Electrolytes and acid–base: common fluid and electrolyte disorders

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Abstract

Disturbances of fluid and electrolyte balance are common in clinical practice, especially in a hospital setting, and can be iatrogenic or compounded by inappropriate medical or surgical treatment. Their recognition and appropriate management are not necessarily difficult or complex. Although specific formulae and standard protocols can be helpful at the bedside, there is no substitute for an understanding and application of some basic principles of renal and endocrine physiology, which this article sets out. Some knowledge of basic renal physiology (including transport function along the nephron and its regulation) also makes it easier to understand most clinical disorders of fluid and electrolyte balance. Unfortunately, patients seldom present with a single acid–base or fluid and electrolyte disturbance, so the real challenge is to determine which disorder came first, before rushing in and treating in isolation what might initially seem to be the predominant clinical abnormality. Here, we start by describing the main homeostatic functions of the kidney and, more specifically, the essential workings of its functional unit, the nephron (glomerulus and renal tubule).

Keywords Acid–base; MRCP; nephron structure; potassium; sodium; water balance

Key points

- A basic understanding of renal physiology can aid the diagnosis and treatment of most electrolyte disorders
- Changes in serum or plasma sodium concentration reflect alterations in water and not sodium balance
- Hypokalaemia can carry a greater mortality risk than hyperkalaemia
- Chronic acid–base disorders usually reflect abnormalities of renal function

The nephron (Figure 1)

At a normal glomerular filtration rate (GFR) of 125 ml/minute/1.73 m^2, the volume filtered by the glomerulus is approximately 180 litres/day, which contains approximately 25,000 mmol Na^+. The filtrate is so large that the renal tubule is concerned principally with reabsorption, although it is also involved in the secretion of a few ions (H^+, K^+) and other solutes, such as weak organic acids and bases (including some drugs and metabolites). Most of the reabsorptive (transport) processes, including the transport of glucose, amino acids, bicarbonate, phosphate and calcium, occurs in the proximal tubule, which can be divided into three parts (S1, S2, S3), and the loop of Henle. However, the different parts of the distal tubule and collecting duct (CD) have an important role in determining the final urinary excretion of Na^+, K^+ and H^+, and also of water.[1]

In the distal tubule and along the CD, reabsorption of Na^+ and Cl^- continues, and their final urinary excretion is usually <1% of what is filtered (known as the fractional excretion); however, a net secretion of K^+ and H^+ occurs in these nephron segments. Some Ca^{2+} and Mg^{2+} reabsorption also takes place in the distal tubule. Water reabsorption in the distal nephron varies, depending on the concentration of circulating vasopressin (AVP; antidiuretic hormone), which is usually determined by plasma osmolality, but also extracellular fluid volume (ECFV), for example after haemorrhage when the additional pressor action of AVP at high concentrations becomes important.

Most of the transport processes taking place along the renal tubule are directly or indirectly coupled to the reabsorption of Na^+. Sodium ions passively enter the lining epithelial cells from the lumen (filtrate) across the apical cell membrane and down the concentration (strictly, electrochemical) gradient via a series of transporters (co-transporters and exchangers) or Na^+ channels. Sodium exit across the basolateral membrane requires the 'sodium pump' (Na^+/K^+-ATPase), which is ultimately responsible for most of the reabsorptive and secretory processes in the renal tubule (except for a few other active pumps transporting H^+, Ca^{2+} and H^+/K^+ exchange that are also energy-requiring ATPases). Indeed, the mechanism of Na^+ reabsorption is essentially the same throughout the tubule; only the route of entry into the cell differs from one segment to another.[1]

Sodium is the dominant extracellular cation and the main determinant of osmolality in the ECFV, and therefore of water distribution between the extracellular and intracellular fluid compartments. Its balance is critically important in maintaining circulating blood volume (which is part of the ECFV) and arterial blood pressure. Hence, many of the extrinsic regulators of renal function are intended to alter Na^+ excretion, preserve sodium balance and regulate blood pressure.[1]

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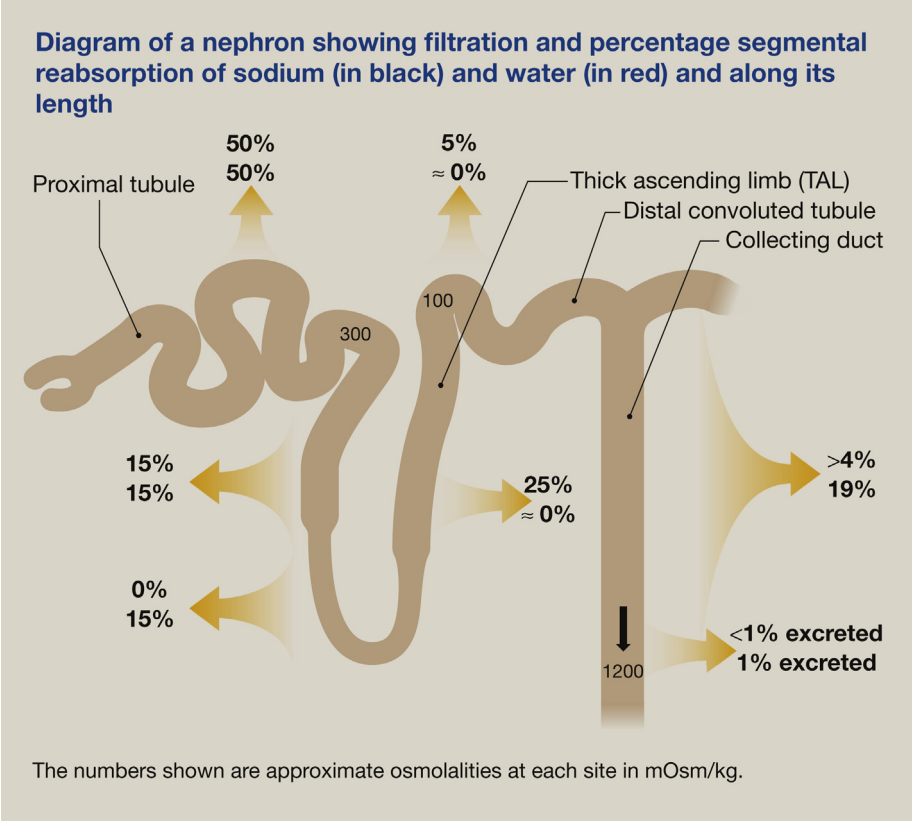

Figure 1

The main extra-renal Na^+-controlling mechanisms

Positive or stimulatory

Aldosterone is the major regulator of Na^+ reabsorption (and K^+ and H^+ secretion) in the distal nephron; it is secreted by the zona glomerulosa of the adrenal cortex in response to a raised plasma angiotensin II concentration or high plasma K^+ concentration. Aldosterone stimulates the sodium pump and the apical Na^+ channel (the epithelial sodium channel) of *principal cells* in the CD; this increases electrogenic Na^+ reabsorption, which depolarizes the apical membrane and facilitates K^+ secretion by these same cells (as well as H^+ secretion by adjacent, acid-secreting *intercalated cells*).

Angiotensin II and sympathetic nerve (noradrenaline (norepinephrine)) stimulation increase Na^+ reabsorption, mainly in the proximal tubule; they also reduce GFR by causing efferent and afferent arteriolar vasoconstriction, respectively.

AVP, in addition to its key role in water handling, increases urea reabsorption in the medullary CD and significantly stimulates Na^+ reabsorption along the thick ascending limb of the loop of Henle.

Negative or inhibitory

Atrial natriuretic peptide is released from the cardiac atria in response to stretch; it increases Na^+ excretion by suppressing the renin–angiotensin–aldosterone system and directly inhibiting Na^+ reabsorption in the (medullary) CD.

Other factors that act locally (paracrine), such as endothelin-1, bradykinin and nitric oxide, seem to inhibit Na^+ reabsorption along the CD. Some of these factors also affect vascular tone directly: angiotensin II, AVP and endothelin-1 act as vasoconstrictors, whereas atrial natriuretic peptide, bradykinin and nitric oxide act as vasodilators.

Water handling

AVP is the key regulator of water reabsorption along the distal nephron (connecting tubule and CD), where it binds to basolateral V2 receptors and stimulates adenylate cyclase, leading to the insertion of apical water channels (aquaporin-2 (AQP2)). However, water reabsorption cannot occur without an osmotic gradient between the tubular lumen and the interstitium. The osmolality of the renal interstitium progressively increases from the cortex to medulla (from around 300 to 1200 mOsm/kg) and is established and maintained by the active reabsorption of Na^+ (without water) along the thick ascending limb (the countercurrent multiplier system). This system allows water reabsorption in the renal medulla and its removal by the vasa recta capillaries by countercurrent exchange.

Acid–base excretion

The renal tubule is also the major regulator of acid–base homeostasis as it is the site of HCO_3^- reabsorption via H^+ secretion, and ammoniagenesis. Bicarbonate reabsorption occurs predominantly in the proximal tubule, and to a lesser extent in the thick ascending

limb, by Na^+/H^+ exchange, which reclaims the normally filtered HCO_3^- (Figure 2). Net H^+ secretion by an ATPase along the CD determines the final urine pH and acid excretion in the urine. To maintain H^+ balance, the distal nephron must secrete about 1 mmol H^+/kg body weight per day (net acid excretion).

Two important urinary buffer systems aid H^+ excretion: $HPO_4^{2-}/H_2PO_4^-$ and NH_3/NH_4^+. The amount of phosphate and other small molecules available as a buffer depends on their filtered load and is known as *titratable acid* (the H^+ that it buffers can be estimated by titrating back to a normal plasma pH of 7.4). NH_3/NH_4^+ is generated in the proximal tubule by the metabolism of glutamine; its production is significantly stimulated by acidosis and hypokalaemia, and inhibited by alkalosis and hyperkalaemia. Figure 2 illustrates the mechanisms of acidification in the proximal tubule and CD.

Effective arterial blood volume (EABV)

EABV is a useful clinical concept that refers to the blood volume on the arterial side of the circulation (remember that most of the blood volume is on the venous side), which is available for organ and tissue perfusion. EABV can be reduced because of a true fall in circulating volume (as in haemorrhagic shock), an apparent fall caused by 'pump' or heart failure (as in cardiogenic shock) or a relative fall (relative to intravascular capacity) because of arterial vasodilatation, as in septic shock, liver failure (hepatorenal syndrome) or (in part) nephrotic syndrome. Hence, EABV is the arterial blood volume judged necessary to maintain adequate tissue perfusion.

The most common clinical electrolyte and acid–base derangements

Regulation of natraemia and water homeostasis

Both of these are primarily problems of water rather than sodium balance. Plasma sodium concentration (P_{Na}) represents the ratio of the amount of sodium to water in the ECFV. Hyponatraemia (P_{Na} <135 mmol/litre) can mean Na^+ loss or water gain, but in clinical practice hyponatraemia usually means water gain or a failure to excrete it; cells can be swollen (when it is acute) or not (when it is chronic). By contrast, hypernatraemia (P_{Na} >146 mmol/litre) means water loss or sodium gain, but again it is usually caused by water loss or a failure to drink enough, and cells are therefore shrunken.

Figure 3 summarizes the main body fluid compartments and their relative volumes; it indicates that water can move freely between them as a result of differences in osmolality. As already mentioned, because Na^+ is the major cation in the ECFV, it is also the main osmolyte. P_{Na} determines ECFV osmolality and so governs fluid shifts between the extracellular and intracellular fluid compartments; it is therefore a measure of total body fluid osmolality. Note also that muscle is an important 'sump' for body water and that a low muscle mass, particularly in (elderly) women, predisposes to water overload and dilutional hyponatraemia.

Hyponatraemia

Almost all hyponatraemia is dilutional, and plasma osmolality is low. Hyponatraemia indicates that water intake exceeds renal

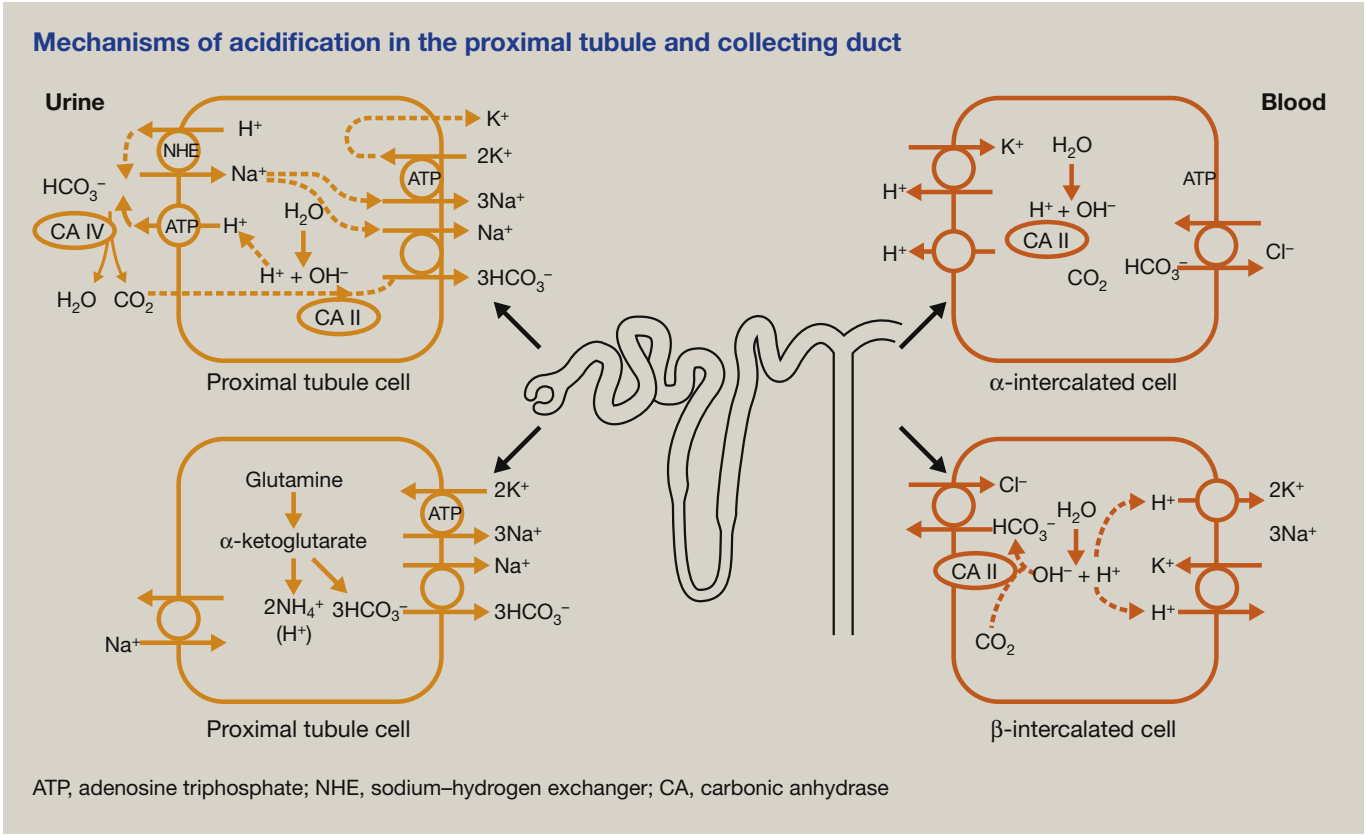

Figure 2

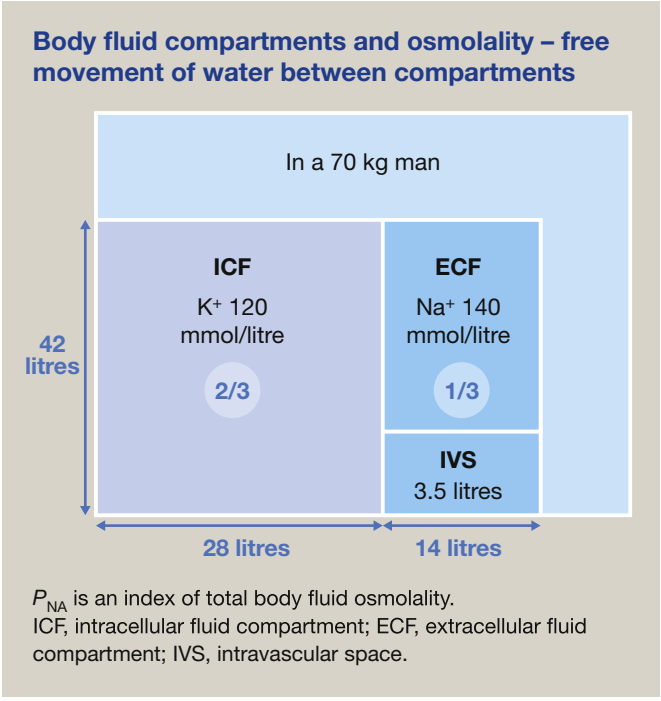

Figure 3

capacity to excrete it. Up to 3% of hospital inpatients and about 15–20% of patients who are emergency admissions are reported to have hyponatraemia, and this correlates with their mortality, morbidity and length of hospital stay. However, the presence of hyponatraemia is really a reflection of the seriousness of any underlying illness, such as severe heart failure or liver disease.

As well as concentrating urine, the kidney is able to dilute urine to avoid water retention. The kidney can dilute urine up to one-tenth of the plasma osmolality under normal conditions. This occurs by stopping AVP release in response to decreased plasma osmolality secondary to water intake. Therefore, under physiological conditions, any reduction in plasma osmolality matches a corresponding and appropriate decrease in urine osmolality. This implies that hyponatraemia secondary to water intake occurs only for very large amounts of water, about 25–30 litres/day, as in severe primary polydipsia,[2] when the urinary diluting capacity is overwhelmed. Urinary diluting ability is progressively lost in chronic kidney disease (CKD); in patients with advanced or end-stage renal failure, it is a major cause of hyponatraemia. Besides these extreme conditions, hyponatraemia can develop when impairment of the urinary diluting mechanism fails to match water excretion with intake. A failure to suppress AVP release, despite a lowered plasma osmolality, is a common cause of hyponatraemia. A classification of hyponatraemia is set out in Table 1.

When exposed to a hypotonic environment, cells swell; they can initially recover their volume by losing K^+ and Cl^-, but in the longer term they alter (in this instance decrease) their production of endogenous solutes to balance extracellular osmolality and stabilize their volume. This is particularly important for the brain, enclosed as it is in a rigid cranium, meaning it cannot swell by more than about 10% in response to *acute* hyponatraemia. The brain is also more susceptible to cell shrinkage during rapid correction of *chronic* hyponatraemia, because of the adaptive loss of intracellular solutes that has occurred. Thus, when treating hyponatraemia, a distinction must be made between acute and chronic.

Although somewhat arbitrary and based largely on clinical experience, *acute* hyponatraemia is defined as being present for up to 48 hours it can be rapidly corrected, but this is necessary only if the patient is neurologically impaired, with confusion or fits caused by significant brain swelling. (Muscle injury from a fit can increase muscle cell osmolytes and cause a misleading 'normalization' of P_{Na} by drawing in water; therefore a diagnosis of underlying hyponatraemia can be missed, for example after ecstasy intoxication.)

In *chronic* hyponatraemia (present for >48 hours or of unknown duration), symptoms and signs are gradual in onset and

Classification of hyponatraemia

Pseudohyponatraemia is a (rare) measurement artefact caused by reduced plasma water because of excess lipids (triglycerides (triacylglycerols)) or abnormal proteins (e.g. IgM). It is less of a problem now that modern ion-sensitive electrode-based methods of measurement are widely used

Hyperosmolar (*iso-osmolar and other*) hyponatraemia

- Hyperglycaemia (and other impermeant solutes, but not urea)
- Surgical (e.g. TURP) irrigation fluids (mannitol, sorbitol, glycine)

True (*hypo-osmolar*) hyponatraemia

- Total body water (volaemia) ⇑ (TBNa ⇑) — reduced EABV (oedema): U_{Na} <20 mmol/litre — heart failure, liver failure, nephrotic syndrome
- Total body water (volaemia) ⇑ (TBNa ⇑) — increased EABV (oedema): ESRF (low GFR with reduced distal Na^+ and water delivery, and thus free water excretion)
- Total body water (volaemia) ⇓⇑ (TBNa ⇒) — normal EABV (no oedema):
  - U_{Na} 25–40 mmol/litre — diuretics,[a] Addison's disease, hypothyroidism, pregnancy
  - U_{Na} > 40 mmol/litre — SIADH, subarachnoid haemorrhage
- Total body water (volaemia) ⇓ (TBNa ⇓) — reduced EABV (Na^+ loss): renal loss (diuretic), non-renal loss (gastrointestinal tract, skin)

ESRF, end-stage renal failure; IgM, immunoglobulin M; TBNa, total body sodium; TURP, transurethral resection of the prostate.
[a] Except in chronic diuretic therapy, which can lead to Na^+ retention.

Table 1

often non-specific, for example lethargy, forgetfulness or unsteadiness. P_{Na} in chronic hyponatraemia can be much lower than in acute hyponatraemia, but it should not be corrected too rapidly (<10 mmol/litre during the first 24 hours, and <8 mmol/litre during every 24 hours thereafter), unless the patient is comatose or fitting, because of the risk of causing osmotic demyelination syndrome (central pontine myelinolysis). Additional risk factors for central pontine myelinolysis are P_{Na} <105 mmol/litre, alcoholism, malnutrition and chronic liver disease.

Recent joint-guidelines by the European Society of Nephrology, Endocrinology Society and Intensive Care Society recommend the use of 150 ml of hypertonic sodium chloride (3%) given intravenously over 20 minutes for the treatment of severe or symptomatic hyponatraemia. Water restriction, oral urea and removal or treatment of the underlying cause of chronic hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are highly recommended. The use of lithium or demeclocycline is discouraged, because correction of P_{Na} can be too rapid. For the treatment of chronic non-hypovolaemic hypotonic hyponatraemia, AVP antagonists (vaptans) can be effective, but there is no evidence for their long-term benefit, for example in severe heart failure with hyponatraemia.

Although formulae are available to guide correction, there is no substitute for regular (hourly) recordings of input, output and P_{Na} during therapy. It is, however, important to remember that the diagnosis of SIADH should be a diagnosis of exclusion (Table 2).

Hypernatraemia

Hypernatraemia reflects an unreplaced water loss.[3] Indeed, developing hypernatraemia requires solute-free water loss either from the gastrointestinal tract (vomiting, osmotic diarrhoea), from urine (mainly in diabetes insipidus or osmotically driven diuresis secondary to glycosuria or hypertonic solution infusion) or by excessive insensible water loss (from lung or skin). This water loss is a strong trigger for thirst and does not usually induce hypernatraemia unless there is an associated lack of thirst or no ready access to water.

As already mentioned, cells shrink in hypernatraemia, and the body tries to minimize this by producing endogenous osmolytes; this makes rapid correction dangerous, because adapted cells swell more in a hypotonic environment, especially in the enclosed cranium. Therefore, water replacement should be given slowly to lower P_{Na}, at no more than 10 mmol/litre per 24 hours (the same as the safe rate of correction for hyponatraemia). The oral route is safest, but if intravenous fluid is given, its Na^+ content must be lower than that of any continuing urinary losses. The rate of infusion of glucose 5% solution is limited by the rate of glucose metabolism and should not exceed 0.3 litres/hour.

Regulation of potassium homeostasis

In contrast to Na^+, most body K^+ is inside cells, and it is the steep gradient from inside to outside that determines the cell membrane's resting potential difference (around −70 mV inside), which is especially important in excitable tissues such as nerve and muscle. Only about 65 mmol K^+ is present in the ECFV, which can easily be exceeded by a dietary intake of about 50 −100 mmol/day.

SIADH: causes and diagnosis

Causes

Pulmonary disease
- Bacterial pneumonia
- Viral pneumonia
- Tuberculosis
- Aspergillosis
- Asthma
- Cystic fibrosis

Cancer
- Pancreas
- Stomach
- Lymphoma
- Prostate
- Lung

Nervous system disease
- Meningitis
- Encephalitis
- Brain abscess
- Brain tumours
- Neonatal hypoxia
- Hydrocephalus
- Delirium tremens
- Multiple sclerosis

Diagnosis
- Decreased plasma osmolality (<270 mOsm/kg)
- Inappropriately concentrated urine (>100 mOsm/kg)
- Increased urinary sodium concentration
- Decreased plasma urate concentration
- Clinical euvolaemia
- Absence of any endocrine, cardiac, liver or renal disease
- No diuretic use
- Plasma AVP inappropriately elevated relative to plasma osmolality (C-terminal portion of pro-AVP, known as co-peptin, is a surrogate measure)
- No significant correction of P_{Na} with volume expansion, but improvement after fluid restriction

Table 2

The body's defence against acute hyperkalaemia is represented by a rapid intracellular shift promoted through Na/K-ATPase activation by insulin and β_2-adrenoceptor sympathetic activation (α_1-adrenoceptor activation having the opposite effect). There is emerging evidence of an additional mechanism promoting urinary potassium excretion soon after a meal, independent of aldosterone secretion and via an as yet unidentified kaliuretic factor. This factor seems to be produced by the gut in response to potassium intake, although it might involve sensing changes in serum or plasma potassium concentration. Finally, for supraphysiological levels of serum potassium, aldosterone is the main regulator of potassium balance, mainly by inducing renal (90%) and faecal (10%) potassium excretion.

The kidney can also significantly reduce potassium secretion in response to a low-potassium diet. Both low (<3 mmol/litre) and high (>5 mmol/litre) serum potassium levels are associated

with an increased risk of mortality, and potassium disorders can represent an important clinical challenge.

Hypokalaemia

Hypokalaemia is defined as a plasma potassium concentration (P_K) <3.5 mmol/litre, but this concentration rarely causes problems. Patients are not typically symptomatic until P_K is<2.5 mmol/litre or it has fallen rapidly; significant muscle weakness tends to occur at P_K <2.0 mmol/litre. True hypokalaemia can be the result of a shift of K^+ into cells, or to renal or gastrointestinal losses. Dietary deficiency is not usually a cause, unless there is another source of continuing K^+ loss. Examples of cell shifts causing hypokalaemia are rapid cell growth (e.g. anabolism after vitamin B_{12} treatment of megaloblastic anaemia), hypokalaemic periodic paralysis (from a muscle Ca^{2+} channel defect), thyrotoxicosis (especially in male Asian individuals) and excessive use of β_2-adrenoceptor agonists to treat asthma.

A useful measure to distinguish between hypokalaemic paralysis secondary to renal or extra-renal losses is the urinary potassium:creatinine ratio: <13 mmol/g or <1.5 mmol/mmol suggests a non-renal source of potassium loss or previously used diuretics. Renal K^+ loss is caused by increased aldosterone stimulation, increased Na^+ delivery or both (see Table 3); it can also be intermittent, as in postdiuretic Na^+ retention.

Causes of hypokalaemia

A primary *increase* in mineralocorticoid activity

Secondary hyperaldosteronism (high renin and high aldosterone concentrations — not suppressed by intravenous sodium chloride 0.9%)

- Malignant hypertension (in around 50%)
- Renal artery stenosis (in around 15%)
- Renin-secreting tumour

Primary hyperaldosteronism (suppressed renin concentration)

- Conn's syndrome
- Bilateral adrenal hyperplasia
- Glucocorticoid-suppressible hyperaldosteronism

A primary *increase* in a non-aldosterone mineralocorticoid (with low renin and low aldosterone concentrations)

- Cushing syndrome
- Congenital adrenal hyperplasia
- Apparent mineralocorticoid excess (AME)

A primary *increase* in distal Na^+ delivery (to the CD)

With alkalosis and U_{Cl} >25 mmol/L

- Diuretics that act upstream of the CD
- Mg^{2+} deficiency
- Bartter's or Gitelman's syndrome

With alkalosis and U_{Cl} *<25 mmol/litre*

- Vomiting
- Non-reabsorbed anions (e.g. bicarbonate, ketoacids)

With acidosis

- Chronic acidosis
- Renal tubular acidosis

If urine potassium concentration is <20 mmol/day, the cause is likely to be gastrointestinal loss. CD, collecting duct.

Table 3

Treatment of hypokalaemia is based on potassium repletion and, when possible, resolution of the underlying cause. Intravenous or oral administration depends on the severity of the symptoms and the degree of hypokalaemia. Several salt formulations can be used. In association with metabolic alkalosis, KCl salts are preferred, whereas in metabolic acidosis, potassium with an alkalinizing base should be considered (e.g. potassium aspartate or citrate). In severe forms of renal Fanconi's syndrome with hypophosphataemia, potassium phosphate should be used. For successful treatment, it is recommended always to check the serum or plasma magnesium concentration first because hypomagnesaemia can prevent potassium replacement therapy being effective.[4]

Hyperkalaemia

The causes of hyperkalaemia are listed in Table 4. In an intensive care setting, rapid cell shifts and acute kidney injury are the most likely causes. In an outpatient setting, a primary lack of aldosterone or chronic renal failure is most common. Although defined as P_K >5.0 mmol/litre, this concentration rarely causes problems; as in hypokalaemia, it is the rate of change of P_K (and from what baseline) that matters more than its absolute value (except when it is >7.0 mmol/litre), even in patients with CKD.

In presence of electrocardiographic abnormalities, acute treatment require initial administration of calcium chloride or gluconate. This is followed by an intervention promoting an intracellular shift: glucose plus insulin and/or a β_2-adrenoceptor agonist (intravenous, inhaled) and sodium bicarbonate. This should be coupled with treatment promoting potassium excretion through the kidneys (diuretics, mainly furosemide), or haemodialysis) and/or via faecal excretion (using a K^+-exchange resin such as sodium or calcium polystyrene sulphate or one of the newer potassium 'binders'). Two novel therapeutic options promoting faecal potassium excretion have recently become available: patiromer and sodium zirconium crystals.

Regulation of acid–base homeostasis

Acid–base homeostasis is crucial for enzyme activity and proper protein-folding. To minimize variation in the serum or plasma concentration of H^+, blood contains a complex buffer system in addition to the main HCO_3^-/PCO_2 system. The kidney contributes to the reabsorption and regeneration of bicarbonate (HCO_3^-) and to the direct elimination of H^+ in the urine. The body is exposed to a daily acid load of around 70–90 mmol H^+, depending on dietary composition, and is more efficient in tolerating an increase than a decrease in H^+ load and concentration.

Metabolic acidosis is defined by high plasma H^+ (low pH <7.4) and low plasma HCO_3^- (<25 mmol/litre) concentrations. (The term 'acidaemia' is more correct in describing the state of a low blood pH, and the term 'acidosis' in referring to the processes causing it.) Some causes of metabolic acidosis can also be detected as an increase in plasma anion gap (AG), but without a change in pH or plasma HCO_3^- concentration. The formula for calculating AG is:

$AG = P_{Na} - (P_{Cl} + P_{HCO3}^-)$ = around 12 mmol/litre (with a normal serum albumin)

Some authorities include P_K, making the AG higher, but its 'normal' value depends on local biochemical measurements and should be checked first with each laboratory. A reduced concentration of serum albumin (which is negatively charged) decreases AG, as does the presence of a positively charged myeloma protein (immunoglobulin G (IgG) is positive; IgA is negative).

Compensatory mechanisms for metabolic acidosis consist in reducing the volatile component of blood acid — PCO_2 — by the lungs, with the kidneys increasing NH_3 synthesis (and thereby generating 'new' HCO_3^-) and thus NH_4^+ excretion. An index of NH_4^+ excretion is the urine net negative charge or AG ($U_{Cl} - [U_{Na} + U_K]$), which is usually about 80 mmol/litre.

Causes of metabolic acidosis with an increased AG include diabetic ketoacidosis, lactic acidosis, some poisons (ethylene glycol, methanol, aspirin) and late-stage CKD. Metabolic acidosis with a normal AG and raised plasma Cl^- concentration ('hyperchloraemic acidosis') means either a primary loss of HCO_3^- (from the gastrointestinal tract, as in diarrhoea or a small bowel fistula, or from the kidney, as in proximal renal tubular acidosis (RTA)), or failure to excrete H^+ (via the CD, as in distal RTA) and/or to generate 'new' HCO_3^- from NH_3 synthesis and NH_4^+ excretion.

The treatment of metabolic acidosis implies the resolution of its underlying causes and supplementation with bicarbonate-containing salts. It should be noted that lactate ketoacids in lactic acidosis and ketoacidosis are eventually metabolized to bicarbonate when the underlying cause has been treated and corrected. Therefore giving too much bicarbonate should be avoided, and volume correction with sodium chloride 0.9% remains an important first step in management. Potassium should

Causes of hyperkalaemia

Pseudo-hyperkalaemia

- High white blood cell or platelet counts, and leaky red cells (but check the ECG is normal)
- Repeated fist-clenching
- Haemolysis from a small gauge needle
- Sample stored on ice and/or delayed transfer (causing efflux from red cells)
- Hyperventilation
- Release from leukaemic cells
- Interference with a K^+-sensitive electrode by benzalkonium (topical antiseptic) or heparin
- Familial (chromosome 16)

True hyperkalaemia

- Excess K^+ intake (usually only if renal K^+ excretion is impaired — GFR <30 ml/minute)
- Cell damage — rhabdomyolysis, haemolysis, tumour lysis
- Diabetic ketoacidosis, hyperosmolar hyperglycaemic state
- Lactic acidosis
- Toxins and drugs — digoxin, tetrodotoxin

Cell shifts of K^+

- Inorganic acids cause K^+ to leave cells (H^+ influx and buffering)
- Organic acids do not cause K^+ to leave cells
- In diabetic ketoacidosis, exit of K^+ from cells is caused by lack of insulin
- Diabetic hyperosmolality also shrinks cells and so steepens the gradient for K^+ exit (loss) from cells
- In lactic acidosis cell, ischaemia (cellular ATP↓) leads to K^+ leakage from cells
- Asymptomatic hyperkalaemia — think of a renal cause (see below)

Renal retention of K^+ (sustained hyperkalaemia)

Primary decrease in mineralocorticoid

- Hyporeninaemic hypoaldosteronism (diabetes mellitus, tubulo-interstitial disease) or drug-related inhibition of the renin—angiotensin—aldosterone system
- Heparin treatment
- Addison's disease

Primary decrease in the distal delivery of Na^+

- Oliguric ARF (cf. non-oliguric ARF in which hyperkalaemia is less likely to occur)
- Acute glomerulonephritis (anuria)
- Gordon's syndrome (pseudohypoaldosteronism type II or familial hyperkalaemic hypertension)

Abnormal CD function

- Pseudohypoaldosteronism type Ia (autosomal recessive; ENaC) or Ib (autosomal dominant; MR (mineralcorticoid receptor)
- Tubulo-interstitial disease (destroys the CD, the site of K^+ secretion) or obstruction
- Amiloride, trimethoprim, pentamidine (all block the ENaC)
- Spironolactone

ARF, acute renal failure; ENaC, epithelial sodium channel.

Table 4

be given in situations where it has been lost, such as diarrhoea, diabetic ketoacidosis or RTA. However, bicarbonate supplementation cannot be used to restore plasma HCO_3^- to normal in proximal RTA, and it can increase urinary potassium losses and worsen hypokalaemia. In distal RTA, as in CKD, bicarbonate is given mainly to ensure normal growth in children and to prevent bone loss; whether it can also slow the progression of CKD is still controversial.

Metabolic alkalosis is defined as P_K >25 mmol/litre and plasma pH >7.4. It is usually a response to deficits in sodium chloride (ECFV depletion) and/or potassium (secondary or primary aldosterone excess). Causes include diuretics and renal tubular disorders resembling chronic diuretic use, such as Bartter's and Gitelman's syndromes; these produce losses mainly of K^+ as a result of high concentrations of circulating aldosterone or other mineralocorticoid, but also of Na^+, Cl^- and Mg^{2+}. Eating disorders (bulimia and anorexia nervosa) can also cause striking and episodic alkalosis (with hypokalaemia and hypomagnesaemia) related to bouts of self-induced vomiting.

Unlike in metabolic acidosis, respiratory compensation in metabolic alkalosis is small; the kidneys respond by excreting less Na^+ and Cl^-, and, because of aldosterone's action (primary or secondary), more K^+. Urinary chloride concentration can be helpful to distinguish between a renal (>10 mmol/litre) or extra-renal (<10 mmol/litre) origin of the metabolic alkalosis. Treatment is to replace the deficits in Na^+, Cl^- and K^+ and/or to deal with the underlying cause, including increased mineralocorticoid activity.[5] ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 30-year-old woman presented with muscle pain and weakness. She was found to have polymyositis and was treated with methylprednisolone 1 g daily for 3 days. After an initial improvement, she became more unwell.

On clinical examination, her temperature was 36.5°C, heart rate 105 beats/minute, and blood pressure 120/76 mmHg. The percussion note was decreased at the right lung base, with bronchial breathing.

Investigations

- Plasma sodium 120 mmol/litre (137–144)
- Plasma potassium 4.5 mmol/litre (3.5–4.9)
- Plasma creatinine 88 micromol/litre (60–110)
- Plasma glucose 12.7 mmol/litre (3.0–6.0)
- Urine sodium 45 mmol/litre
- Urine osmolality 450 mOsm/kg (100–1000)

What is the most likely diagnosis?

A Addison's disease
B Syndrome of inappropriate antidiuretic hormone secretion secondary to pneumonia
C Pseudo-hyponatraemia resulting from hyperglycaemia
D Hyponatraemia secondary to severe volume depletion
E Hyponatraemia secondary to corticosteroid administration

Question 2

A 65-year-old woman presented with an acute onset of feeling unwell and severe painful leg cramps. She had a 5-year history of chronic kidney disease. She was taking an angiotensin-converting enzyme inhibitor and a calcium channel blocker.

On clinical examination, her heart rate was 88 beats/minute, blood pressure 150/90 mmHg, and body mass index 32 kg/m^2.

Investigations

- pSodium 140 mmol/litre (137–144)
- pPotassium 7.5 mmol/litre (3.5–4.9)
- pChloride 115 mmol/litre (95–107)
- pCreatinine 318 micromol/litre (60–110)
- ECG showed sinus rhythm, peaked T waves and flattened P waves

What is the best treatment to lower plasma potassium?

A Sodium bicarbonate infusion
B Glucose + insulin
C Furosemide
D Haemodialysis
E Calcium gluconate infusion

Question 3

A 25-year-old man presented with fatigue and general malaise after a short section of jogging on a summer evening, and once he had got home, he had severe impairment of movements of his legs. On clinical examination, his heart rate was 90 beats/minute, and blood pressure 90/60 mmHg supine.

Investigations

- pSodium 138 mmol/litre (137–144)
- pPotassium 1.8 mmol/litre (3.5–4.9)
- pChloride 95 mmol/litre (95–107)
- pMagnesium 0.41 mmol/litre (0.75–1.05)
- pBicarbonate 30 mmol/litre (20–28)
- pH 7.50
- PCO_2 6.2 kPa (4.7–6.0)
- PO_2 12.1 kPa (11.3–12.6)
- Urine chloride 30 mmol/litre
- Urine potassium 25 mmol/litre

What is the most likely diagnosis?

A Classic Bartter's syndrome
B Vomit-mediated hypokalaemia
C Gitelman's syndrome
D Previous diuretic abuse
E Distal renal tubular acidosis