth. Severe dehydration in the first few days of life or during intercurrent illness is associated with a high mortality rate before diagnosis. Other clinical manifestations in survivors include short stature, intellectual disability, generalized weakness, muscle cramps, and rickets. Aside from hypokalaemic alkalosis, biochemical and radiological features include severe hypercalciuria and nephrocalcinosis. Dehydration must be avoided, potassium supplementation is needed, and (by suppressing an elevated level of renal prostaglandin E2 secretion) NSAIDs may be helpful. Type III Type III is caused by mutations in the CLCNKB gene encoding a kidney-specific chloride channel (ClC-Kb). This is the cause of the ‘classic’ form of Bartter’s syndrome. The clinical pic- ture is more varied than that for types I or II and ranges in severity from near-fatal volume depletion with hypokalaemic alkalosis and respiratory arrest, to mild disease presenting in a teenager with polyuria and weakness, as can be seen in Gitelman’s syndrome (see ‘Gitelman’s syndrome’). Nephrocalcinosis is not a feature, but late manifestations can include proteinuria. Management is with potas- sium supplementation and care to avoid dehydration. Long-term prognosis is uncertain. Type IV This condition is caused by defects in function of two chloride channels, ClC-Ka and ClC-Kb. It may (type IV) be due to mutations in the BSND gene that encodes barttin, a protein which colocalizes with chloride channels in the kidney and inner ear, or (type IVb) to simultaneous mutations in CLCNKA and CLCNKB genes. Presentation is antenatal or in infancy, with congenial sen- sorineural deafness in addition to features as described for type I and type II Bartter’s syndrome. Type V In this condition, a gain-of-function mutation in the cal- cium sensing receptor (CaSR) leads to inhibition of secretion of parathyroid hormone at a lower than normal level of serum calcium and hence to persistent hypocalcaemia. The CaSR receptor is also expressed in the medullary thick ascending limb, where its over- activity can affect ROMK and NKCC2 in such a way as to create a Bartter phenotype with hypokalaemia and metabolic alkalosis. Ureteric diversion into the colon Surgical diversion of the ureters into the colon (ureterosigmoido stomy) was previously performed as a method of urinary drainage, most commonly in children for the treatment of bladder exstrophy and in adults following total cystectomy. The operation is now rarely (if ever) performed because of the metabolic consequences, which have driven improvement in surgical techniques for ileal conduits and alternative urinary diversions. However, the consequence of ureterosigmoidostomy is that urine remains in contact with the co- lonic mucosa for a long time, in which case its response is to re- absorb urinary ammonium and secrete bicarbonate, leading to hyperchloraemic acidosis, and also for there to be stimulation of colonic potassium secretion, resulting in hypokalaemia. Profound and life-threatening acidosis can occur with concurrent illness, and chronic renal failure can develop. Rare causes of hypokalaemia due to abnormal internal potassium balance Although there are many causes of hypokalaemia (Box 21.2.2.3), there are relatively few causes of hypokalaemia associated with ex- treme weakness, the most common explanation for this rare presen- tation being hypokalaemic periodic paralysis. In Western countries, most cases of hypokalaemic periodic paralysis are familial, termed familial periodic paralysis, whereas in Asian populations, the most common cause is thyrotoxic periodic paralysis. In all forms of hypo- kalaemic periodic paralysis the hypokalaemia and paralysis result from an acute shift of potassium into cells, the mechanism for which is unknown, although there is speculation that it is due to a transient hyperadrenergic state.

Infection with dengue virus also needs to be considered in areas where this is endemic. One study reviewed the medical records of 97 patients who pre- sented over a 10-year period to hospital in Taiwan with severe hypo- kalaemia (serum potassium <3.0 mmol/litre, mean 2.2 mmol/litre) and acute loss of muscle strength with inability to walk. The final diagnoses established are shown in Table 21.2.2.2. Treatment of acute attacks of hypokalaemic periodic paralysis traditionally involves the administration of intravenous potassium. Some patients recover with as little as 20 mmol, but others require over 200 mmol. In all types of this condition, a paradoxical fall in serum potassium concentration can occur at the start of treatment, and rebound hyperkalaemia is also seen.

section 21 Disorders of the kidney and urinary tract 4756 Thyrotoxic periodic paralysis The diagnosis of thyrotoxic periodic paralysis is established if hyper- thyroidism, usually but not always due to Graves' disease, is present when hypokalaemic paralysis occurs. The condition is commonest in Asians, in whom about 2% of those with thyrotoxicosis are af- fected (compared to 0.1–0.2% in non-Asians), and over 95% of cases occur in men, with age of onset usually 20 to 40 years. Thyrotoxic periodic paralysis is associated in some cases with variants in genes encoding potassium channels: a study of Caucasian or Brazilian patients found that one-third had a mutation in the KCNJ18 gene, which encodes Kir2.6, an inwardly rectifying potas- sium channel that is transcriptionally regulated by thyroid hormone; a case–control study of Korean patients found the allelic frequency of a particular single nucleotide polymorphism adjacent to the KCNJ2 gene was significantly associated with the condition; muta- tions in various other genes have also been incriminated. This has led to the hypothesis that patients who are susceptible to thyrotoxic periodic paralysis may have an ion channel or other genetic defect that does not manifest clinically when they are euthyroid, but is prone to under the stress of hyperthyroidism. Typical presentation is with sudden attacks of generalized weak- ness, which most commonly begin at the same time as clinical mani- festation of hyperthyroidism, but can occur before or after. Weakness usually lasts for several hours. A variety of stimuli have been reported to provoke attacks, including large carbohydrate meals (perhaps via the mechanism of an exaggerated response to insulin), excessive physical activity, and stress. Aside from weakness (legs > arms, prox- imal > distal), physical findings during an attack include tachycardia (a useful diagnostic discriminator from sporadic periodic paralysis) and high blood pressure; signs of hyperthyroidism are absent in 20 to 40% of cases. Laboratory findings include hypokalaemia (mean serum potassium 2.1 mmol/litre in one large series), elevated serum T4, and low serum TSH. Hypophosphataemia and hypomagnes- aemia are also found. Although treatment of thyrotoxic periodic paralysis has conven- tionally involved administration of potassium, there is considerable experience suggesting that patients with this condition respond rap- idly to the β-blocker propranolol, which can be given intravenously (up to 3 mg total dose) or orally (3 mg/kg) with the expectation that serum potassium concentration will return to normal and paralysis will resolve within 2 h. Effective treatment of hyperthyroidism prevents attacks, but about two-thirds of patients will have recurrent paralytic attacks, most commonly in the first 3 months after diagnosis, while their hyper- thyroidism is brought under control. Propranolol, with or without potassium supplements, can also reduce the frequency of attacks. Familial hypokalaemic periodic paralysis Attacks typically begin in late childhood or adolescence and are vari- able in frequency (the typical interval between attacks is weeks to months) and duration (typically hours, but can range from minutes to days). They can sometimes be precipitated by administration of insulin or glucose and aborted by exercise, which induces an exag- gerated rise in serum potassium concentration. Rhabdomyolysis has been reported. A progressive proximal myopathy eventually de- velops in most patients. The diagnosis is

established by finding a family history of attacks of flaccid weakness and hypokalaemia. Familial hypokalaemic peri- odic paralysis can be caused by mutations in several genes. The most common, accounting for about 70% of cases, is CACN1AS, which encodes a dihydropyridine receptor that functions as a voltage-gated calcium channel and is also critical for excitation–contraction coup- ling in a voltage-sensitive and calcium-independent manner. Other causes include mutation in (1) SCN4A, which encodes for a sodium channel and is also the site of mutations causing hyperkalaemic periodic paralysis; (2) KCNJ2, which encodes a potassium channel; and—possibly but not certainly a cause of hypokalaemic periodic paralysis—(3) KCNE3, which encodes a potassium channel β sub- unit. The conditions are autosomal dominant, with 100% pene- trance in males, but much less in females. Emergency treatment is with intravenous potassium: propranolol is ineffective. Dichlorphenamide (a carbonic anhydrase inhibitor) is effective at preventing attacks in most cases; acetazolamide (an- other carbonic anhydrase inhibitor), pinacidil (a potassium channel opener), potassium-sparing diuretics, and verapamil have also been used. Nonfamilial (sporadic) periodic paralysis The cause of this condition is not known: patients do not have a family history of hypokalaemic periodic paralysis and do not have hyperthyroidism. A genome-wide association study in a Han Chinese population found a novel disease-associated gene (CTD-2378E21.1) for both thyrotoxic periodic paralysis and sporadic peri- odic paralysis that may negatively regulate KCNJ2 expression. There Table 21.2.2.2 Final diagnoses established in 97 patients initially diagnosed as having hypokalaemic periodic paralysis Final diagnosis Number Mean age (years) Male:female ratio Patients with hypokalaemic periodic paralysis Thyrotoxic periodic paralysis 39 28 39:0 Sporadic periodic paralysis 29 26 23:6 Hypernatraemic hypokalaemic periodic paralysisa 3 18 3:0 Familial periodic paralysis 2 16 2:0 Patients who did not have hypokalaemic periodic paralysis Metabolic alkalosis Primary aldosteronism 6 39 2:4 Bartter’s or Gitelman’s syndromes 6 21 4:2 Diuretics 3 40 0:3 Hyperchloraemic acidosis Distal renal tubular acidosis 6 47 3:3 Toluene abuse 3 28 1:2 a Mean serum sodium concentration was 167 mmol/litre. Two patients had brain tumours and one patient had hypothalamic involvement with tuberculosis. It is possible that diabetes insipidus was the explanation for their presentation and there is insufficient evidence in the paper to justify the naming of a new syndrome. Patients with hypokalaemic periodic paralysis do not have an acid–base disorder: arterial pH, Pco2, and bicarbonate are all within the normal range. A key finding is that the urinary potassium concentration is low (mean 8 mmol/litre). There is also a low transtubular potassium concentration gradient (TTKG = (urine K/serum K)/(urine osmolality/serum osmolality)) of <3: the normal renal response to hypokalaemia of nonrenal origin being a TTKG <2, whereas a renal cause of hypokalaemia is usually associated with TTKG >5). Reproduced with permission from Lin et al. (2001). Quarterly Journal of Medicine 94, 133–9.

 are no obvious precipitating factors for acute attacks. Heart rate at presentation is lower than for those with thyrotoxic periodic par- alysis (mean 76 compared with 105 beats/min). Treatment is as for familial hypokalaemic periodic paralysis. Sudden unexplained death during sleep Sudden unexplained death during sleep (SUDS), known in Japan as ‘Pokkuri Death Syndrome’, in Thai as lai-tai, and as the Filipino folk term bangungut (meaning ‘to rise and moan during sleep’), is not uncommon in Asians and is a leading cause of death in young men in rural north-eastern Thailand. A survey in the Philippines reported an annual incidence of 22 per 100 000 in the 20- to 39-year age group (mostly in men) and 43 per 100 000 overall. It has been recorded over the years as the cause of death of many hundreds of apparently healthy male Thai migrant workers in Singapore. Women are rarely, if ever, affected. Death occurs at rest and is nocturnal in most (84%) cases. In cases that are observed, witnesses often report

that death is preceded by a few minutes of groaning, choking, coughing, and muscular spasticity or paralysis. There has been much speculation over the cause of SUDS, with a popular hypothesis being that it could be caused by potassium deficiency. Survivors of SUDS-like attacks and relatives of victims of SUDS have been reported to have significantly lower activity of erythrocyte Na+,K+-ATPase and lower serum potassium con- centration than controls. However, a recent forensic autopsy of 42 Thai SUDS victims has given important new insight. This re- vealed possible causes of death (e.g. coronary artery disease) in 17 cases. Whole-exome sequencing was undertaken in the remaining 25 and enabled potential identification of the cause of death in 18 (72%). The commonest (8/18) was a mutation in the TTN gene, which encodes for titin, a protein expressed in cardiac and skeletal muscle and implicated in some forms of cardiomyopathy. One case had a mutation in the cardiac sodium channel gene SCN5A that causes Brugada syndrome. Whether or not hypokalaemia plays any significant role in SUDS remains uncertain. Dengue virus Case reports describe patients presenting after a short-lasting febrile illness with acute onset, rapidly worsening pure motor paralysis as- sociated with hypokalaemia. In one series of 12 patients, baseline serum potassium was 2.7 mmol/litre and weakness improved in all over 24 to 72 h with correction of serum potassium. Hyperkalaemia Clinical features Hyperkalaemia is the most serious of all electrolyte disorders, des- pite being relatively infrequent, because it can cause cardiac ar- rest. Some patients report muscular symptoms such as weakness, stiffness, or simply a ‘funny feeling’, but the significance of these is rarely appreciated. A high serum potassium concentration leads to membrane depolarization in excitable tissues, making the initi- ation of an action potential more likely, and to increased membrane potassium conductance, which impairs recovery after an action potential. The effect is to cause electrical instability with the risk of life-threatening arrhythmia. The likelihood of such an event increases as the serum potassium concentration rises, but some patients are more resistant to the cardiac effects of hyperkalaemia than others: for instance, those with endstage renal failure on long- term dialysis may be habitually hyperkalaemic (although this is not to be encouraged) and tolerate a serum potassium concentra- tion that would kill a normal person if imposed acutely. Management In emergencies The best guide to the significance of hyperkalaemia in any particular individual is the impact that it is having on the ECG, and an ECG should be obtained immediately in any patient in whom the question of hyperkalaemia arises. The earliest change is tenting of the T wave, progressing as the serum potassium concentration rises to P-wave flattening, prolongation of the PR interval, widening of the QRS com- plex, and eventually a ‘sine wave’ pattern as a prelude to ventricular fib- rillation and death. All involved in the care of acutely ill patients must be able to recognize this pattern of ECG changes and give effective emer- gency treatment for severe hyperkalaemia, as described in Chapter 21.5. In cases that are not emergencies The management of patients with hyperkalaemia but without sig- nificant ECG changes is also discussed in Chapter 21.5. Key elem- ents are advice to avoid high potassium foods and drinks (Table 21.2.2.3) and stop drugs that increase serum potassium. Use of cal- cium resonium, patiromer or other similar agents that exchange cal- cium for potassium in the gastrointestinal tract is rarely the most appropriate method of clinical management. Causes of hyperkalaemia There are many causes of a high serum potassium concentra- tion (Box 21.2.2.4), but a survey of over 400 cases found that renal failure was present in 43% and potassium supplements or potassium-sparing diuretics had been taken by 37%. Life- threatening hyperkalaemia is almost exclusively seen in those with renal failure, often in conjunction with another exacerbating cause. Common scenarios would be a patient with acute kidney injury who is hypercatabolic or who has extensive tissue destruction, as in rhabdomyolysis, or a patient with endstage renal failure who has missed a dialysis treatment, not adhered to a low-potassium diet

(Table 21.2.2.3), or suffered an upper gastrointestinal haem- orrhage, thereby inadvertently consuming a high-potassium meal. Hyperkalaemia is not a prominent feature of many of the conditions listed in Box 21.2.2.4: further discussion in this chapter is limited to disorders other than renal failure that are not discussed elsewhere in this textbook and in which hyperkalaemia is a common or important manifestation. Pseudohyperkalaemia Haemolysed samples show hyperkalaemia, which also occurs when there is considerable delay between venepuncture and separation of red cells and plasma or serum in the laboratory, allowing potas- sium to leak out of red cells after venesection. However, aside from these common and banal explanations, there are other reasons for pseudohyperkalaemia. Potassium is released from white blood cells and platelets as blood coagulates, causing the serum potassium concentration to exceed, by a few tenths of a millimole per litre, that of plasma estimated in a parallel sample. This process is greatly exaggerated when gross

 leucocytosis or thrombocytosis is present, such that the serum po- tassium concentration can be over 2 mmol/litre higher than that in plasma. The plasma and not the serum potassium concentration should obviously be measured in this circumstance. There is also the rare syndrome of familial pseudohyperkalaemia, where mutation of the ABCB6 gene, which encodes a red blood cell membrane ABC transporter protein, leads to a cold-induced leak of red cell potassium ions into plasma. This can be of clinical import- ance if a person with the condition donates blood, when after storage for 5 or 6 days the plasma potassium concentration is much higher than expected. Surveys of European blood donors suggest that the prevalence of familial pseudohyperkalaemia is about 1:500, leading to the suggestion that donors should be screened for the condition. Abnormal external potassium balance Mineralocorticoid deficiency Hyporeninaemic hypoaldosteronism It is not uncommon to find patients with chronic kidney disease who have hyperkalaemia despite a glomerular filtration rate (GFR) that should be sufficient to maintain normokalaemia. Two-thirds of these will have the syndrome of hyporeninaemic hypoaldosteronism, which should be suspected in any patient with hyperkalaemia without other obvious explanation. The condition typically occurs at age 50 to 70 years, in women more than men, with diabetes mellitus and/or chronic tubulointerstitial nephritis being the commonest forms of renal disease. The hyperkalaemia is usually asymptomatic, but presentation with cardiac arrhythmia and/or muscle weakness has been described. Characteristics of the syndrome include low levels of plasma renin activity, which are unresponsive to sodium restriction or fur- osemide, low plasma and urinary aldosterone, hyperkalaemia, and hyperchloraemic metabolic acidosis. Fractional potassium excretion is low for the GFR, and the response to kaliuretic stimuli is blunted. Glucocorticoid metabolism is normal. The cause of both hyporeninism and hypoaldosteronism is not known, but reduced renin secretion in patients with diabetes mellitus may arise from injury to the juxtaglomerular apparatus, de- ficient conversion of prorenin to renin, autonomic dysfunction, or volume expansion due to a primary increase in renal salt retention. Hypoaldosteronism is probably related to the low level of plasma renin activity, but the situation is probably more complicated than this since most patients secrete subnormal amounts of aldosterone in response to infusion of both angiotensin II and ACTH, suggesting a defect in the function of the adrenal gland. Criteria for establishing the diagnosis of hyporeninaemic hypoaldosteronism are not well defined, but supportive evidence would be finding levels of renin and aldosterone below their reference Box 21.2.2.4 Causes of hyperkalaemia Pseudohyperkalaemia (test-tube phenomena where measured serum potassium concentration does not reflect that in the patient’s plasma in vivo) • Tight tourniquet with or without limb exercise

• Test-tube haemolysis • Leukaemia with very high white cell count • Thrombocytosis Altered internal balance (redistribution of potassium from extracellular to intracellular compartment) • Exercise • Metabolic acidosis (inorganic) • Massive tissue destruction:a

— Crush injuries

— Rhabdomyolysis

— Burns

— Tumour lysis • Insulin deficiency, hyperglycaemia, hyperosmolality • Drugs/toxins:

— Digoxin poisoning

— Succinylcholine

— Arginine

— Fluoride intoxication

— β-blockade • Malignant hyperthermia • Hyperkalaemic periodic paralysis Altered external balance (high total body potassium) Excessive ingestionb • Consumption of high-potassium foods (Table 21.2.2.3) • Potassium supplements • Low-salt diet (high in potassium) • ‘Salt substitutes’ (contain potassium) • Upper gastrointestinal haemorrhage (‘blood meal’) Impaired excretion General impairment of renal function • Acute kidney injury • Chronic kidney disease Defects that specifically impair renal potassium excretion • Mineralocorticoid deficiency:

— Renin deficiency—hyporeninaemic hypoaldosteronism, which can be either idiopathic or drug induced (NSAIDs or calcineurin inhibi- tors such as tacrolimus and ciclosporin)

— ACE inhibition—drug induced (lisinopril, ramipril, enalapril, etc.)

— Angiotensin II receptor blockade—drug induced (losartan, candesartan, etc.)

— Defective aldosterone production—generalized adrenal failure (Addison’s disease) • Deficiency of aldosterone synthesis:

— Drug induced (heparin)

— Enzyme deficiencies

— Idiopathic Impaired tubular ion transport • Drugs:

— Potassium-sparing diureticsc

— Trimethoprim

— Calcineurin inhibitors (ciclosporin, tacrolimus) • Pseudohypoaldosteronism:

— Type 1

— Type 2 (Gordon’s syndrome) a Often associated with acute kidney injury. b Note that it is very rare for hyperkalaemia to be caused by excessive ingestion if renal excretory mechanisms for potassium are working normally. c These drugs should generally be avoided in patients with significant renal impairment.

21.2.2 Disorders of potassium homeostasis 4759 Table 21.2.2.3 Potassium content of various foodstuffs High-potassium foods (to be avoided in those with hyperkalaemia) Suitable low-potassium alternatives Dairy products Single cream Reasonable daily allowance of milk Condensed/evaporated milk Various commercial coffee whiteners Food drinks Meats Ready cooked meals in sauce All kinds of meat Fish Ready cooked fish pies, fish in sauce, etc. All kinds of fish Fruit All dried fruit Apples Apricots Grapefruit Avocado pears Kiwi fruit Bananas Passion fruit Cherries Pears Grapes Satsumas Melons Tangerines Oranges Peaches Pineapples Plums Raspberries Rhubarb Strawberries Tinned fruit of all types—but after draining off the juice or syrup, which contains a lot of potassium Vegetables Artichokes Aubergines Bamboo shoots Beans—French, runner Beans—baked, butter, haricot Cabbage Beetroot Carrots Cabbage—red Cauliflower Corn on the cob Celery Mushrooms Courgettes Peas—chick, split Cucumber Potatoes—jacket, chips, crisps, sweet Lettuce Spinach Marrow Tomato Onions Watercress Peas Potato—boiled in plenty of water Radish Spring greens Sprouts Swedes Turnips Cakes Any containing dried fruit or nuts Dough Chocolate Fruit pies—if fruit not high potassium Coffee Jam tarts Flapjacks Meringue Gingerbread Scones—plain (continued)

section 21 Disorders of the kidney and urinary tract 4760 ranges after a manoeuvre to stimulate the renin–angiotensin– aldosterone system (by upright posture or furosemide). However, it is uncommon for patients to be investigated intensively in routine clinical practice since treatment is usually straightforward. Therapy for hyporeninaemic hypoaldosteronism includes dietary potassium restriction and avoidance of drugs that can cause hyper kalaemia. Measures to increase urinary excretion of potassium, such as the use of thiazide or loop diuretics, can be useful. Although min-eralocorticoid replacement (fludrocortisone, 0.2 mg/day) effectively treats the hyperkalaemia, sodium retention and worsening hyper- tension are often unacceptable side effects. Cation exchange resins can be used to increase elimination of potassium from the gut, but compliance with long-term use of these medications can be difficult to achieve, although newer preparations (e.g. patiromer) may be better tolerated. Effects of drugs on the renin–angiotensin–aldosterone system NSAIDs Prostaglandin synthetase inhibitors produce hypo reninaemic hypoaldosteronism by interfering with prostacyclin- mediated renin secretion, with reduction in GFR and distal sodium delivery as potential contributory factors. These effects, as might be expected, become more important in the context of renal im- pairment: in one study, approximately one-quarter of patients with chronic renal failure developed hyperkalaemia after treatment with indometacin. ACE inhibitors and angiotensin II receptor blockers These pro- duce hyperkalaemia by impairing angiotensin II-mediated secretion of aldosterone. In one study, hyperkalaemia was found in 46 of 119 (39%) patients taking ACE inhibitors who were attending a renal clinic. The higher the serum creatinine concentration, the greater the chance of hyperkalaemia. Those with diabetes were also at par- ticular risk. The treatment had to be stopped in 15 patients (13%). ACE inhibitors and spironolactone have been found to improve prognosis in heart failure, but care is needed when prescribing for those who might be prone to hyperkalaemia.

One study reported life-threatening hyperkalaemia (mean serum potassium 7.7 mmol/ litre) in 25 patients who had received this combination of medica- tions. Combined treatment with both an ACE inhibitor and an angio- tensin II receptor blocker is more likely to induce hyperkalaemia than either agent given alone, but this combination of drugs is no longer recommended for any indication. Heparin Hyperkalaemia occurs in about 7% of patients given heparin, which is a potent inhibitor of aldosterone production. It can arise with doses as low as 10 000 units/day, but—as with most other hyperkalaemic stimuli—clinically important elevations in the High-potassium foods (to be avoided in those with hyperkalaemia) Suitable low-potassium alternatives Mince pies Victoria sandwich—plain Parkin Sweets and biscuits Any containing dried fruit or nuts Chocolate Barley sugar Biscuits—plain Fruit gums Honey Fudge Humbugs Liquorice Jam Marzipan Marmalade Toffee Mints Beverages Cocoa Coca-Cola Coffee—instant Coffee—percolated Drinking chocolate Fruit juices—if pure and containing any high-potassium fruit Fruit squashes—unless with high juice content Lemonade and other fizzy drinks Tea—instant Soda water Tea—infusion Tonic water Cereals Muesli and other cereals containing dried fruit or nuts Bread Breakfast cereals—most types Pasta Rice Other Salt substitutes This list is not exhaustive. If a patient with hyperkalaemia seems to be consuming an unusual diet, then obtain dietetic advice. Table 21.2.2.3 Continued

21.2.2 Disorders of potassium homeostasis 4761 serum potassium concentration are found only when more than one homeostatic mechanism for potassium is deranged. Patients with endstage renal failure who receive unfractionated heparin to pro- vide anticoagulation during haemodialysis treatments have a higher predialysis serum potassium than those given low molecular weight heparin. The most important mechanism of aldosterone inhibition appears to involve reduction in both numbers and affinity of angio- tensin II receptors in the zona glomerulosa, which is reduced in width by prolonged use of heparin. Direct inhibition of the enzyme 18-hydroxylase has also been postulated. Production of other cor- ticosteroids is not affected. Calcineurin inhibitors Hyperkalaemia is a well-documented complication of the immunosuppressive drugs ciclosporin and tacrolimus. Two mechanisms are possible, both of which may be exacerbated by reduction in GFR caused by nephrotoxicity: (1) drug-induced hyporeninaemic hypoaldosteronism, which is well documented with tacrolimus; and (2) in association with a distal tubular acidification defect that is caused (mechanism un- known) by both ciclosporin and tacrolimus. Renal transport abnormalities Tubulointerstitial renal disease A few hyperkalaemic patients with chronic renal failure but a GFR that should be adequate for potassium homeostasis have normal levels of aldosterone and plasma renin activity and seem to have a primary defect in the ability of the distal nephron to excrete po- tassium. They also typically have tubulointerstitial types of renal diseases, the abnormality being documented in patients with obstructive uropathy, renal transplants, sickle cell disease, sys- temic lupus erythematosus, amyloidosis, and medullary sponge kidney—all of which can also be associated with hyporeninaemic hypoaldosteronism. In contrast to patients with hyporeninaemic hypoaldosteronism, their hyperkalaemia is unresponsive to min- eralocorticoid replacement therapy. Type IV renal tubular acidosis Hyperkalaemia due to impaired renal excretion of potassium may be a feature of type IV or voltage-dependent renal tubular acidosis. The lumen-negative potential difference along the distal nephron normally facilitates the excretion of potassium and hydrogen ions, and hyperkalaemia and metabolic acidosis occur when this is re- duced. This condition is discussed in Chapter 21.15. Potassium-sparing diuretics Spironolactone is increasingly used in the management of resistant hypertension. This, and other potassium-sparing diuretics, are obvi- ously likely to cause hyperkalaemia in patients with any predispos- ition to this condition, and they should only be used with great care in those with renal failure. The serum

potassium concentration must be monitored closely in patients taking these agents who become acutely unwell. Trimethoprim–sulfamethoxazole and pentamidine A review of 80 patients treated with standard-dose trimethoprim (up to 320 mg/day) and sulfamethoxazole (up to 1600 mg/day) showed that this increased the serum potassium concentration by an average of 1.2 mmol/litre, whereas there was no change in a control group receiving other antibiotics. Some studies have shown a lesser effect than this, but even larger increases in serum potas- sium concentration have been reported in patients receiving high- dose trimethoprim–sulfamethoxazole to treat pneumocystis, and hyperkalaemia is also reported with use of pentamidine. Both tri- methoprim and pentamidine block the apical sodium channel in the distal nephron in a manner similar to amiloride. Pseudohypoaldosteronism type 1 There are autosomal recessive and autosomal dominant forms of this rare condition (see Chapter 16.17.4 for further discussion of the gen- etic abnormalities). The recessive form typically presents in infancy with vomiting and feeding difficulty. There are signs of volume de- pletion and laboratory findings of hyponatraemia, hyperkalaemia, and acidaemia. The plasma renin concentration is usually increased and plasma aldosterone concentration is markedly elevated. The sodium concentration in urine, sweat, saliva, and stool is high. Treatment is with salt supplements that must usually be continued into adulthood. By contrast, the autosomal dominant form has a milder phenotype, with symptoms that remit with age. Pseudohypoaldosteronism type 2 (Gordon’s syndrome) This is a rare autosomal dominant condition (see Chapter 16.17.4 for further discussion of the genetic abnormalities) in which hyper- tension is accompanied by hyperkalaemia despite normal GFR. The condition is usually asymptomatic and detected fortuitously if serum potassium concentration is measured for any reason, or in the course of family studies, but it can rarely present in late child- hood or adulthood with hyperkalaemic periodic paralysis. There is a hyperchloraemic acidosis, a low level of plasma renin activity, and normal or slightly low plasma aldosterone concentration. Giving exogenous aldosterone does not increase urinary potassium excre- tion or reduce hyperkalaemia. Because a kaliuresis can be provoked by infusion of sodium sulphate or sodium bicarbonate, but not so- dium chloride, it has been suggested that enhanced reabsorption of chloride at a distal nephron site may underlie the abnormality in potassium secretion. Physiological abnormalities can be corrected with thiazide diuretics, which may provide effective treatment. Abnormal internal potassium balance Exercise Exercise-related rises in the serum potassium concentration are a normal phenomenon and usually modest, but increases to 7 mmol/ litre occur during acute, maximal, physical performance and levels as high as 10 mmol/litre have been reported with prolonged exhaustive exercise such as in marathons. Exercise-induced hyperkalaemia is accentuated by β-adrenergic blockade or α-adrenergic agonists, and in patients with chronic kidney disease. Acidosis Acidosis diminishes potassium uptake by cells (Box 21.2.2.1) and causes hyperkalaemia. The increase in the serum potassium con- centration is greater with metabolic than respiratory acidosis, and occurs more markedly with hyperchloraemic than with organic acid-induced forms of metabolic acidosis. Stimulation of insulin re- lease by organic acids appears to account for this divergent response, explaining the pathophysiology of disturbed potassium homeostasis

 in diabetic ketoacidosis. At presentation, when insulin is deficient, potassium is redistributed in a fashion comparable with mineral acid-induced metabolic acidosis and patients are hyperkalaemic. However, the preceding kaliuresis (caused by polyuria) has ren- dered the body enormously deficient in potassium, and the serum potassium concentration falls rapidly as soon as insulin is provided, allowing potassium to return to

the cells. Indeed, dangerous hypo- kalaemia can develop if adequate potassium is not given during treatment. Drugs Several drugs can produce hyperkalaemia by altering the transcellular distribution of potassium. Digoxin and similar preparations diminish cellular potassium uptake by inhibiting the Na+,K+-ATPase pump, and substantial hyperkalaemia can accompany digoxin intoxication. Succinylcholine and other depolarizing muscle relaxants increase the potassium permeability of muscle: the serum potassium concentra- tion typically increases by 0.5 to 1.0 mmol/litre, but hyperkalaemia can be more severe in patients with burns or neuromuscular diseases. Infusion of 30 g of the cationic amino acid arginine HCl increases serum potassium concentration by 0.5 to 1.0 mmol/litre and can pro- duce life-threatening hyperkalaemia in individuals with deranged potassium metabolism. Fluoride intoxication appears to increase the serum potassium concentration by provoking leakage from the intra- cellular compartment, and associated hypocalcaemia enhances the cardiac risks of fluoride-induced hyperkalaemia. Although β2-adrenergic stimulants cause hypokalaemia and can be used to treat hyperkalaemia (see Chapter 21.5), the adminis- tration of β-blockers typically increases the serum potassium con- centration only modestly (by 0.1 to 0.2 mmol/litre). However, the hyperkalaemic effect can be much more prominent when other potassium homeostatic mechanisms are deranged, for example, in patients receiving intermittent haemodialysis, the predialysis serum potassium concentration is increased on average by 1.0 mmol/litre. Hyperkalaemic periodic paralysis Hyperkalaemic periodic paralysis is a rare (prevalence of five per million population) autosomal dominant condition caused by mu- tations in the sodium channel gene SCN4A, mutations in which can also cause hypokalaemic periodic paralysis. Clinical presentation is with episodic attacks of focal weakness (rather than paralysis), often of the thigh/calf muscles or arms/hands, that typically last 1 to 2 h. The bulbar and respiratory muscles are sometimes involved. Attacks usually begin in the first decade of life, with frequency that plateaus in early adulthood and later declines. They may come out of the blue, but the most commonly reported triggers are cold envir- onments, rest after exercise, stress or fatigue, alcohol, and hunger. The serum potassium concentration is usually, but not always, raised during an acute attack, and it may be low in rare instances. Many pa- tients report myotonia and paramyotonia, and one-third develop a progressive myopathy. Thyroid dysfunction affects about 20%. Attack frequency may be reduced by consuming regular small/ medium-sized meals and taking carbohydrate rich snacks in be- tween, and by avoidance of alcohol, cold foods and drinks, and high potassium foods. Hydrochlorothiazide (reduces the serum potas- sium level), mexiletine (for myotonia) and flecainide were the drugs most commonly taken by patients who regarded their condition as ‘mostly controlled’ in one careful study. Patients very variably report that an acute attack can be amelior- ated by manoeuvres such as doing gentle exercise, keeping warm, eating sweet foods, and drinking water. Treatment with an inhaled β2- agonist is helpful, and intravenous glucose and insulin is war- ranted in severe cases. FURTHER READING Blanchard A, et al. (2017). Gitelman syndrome: consensus and guid- ance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int, 91, 24–33. Charles G, et al. (2013). Characterization of hyperkalemic periodic paralysis: a survey of genetically diagnosed individuals. J Neurol, 260, 2606–13. Ernst ME, Moser M (2009). Use of diuretics in patients with hyperten- sion. N Engl J Med, 361, 2153–64. Fergeson SB, Linas S (2010). Mechanisms of type I and type II pseudohypoaldosteronism. J Am Soc Nephrol, 21, 1842–5. Gennari FJ (1998). Hypokalemia. New Engl J Med, 339, 451–8. Gladziwa U, et al. (1995). Chronic hypokalaemia of adults: Gitelman’s syndrome is frequent but classical Bartter’s syndrome is rare. Nephrol Dial Transplant, 10, 1607–13. Grier JF (1995). WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome: clinical features, diagnosis, and treatment. Southern Med J, 88, 22–4. Halevy J, et al.

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