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SPECIAL REPORT

Dutch guideline for the management of electrolyte disorders – 2012 revision

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ABSTRACT

Electrolyte disorders are common and often challenging in terms of differential diagnosis and appropriate treatment. To facilitate this, the first Dutch guideline was developed in 2005, which focused on hypernatraemia, hyponatraemia, hyperkalaemia, and hypokalaemia. This guideline was recently revised. Here, we summarise the key points of the revised guideline, including the major complications of each electrolyte disorder, differential diagnosis and recommended treatment. In addition to summarising the guideline, the aim of this review is also to provide a practical guide for the clinician and to harmonise the management of these disorders based on available evidence and physiological principles.

KEYWORDS

Algorithm, hyperkalaemia, hypokalaemia, hypernatraemia, hyponatraemia

INTRODUCTION

The first Dutch guideline on electrolyte disorders was published in 2005 under the auspices of the Dutch Society of Internal Medicine.[1] This guideline was recently revised not only to include new evidence but also to make the guideline more clinically applicable. For example, recommended tests, diagnostic algorithms, treatment options including dosing, and recommended formulae have now been incorporated. In addition, for each electrolyte disorder we have specified which key questions should be asked to assess whether the patient is in immediate danger and what the most likely cause of the electrolyte disorder is. In addition to these practical elements, the emphasis on physiological principles has remained.[1] The recommendations for the acute treatment of electrolyte disorders have been synchronised with another commonly used national reference work ('acute boekje' – guidelines for the diagnosis and management of disorders in internal medicine).[2] This article is not only a summary of the 2012 revision of the Dutch guideline on electrolyte disorders,[3] it also aims to be a practical summary of the diagnosis and treatment of hypernatraemia, hyponatraemia, hyperkalaemia, and hypokalaemia. The reader is referred to other reviews for more detailed background information.[4-9] The guideline can be accessed at www.internisten.nl/gzi2 and http://internisten-apps.nl/elektrolytstoornissen/index.php/Hoofdpagina.

METHODS

The 2012 guideline on electrolyte disorders is a revision of the first guideline that was published in 2005.[1,3] The guideline aims to facilitate and harmonise the management of electrolyte disorders. The guideline is primarily intended for use by internal medicine trainees and specialists, but also for other specialists who are confronted with electrolyte disorders such as cardiologists, lung physicians, gastroenterologists, intensivists, and anaesthesiologists. The guideline was developed by a working group consisting of five experts in the field and one methodological expert (M.K.T.). None of the guideline working group members had a conflict of interest during the guideline development process. At the start of the guideline development, the working group agreed that

Table 1. *Signs, symptoms, and clinical dangers*

	Hypernatraemia	Hyponatraemia	Hyperkalaemia	Hypokalaemia
Signs and symptoms	Thirst Fever Sensorium changes Seizures Focal neurological deficits Hyperventilation	Nausea Vomiting Headache Diplopia Falls Seizures Coma	Muscle cramps Muscle weakness ECG changes	Muscle cramps Muscle weakness Paresthesia ECG changes
Complications	Brain cell shrinkage Intracranial haemorrhage Dural sinus thrombosis Osmotic demyelination Cerebral oedema*	Cerebral oedema Osmotic demyelination*	Arrhythmia Paralysis	Arrhythmia Paralysis Ileus Respiratory failure due to respiratory muscle weakness Rhabdomyolysis Glucose intolerance Urinary concentrating defect Hypokalaemic nephropathy

*** During treatment.**

electrolyte disorders constitute an area of medicine that lacks studies with a high level of evidence. Instead of restricting the guideline to available evidence, the working group decided to develop a didactic and practical guideline supported by evidence if available. In addition, 17 clinical questions were elaborated in evidence reviews based on a systematic review of the literature. After preparing a draft guideline, all members of the Dutch Society of Internal Medicine were invited to comment. All comments were reviewed by the working group and incorporated in the final guideline, which was endorsed at the 2012 annual meeting of the Dutch Society of Internal Medicine.

HYPERNATRAEMIA

Hypernatraemia is defined as a serum sodium concentration >145 mmol/l and can be further classified as acute or chronic and symptomatic or asymptomatic. Patients are more likely to be symptomatic when hypernatraemia develops acutely (usually <48 hours, *table 1*). However, when patients present to the hospital with hypernatraemia, the time in which it developed is usually unknown. Therefore, for the assessment whether hypernatraemia is acute or chronic, one often needs to rely on symptoms. The same holds true for hyponatraemia (see further). Acute hypernatraemia causes brain cell shrinkage due to a shift of water from the intracellular to the extracellular fluid compartment.[5] In severe cases and especially in neonates, this can cause intracerebral haemorrhage because vessels are stretched when brain volume decreases rapidly.[10] When hypernatraemia is documented to be acute or when severe symptoms are present, immediate treatment is indicated and should precede diagnostic evaluation (*table 2*). Conversely, when hypernatraemia is chronic or when few symptoms are present, the underlying cause should be identified and serum sodium should be corrected gradually. Indeed, when serum sodium is corrected too rapidly during chronic hypernatraemia, there is a risk of cerebral oedema (*table 2*).[5] The most common causes of hypernatraemia are shown in *table 3*. In general, the causes of hypernatraemia can be divided into those primarily caused by a negative water balance (due to a water or solute diuresis) and those primarily caused by a positive sodium balance, although combinations also exist.[11] The recommended diagnostic tests in a patient with hypernatraemia are shown in *table 4*. Hypernatraemia can usually be differentiated by using three parameters, including urine osmolality, urine sodium concentration, and urine output (*table 5*).[5] The differentiation between central and nephrogenic diabetes insipidus requires a functional test, namely the response in urine osmolality to a single dose of desmopressin.[12] A water restriction test is indicated to evaluate whether

Table 2. *Recommendations regarding the correction of hypernatraemia*

- When hypernatraemia is acute or severely symptomatic, immediate treatment with hypotonic fluids should be started, regardless of the underlying cause
- When a patient with hypernatraemia is hypotensive, isotonic fluids should be started
- When hypernatraemia is chronic, rapid correction should be avoided to prevent cerebral oedema and treatment should be directed to the underlying cause
- For all causes of hypernatraemia the correction rate is *limited* to 8 mmol/l in the first 24 hours and 18 mmol/l in the first 48 hours
- Acute hypernatraemia may be corrected faster initially (1-2 mmol/l/hour); a rise of 5 mmol/l is usually sufficient to improve symptoms

Table 3. *Most common causes*

Hypernatraemia	Hyponatraemia	Hyperkalaemia	Hypokalaemia
Osmotic diuresis (e.g. hyperglycaemia)	Pseudohyponatraemia	Pseudohyperkalaemia	Redistribution (shift)
High protein enteral feeding	Hyperglycaemia	Redistribution (shift)	Diarrhoea
Diabetes insipidus (central, nephrogenic, gestational)	Diuretics	Acute or chronic kidney disease	Laxative abuse
Breastfeeding	SIADH	Drugs inhibiting RAAS	Vomiting
Infusion of fluids hypertonic to the urine	Adrenal insufficiency	Primary adrenal insufficiency	Tube drainage
Primary aldosteronism (mild)	Cerebral salt wasting	Renal tubular acidosis (type IV)	Diuretics
	Heart failure	Pseudo-hypoaldosteronism (types I and II)	Primary or secondary aldosteronism
	Liver cirrhosis		Renal tubular acidosis (types I and II)
	Nephrotic syndrome		Bartter, Gitelman, and Liddle syndromes
	Primary polydipsia		Nonreabsorbable anions
	Low solute intake		Hypomagnesaemia
	Nonrenal sodium loss		Dialysis

RAAS = renin-angiotensin-aldosterone system; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Table 4. *Recommended diagnostic testing*

	Hypernatraemia	Hyponatraemia	Hyperkalaemia	Hypokalaemia
Always	Serum creatinine Serum urea Serum glucose Serum calcium Serum potassium Urine sodium Urine osmolality	Serum creatinine Serum glucose Serum potassium Serum osmolality Urine sodium Urine potassium Urine osmolality	Serum creatinine Thrombocytes Leukocytes Serum bicarbonate (or blood gas)	Serum creatinine Serum magnesium Urine potassium Serum bicarbonate (or blood gas) Blood pressure
Sometimes	Response in urine osmolality to desmopressin Urine urea	Serum uric acid Urine chloride FE uric acid FE urea FE sodium TSH and free T4 Cortisol or Synachten test	Urine potassium Urine creatinine Plasma renin and aldosterone TTKG	Urine potassium-to-creatinine ratio Urine chloride Plasma renin and aldosterone TTKG TSH and free T4

FE = fractional excretion; TSH = thyroid stimulating hormone; TTKG = transtubular potassium gradient.

polyuria is due to diabetes insipidus or polydipsia, but is *not* indicated in hypernatraemia, because polydipsia does not cause hypernatraemia.[13] For the various causes of diabetes insipidus, the reader is referred to two review articles.[12,14] Hypernatraemia is most commonly caused by a negative water balance, especially in patients with community-acquired hypernatraemia. Hypernatraemia should therefore be considered primarily a disorder of *water balance*. Prior to starting treatment, this water deficit can be estimated using the following formula: 0.6 * lean body weight * ([serum sodium/140] – 1). When a patient with hypernatraemia is hypotensive, we recommend to start with isotonic intravenous fluids (either crystalloids or colloids), because they restore haemodynamics more efficiently and are still hypotonic relative to the patient (*table 2*).[2] In all other settings, hypernatraemia can be treated with hypotonic fluids. These can be administered orally, via nasogastric tube or intravenously as half-isotonic saline with glucose (0.45% NaCl–2.5% glucose) or glucose 5%. Because glucose is metabolised to water, intravenous glucose infusions will generate electrolyte-free water. To calculate the anticipated decrease in serum sodium with 1 litre of infusate, we recommend the Adrogué-Madias formula (*figure 1*),[5] which has been validated in one study.[15] In addition to hypotonic fluids, patients with central and gestational diabetes insipidus can be treated with desmopressin, while patients with nephrogenic diabetes insipidus can be treated with thiazide diuretics or amiloride.[14] A recent cross-over trial demonstrated the efficacy of amiloride in curtailing polyuria in lithium-induced nephrogenic diabetes insipidus.[16] An important question to ask when evaluating patients with hypernatraemia is why thirst and subsequent water intake did not prevent hypernatraemia. A good example is patients with diabetes insipidus who under normal circumstances remain normonatraemic by increasing water intake, often even without additional medication. Possible causes why hypernatraemia develops include no access to water, immobility, inability to express thirst, or a defective thirst mechanism (hypodipsia). This also explains why certain groups are at increased risk of developing hypernatraemia, including children, the elderly, and patients admitted to the intensive care unit (ICU). In neonates who are exclusively breastfed,

Table 5. *Differentiation of hypernatraemia*

	Inadequate water intake	Diabetes insipidus	Osmotic diuresis	Extrarenal water loss	Positive sodium balance
Urine osmolality	Maximal	$U_{osm} < P_{osm}$	$U_{osm} > P_{osm}$	Maximal	Maximal
Urine sodium	<25 mmol/l	<25 mmol/l	>25 mmol/l	<25 mmol/l	>25 mmol/l
Urinary flow rate	Oliguria	Polyuria	Polyuria	Oliguria	Normal to high

Table 6. *Recommendations regarding the correction of hyponatraemia*

- When hyponatraemia is acute or severely symptomatic, immediate treatment with hypertonic saline should be started, regardless of the underlying cause
- When hyponatraemia is chronic, rapid correction should be avoided to prevent osmotic demyelination and treatment should be directed to the underlying cause
- For all causes of hypotonic hyponatraemia the correction rate is *limited* to 10 mmol/l in the first 24 hours and 18 mmol/l in the first 48 hours
- Acute hyponatraemia may be corrected faster initially (1-2 mmol/l/hour); a rise of 5 mmol/l is usually sufficient to improve symptoms and treat cerebral oedema
- The strategy to correct serum sodium rapidly to 120 mmol/l and then more slowly has no evidence base and does not prevent osmotic demyelination. It should therefore be abandoned
- Overcorrection and autocorrection should be anticipated during treatment with hypertonic or isotonic saline

Figure 1. *Adrogué-Madias formula*

$$\text{Change in serum } Na^+ = \frac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{serum } Na^+}{\text{total body water} + 1}$$

$$\text{Volume (liter)} = \frac{\text{Desired } \Delta [Na]_s}{\Delta [Na]_s \text{ (with 1 liter)}}$$

The formula in the upper panel calculates the anticipated rise in serum sodium ($\Delta[Na]_s$) after the administration of 1 litre of a selected infusion. The required information includes the sodium and potassium concentrations of the infusion (infusate Na^+ + infusate K^+), the serum sodium concentration of the patient (serum Na^+) and total body water (usually 0.6 * body weight). The formula in the lower panel calculates how much volume of the selected infusion should be given based on the desired rise in serum sodium (desired $\Delta[Na]_s$) and the calculated rise in serum sodium using the formula in the upper panel ($\Delta[Na]_s$ (with 1 litre)). For example, if the anticipated rise in serum sodium with 1 litre of 3% NaCl is 10 mmol/l, and the desired rise in serum sodium is only 5 mmol/l, then 5/10 = 0.5 litre of the infusion should be administered. The time in which this infusion is administered should be based on the recommended correction limits (tables 2 and 6).

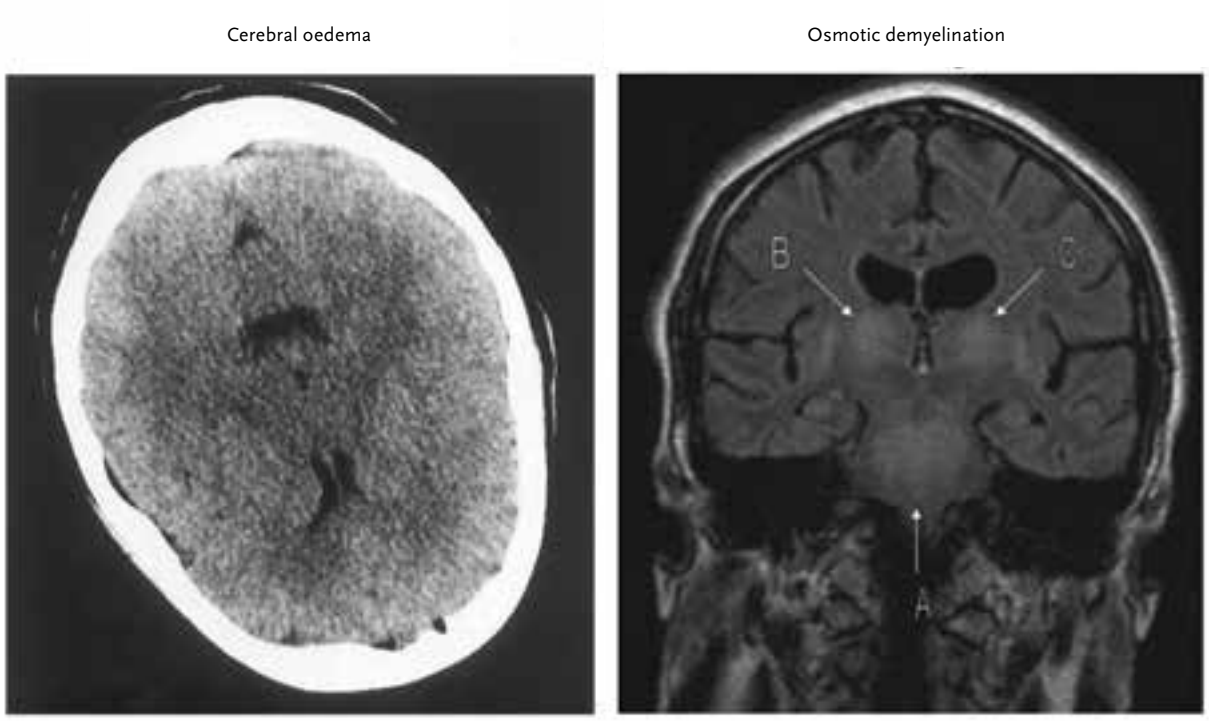
hypernatraemia may develop when there is lactation failure.[17] In the elderly a reduction in thirst sensation and urinary concentration ability as well as an increase in insensible loss predispose to hypernatraemia.[18] In the ICU, hypernatraemia is usually hospital-acquired, suggesting an iatrogenic component.[19,20] Indeed, studies have shown that a positive sodium balance often plays a role in the pathogenesis of ICU-acquired hypernatraemia.[11,19] This may be due to a shift towards using primarily isotonic intravenous fluids. If the patient for some reason has a reduced urinary concentrating ability, isotonic fluids are hypertonic to the urine and result in a positive sodium balance. In this setting treatment should rely on adding more water, but diuretics may also be useful.[21,22]

Importantly, hypernatraemia in the ICU is independently associated with mortality,[19,23,24] although it is unknown whether preventing or correcting hypernatraemia improves outcome. Although hyperglycaemia usually causes hyponatraemia (see further), it can also present with hypernatraemia if there is a large osmotic diuresis with renal water loss that is not compensated by intake.[25] Hypernatraemia also develops frequently during the treatment of hyperglycaemia because less water is attracted from the intracellular fluid compartment when serum glucose is lowered during therapy. Hypernatraemia in this context is often useful to prevent a rapid decrease in effective serum osmolality caused by decreasing serum glucose and helps to prevent the development of cerebral oedema.[26,27]

HYPONATRAEMIA

Hyponatraemia is defined as a serum sodium concentration <135 mmol/l and can be further classified as acute or chronic and symptomatic or asymptomatic. Patients are more likely to be symptomatic when hyponatraemia develops acutely (usually <48 hours, *table 1*). Acute hyponatraemia causes brain cell swelling due to a shift of water from the extracellular to the intracellular fluid compartment.[4] Cerebral oedema due to acute hyponatraemia is a medical emergency especially when there is concurrent hypoxia (*figure 2*).[28,29] Therefore, when hyponatraemia is documented to be acute or when severe symptoms are present, immediate treatment with hypertonic saline is indicated and should precede diagnostic evaluation (*table 6*). As for hypernatraemia, we recommend the use of the Adrogué-Madias formula

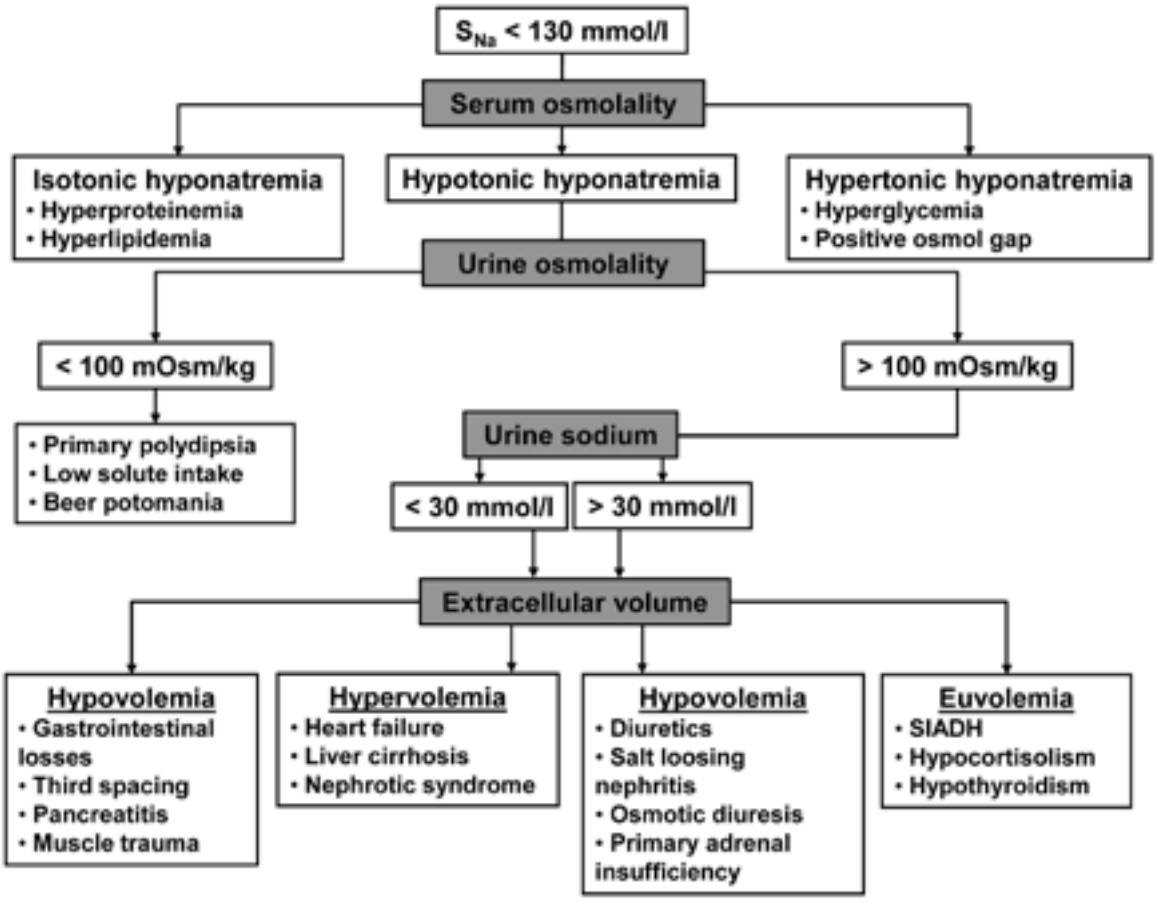
Figure 2. *Complications of hyponatraemia: cerebral oedema versus the osmotic demyelination syndrome*



Left panel: computed tomography image of a patient with acute cerebral oedema due to desmopressin-induced hyponatraemia (serum sodium 111 mmol/l). Right panel: magnetic resonance image of a patient with the osmotic demyelination syndrome due to too rapid correction of chronic hyponatraemia (14 mmol/l in 18 hours; A indicates the pons, while B and C indicate the basal ganglia). Sources: Schreiber A et al., Am J Kidney Dis 2004; 44: e3-6 and Abbott R et al., BMJ 2005; 331: 829-30. Reprinted with permission.

to estimate the anticipated rise in serum sodium during treatment with hypertonic saline (*figure 1*). Although a bolus of 100 ml of 3% NaCl has recently been advocated as a simple alternative to a continuous infusion of hypertonic saline,[30] there is as yet no evidence to support this. Conversely, when hyponatraemia is chronic or when few symptoms are present, the underlying cause should be identified and serum sodium should be corrected gradually. Indeed, when serum sodium is corrected too rapidly in chronic hyponatraemia, there is a risk of developing the so-called osmotic demyelination syndrome (*table 6, figure 2*).[31] Patients at increased risk of cerebral oedema due to hyponatraemia include postoperative patients, children, elderly women using thiazides, psychiatric patients with primary polydipsia, and patients with hypoxia.[32] Risk factors for the osmotic demyelination syndrome during overly rapid correction of chronic hyponatraemia include alcoholism, thiazide diuretics, malnutrition, hypokalaemia, and hypoxia.[32] It is important to note that some risk factors predispose to both cerebral oedema and osmotic demyelination. In addition to cerebral oedema and osmotic demyelination, which are relatively rare, hyponatraemia in general is independently associated with increased mortality.[33] It remains unknown, however, whether hyponatraemia contributes directly to mortality and whether correction of hyponatraemia reduces mortality.[34,35] The most common causes of hyponatraemia are shown in *table 3*. The differential diagnosis of hyponatraemia is often challenging.[36] The recommended diagnostic tests in a patient with hyponatraemia are shown in *table 4*. A diagnostic algorithm illustrates how serum osmolality, urine osmolality, urine sodium, and assessment of volume status help to differentiate hyponatraemia (*figure 3*). Although many algorithms are available, we recommend this specific algorithm for three reasons. First, a recent study showed that the diagnostic accuracy of junior physicians following this algorithm was higher than that of senior physicians not using the algorithm.[37] Second, this algorithm relies primarily on objective diagnostic tests and does not start with a clinical assessment of the extracellular fluid status, which has a low sensitivity and specificity in patients with hyponatraemia.[38] Third, this algorithm starts with a differentiation between hypotonic, isotonic, and hypertonic hyponatraemia, which is an important diagnostic step. Isotonic hyponatraemia is usually caused by pseudohyponatraemia, which is a laboratory artefact due to the fact that all venous samples undergo a dilution step prior to measurement.[39] Pseudohyponatraemia should be distinguished from

Figure 3. *Diagnostic algorithm for hyponatraemia*



See text for details. S_{Na} = serum sodium; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

hyperglycaemia-induced hyponatraemia, which is usually a form of hypertonic hyponatraemia and is caused because glucose (an effective osmole) attracts water from the intracellular fluid compartment.[40] The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatraemia with a specific set of essential and supplemental diagnostic criteria (*table 7*).[41] A number of causes should be excluded prior to establishing a diagnosis of SIADH, including diuretic use, adrenal insufficiency, and hypothyroidism. Especially secondary adrenal insufficiency mimics SIADH because hypocortisolism increases vasopressin secretion.[42] However, primary adrenal insufficiency can also present with isolated hyponatraemia while other characteristic signs are absent, including hyperkalaemia and orthostatic hypotension.[43,44] Although hypothyroidism can cause hyponatraemia, this appears to be rare and probably only occurs in myxoedema coma when there is also a decrease in cardiac output and glomerular filtration rate.[45] A recent study did identify a correlation between hypothyroidism and decreased serum sodium, but found this effect to be small and clinically irrelevant.[46] The causes of SIADH are myriad, but can be classified into malignancy (e.g., small cell lung carcinoma), pulmonary disease (e.g., pneumonia), neurological disease (infections, stroke, neurodegenerative diseases), and drugs (e.g., antidepressants, antiepileptics, and antipsychotic drugs).[41,47,48] A number of miscellaneous causes is also important and include transient causes such as the postoperative state, nausea, pain, and exercise.[41] The nephrogenic syndrome of inappropriate antidiuresis is a relatively novel cause of SIADH and is caused by an activating mutation in the gene encoding the vasopressin type 2 receptor.[49] A complete list of all possible causes of SIADH can be found in a recent review article.[41] Cerebral salt wasting is a rare and incompletely understood cause of hyponatraemia that is sometimes difficult to differentiate from SIADH.[50] It has been described most clearly after subarachnoid haemorrhage and does not always lead to hyponatraemia.[51] Cerebral salt wasting can cause a contracted extracellular fluid volume due to profound natriuresis. Therefore, polyuria, a very high urine sodium concentration, a high serum urea, orthostatic

Table 7. *Criteria for the syndrome of inappropriate antidiuretic hormone secretion*

Essential features	Supplemental features
• Decreased effective serum osmolality (<275 mOsm/kg)	• Serum uric acid <0.24 mmol/l
• Urine osmolality >100 mOsm/kg during hypotonicity	• Serum urea <3.6 mmol/l
• Clinical euvolaemia	• Fractional sodium excretion >1%
• Urine sodium > 30 mmol/l with normal dietary sodium intake	• Fractional urea excretion >55%
• Normal thyroid and adrenal function	• Failure to correct hyponatraemia after 0.9% saline infusion
• No recent use of diuretic agents	• Correction of hyponatraemia by fluid restriction
	• Abnormal results on test of water load*
	• Elevated plasma vasopressin levels despite the presence of hypotonicity and clinical euvolaemia

*** < 80% excretion of 20 ml water/kg during 4 hours and/or inability to dilute urine to osmolality < 100 mOsm/kg.**

hypotension, and a low central venous pressure argue in favour of cerebral salt wasting.[52] The treatment options for hyponatraemia, including indications, advantages and disadvantages, are shown in *table 8*. The vasopressin type 2 receptor antagonist tolvaptan was recently approved by the European Medicines Agency for treatment of hyponatraemia secondary to SIADH. All studies have shown that tolvaptan increases serum sodium effectively in SIADH,[53] but tolvaptan does not reduce mortality and can result in overcorrection.[54,55] In addition, tolvaptan has only been compared against placebo and not against one of the other treatment options for SIADH. Finally, it is important to factor in the cost of tolvaptan (~80 euro per tablet). At present, we therefore not recommend tolvaptan as a first-line treatment of hyponatraemia secondary to SIADH. When hyponatraemia is treated with hypertonic or isotonic saline, one should be aware of the possibility of overcorrection or autocorrection (*table 6*). Overcorrection is defined as exceeding the anticipated rise in serum sodium and usually occurs during treatment with hypertonic saline.[56] Autocorrection can also lead to overcorrection and this can occur when during treatment of hypovolaemic hyponatraemia with isotonic saline, the trigger for volume-mediated vasopressin release suddenly abates. Therefore, during treatment with hypertonic or isotonic saline, serum sodium should be monitored regularly (up to every three hours). Impeding overcorrection should be curtailed by discontinuing hypertonic or isotonic saline and starting a hypotonic infusion.[57] One study suggests that combining hypertonic saline with desmopressin may help prevent overcorrection.[58]

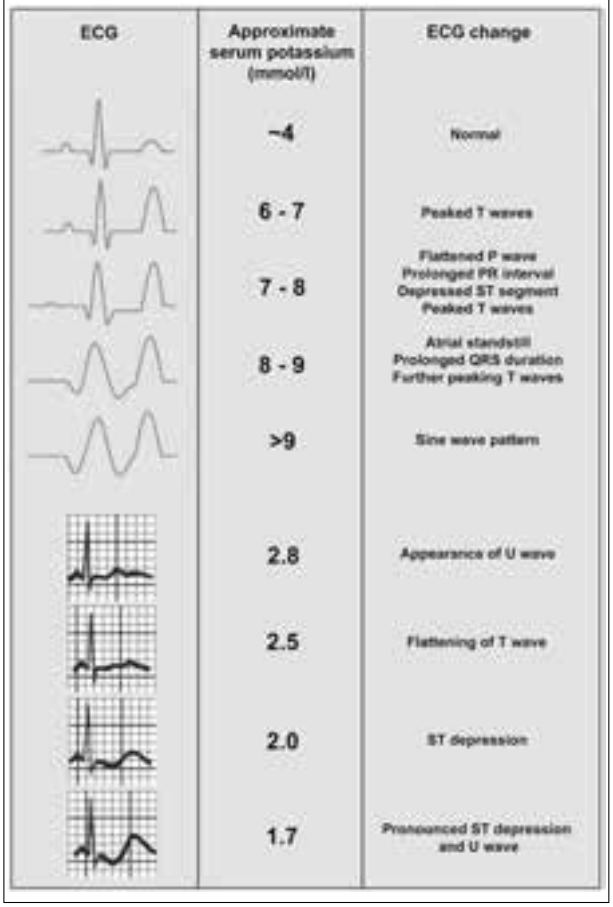
HYPERKALAEMIA

Hyperkalaemia is defined as a serum potassium concentration >5.5 mmol/l. The signs, symptoms and complications of hyperkalaemia are shown in *table 1* and *figure 4*. Hyperkalaemia and hypokalaemia can impair cardiac conduction in the heart and cause muscle weakness or paralysis. Therefore, hyperkalaemia can lead to ECG changes, arrhythmia, and even ventricular fibrillation. The most common causes of hyperkalaemia are listed in *table 3*. Pathophysiologically, these causes can be divided into pseudohyperkalaemia, redistribution of potassium from the intracellular to the extracellular compartment ('shift hyperkalaemia'), reduced glomerular filtration of potassium, and reduced tubular secretion of potassium (*figure 5*). Pseudohyperkalaemia (also called spurious

Table 8. *Therapeutic options in hyponatraemia*

Therapy	Indication(s)	Advantages	Disadvantages
Cause-directed therapy	E.g., steroids in adrenal insufficiency, discontinuation of diuretics	Cause specific	Effect may not be immediate (e.g., half-life medication)
Hypertonic saline (e.g., 3% NaCl)	Acute and/or symptomatic hyponatraemia	Treats or prevents cerebral oedema	Risk of overcorrection and sodium overload
Isotonic saline (e.g., 0.9%)	Hyponatraemia with hypovolaemia; cerebral salt wasting	Corrects hypovolaemia	Risk of autocorrection
Fluid restriction	SIADH, hyponatraemia in heart failure and liver cirrhosis, primary polydipsia	Inexpensive	Compliance
Vasopressin-receptor antagonists	SIADH	Specific and effective	Costs; risk of overcorrection; may be dangerous in hypovolaemia
Loop diuretics	SIADH, primary polydipsia, hyponatraemia in heart failure or liver cirrhosis	Increases free water clearance	Hypokalaemia; ineffective during diuretic resistance
Demeclocycline	SIADH	Inexpensive	Liver toxicity, phototoxicity, risk of overcorrection
Urea	SIADH	Inexpensive and effective	Pallatability

Figure 4. *ECG changes associated with hyperkalaemia and hypokalaemia*



hyperkalaemia) is usually caused by haemolysis related to blood withdrawal (e.g., due to forearm contraction, fist clenching or tourniquet use). When this is suspected (some laboratories report the presence of haemolysis), serum potassium should be measured again by venipuncture or arterial puncture. Less common causes of pseudohyperkalaemia include thrombocytosis and leucocytosis, because these cells can continue to secrete potassium in the blood collection tube.[59,60] Causes of shift hyperkalaemia include acidosis (for each 0.1 fall in pH, potassium increases ~0.4 mmol/l), cell death (tumour lysis, rhabdomyolysis, intravascular coagulation, trauma), drugs (succinylcholine, thalidomide, minoxidil), exercise, and the hyperkalaemic paralysis disorder (see 'hypokalaemia' for further discussion).[9] Any cause of a reduced glomerular filtration rate can cause hyperkalaemia, including acute kidney injury and chronic kidney disease. Reduced renal tubular secretion of potassium can be caused by a disruption of the aldosterone-renal axis, including reduced secretion of aldosterone, inhibition of the renin-angiotensin-aldosterone system, inhibition of the mineralocorticoid receptor, or inhibition of the epithelial sodium channel (ENaC). ENaC is electrochemically coupled to the main transporter responsible for potassium secretion, the renal outer medullary potassium channel (ROMK). Many drugs interfere with the aldosterone-renal axis and drug-induced hyperkalaemia is therefore a common clinical entity (*table 9*).[61] Other causes include primary adrenal insufficiency and genetic causes, including pseudohypoaldosteronism type 1 and type 2.[62] The recommended diagnostic tests to differentiate between the causes of hyperkalaemia are shown in *table 4*. The cause of hyperkalaemia is usually evident from the previous medical history, medication, or accompanying laboratory results. When the cause of hyperkalaemia is less evident, the measurement of plasma renin and aldosterone may be useful. The transtubular potassium gradient (TTKG) is an indirect measure to evaluate whether hyperkalaemia is due to hypoaldosteronism.[63] The treatment of hyperkalaemia is summarised in *table 10*, and relies on membrane stabilisation to prevent cardiac arrhythmia, induction of a shift of potassium into cells, and removal of potassium either naturally (binding in the gut or promoting kaliuresis) or artificially (haemodialysis).[6] The treatment options listed in *table 10* are primarily for the emergency treatment of hyperkalaemia. Chronic hyperkalaemia can usually be treated with ion exchange resins (sodium or calcium polystyrene sulphonate), a low potassium diet, diuretics, or alkali therapy. Recently, a critical review was published on ion exchange resins stating that little evidence is available on their efficacy and that they may cause colonic necrosis.[64]

Table 9. *Drugs that can cause hyperkalaemia*

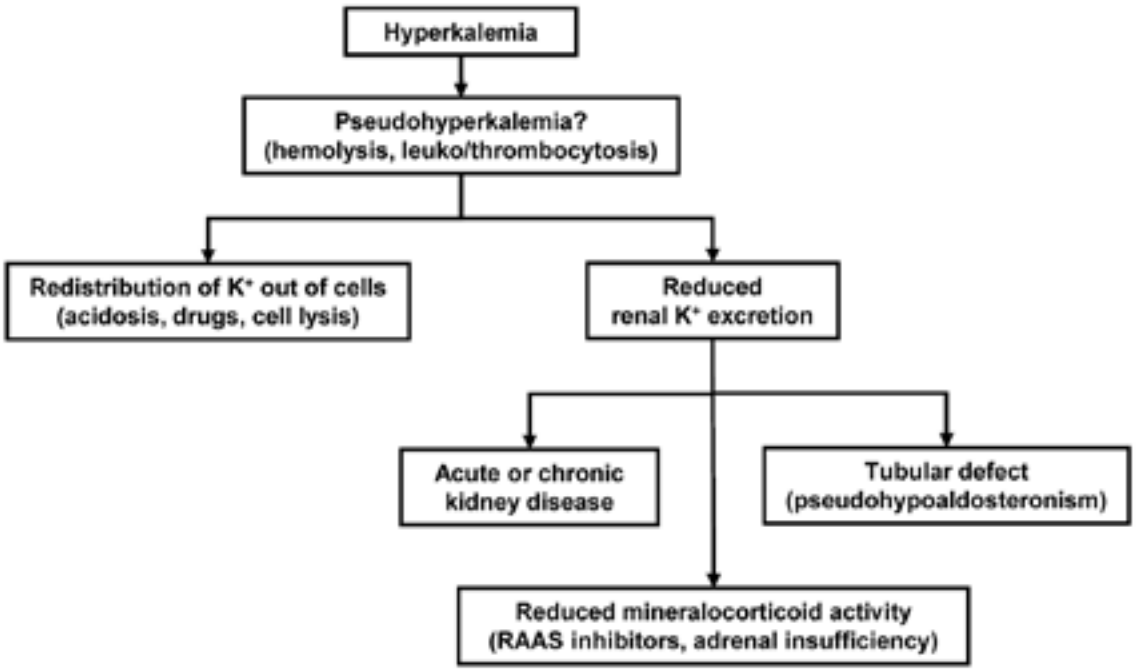
Drugs interfering with the renin-angiotensin-aldosterone system
- Beta-blockers (lower renin)
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers
- Mineralocorticoid receptor blockers (spironolactone, eplerenone, drosperinone)
- Renin inhibitors
- Nonsteroidal anti-inflammatory drugs
- Heparin
- Antifungal drugs
- Calcineurin inhibitors (cyclosporine, tacrolimus)*

Drugs that block the epithelial sodium channel
- Amiloride
- Triamterene
- Trimethoprim and co-trimoxazole
- Pentamidine

Potassium-containing compounds
- Potassium supplementation
- Potassium chloride in table salt
- Medicinal herbs
- Blood transfusions

*** Calcineurin inhibitors also have direct tubular effects that contribute to hyperkalaemia.**

Figure 5. *Diagnostic algorithm for hyperkalaemia*



See text for details. K^+ = potassium; RAAS = renin-angiotensin-aldosterone system.

HYPOKALAEMIA

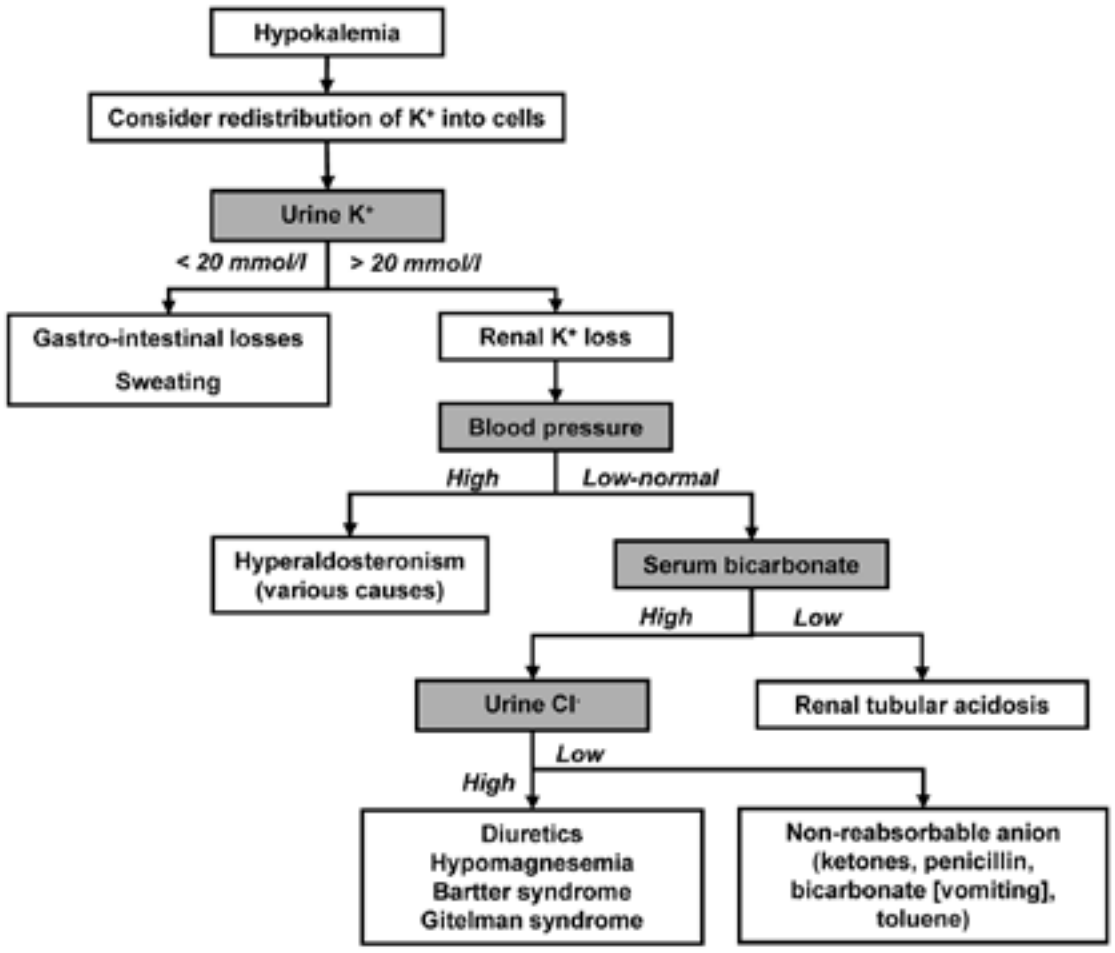
Hypokalaemia is defined as a serum potassium <3.5 mmol/l. When hypokalaemia is severe (usually serum potassium <2.5 mmol/l), it can cause ECG changes, arrhythmia, muscle weakness or paralysis (*table 1, figure 4*). The most common causes of hypokalaemia are listed in *table 3*. The causes of hypokalaemia can be divided into redistribution of potassium from the extracellular to the intracellular fluid compartment ('shift hypokalaemia'), extra-renal loss of potassium, and renal loss of potassium (most common). The recommended diagnostic tests to differentiate between these causes are shown in *table 4*. *Figure 6* shows a diagnostic algorithm which uses the urine potassium concentration, blood pressure, serum bicarbonate, and urine chloride to differentiate between the various causes of hypokalaemia. The urine potassium cut-off of 20 mmol/l is somewhat arbitrary and does not account for the concentration of the urine sample. Instead, the urine potassium to creatinine ratio may be

Table 10. *Treatment of hyperkalaemia*

Principle	Treatment	Comment
Membrane stabilisation	Calcium	• Only if serum potassium >7 mmol/l and/or ECG changes • Does not lower potassium, but reduces risk of arrhythmia
Move potassium into cells ('shift')	Insulin with glucose	• 10-20 units may be needed • Serum potassium and glucose should be monitored frequently
	Sodium bicarbonate	Especially if there is concurrent acidosis
	β2-adrenergic agonists	Because of side effects only recommended as rescue therapy
Remove excess potassium ('drift')	Restore diuresis	Intravenous fluids in hypovolaemia; urinary catheter or nephrostomy drain placement in post-renal causes
	Haemodialysis or haemofiltration	Especially in dialysis patients, patients with chronic kidney disease or in the intensive care
	Ion exchange resin (e.g., sodium or calcium polysterene sulphonate)	• Can be given orally or rectally • Takes ~4 hours before it works
	Loop diuretics	Especially if there is hypervolaemia
	Fludrocortisone	Especially if there is adrenal insufficiency

a better parameter and a cut-off of 2.5 mmol/mmol has been suggested by one study.[65] This study also showed that the urine potassium to creatinine ratio and the TTKG can be used to differentiate shift hypokalaemia from renal causes of hypokalaemia.[65] During shift hypokalaemia, the kidney will retain potassium, and therefore the urine potassium to creatinine ratio and the TTKG will be low. Causes of shift hypokalaemia include alkalosis (for each 0.1 increase in pH, the potassium falls ~0.4 mmol/l), insulin, hypothermia, increased production of erythrocytes (e.g., during folate or vitamin B12 therapy), stimulation of β2-adrenergic receptors, drugs (chloroquine, risperdal, quetiapine), and hypokalaemic paralysis.[7] Hypokalaemic and hyperkalaemic periodic paralysis represent a group of rare disorders in which patients experience periodic shifts of potassium into or out of cells triggered by food intake or exercise.[66] The cause is often genetic and various mutations in calcium and sodium channels in muscle have been identified.[67] An important cause of acquired hypokalaemic paralysis is thyrotoxicosis.[68] The combination of hypertension and hypokalaemia has a specific differential diagnosis that requires the measurement of plasma renin and aldosterone. Possible causes include renal artery stenosis and renin-producing tumour (*high renin, high aldosterone*), primary aldosteronism (Conn's disease) and glucocorticoid remediable hyperaldosteronism (*low renin, high aldosterone*), Liddle's syndrome, syndrome of apparent mineralocorticoid excess, and the use of liquorice *(low renin, low aldosterone*). Of these, renal artery stenosis, primary aldosteronism, and liquorice use are the most common. Hypokalaemia with non-anion gap metabolic acidosis also has a specific differential diagnosis that includes diarrhoea and renal tubular acidosis (RTA). These two causes can be differentiated based on the urine potassium excretion (low in

Figure 6. *Diagnostic algorithm for hypokalaemia*



See text for details. Cl^- = chloride; K^+ = potassium.

diarrhoea, high in RTA), the urine anion gap (negative in diarrhoea, positive in RTA), or the urinary electrogram which estimates renal ammonium secretion (high in diarrhoea, low in RTA). RTA can be further classified as type I (distal) and type II (proximal), which can be distinguished based on the presence of proximal tubular dysfunction (type II), fractional excretion of bicarbonate after bicarbonate infusion (type II), or a urinary acidification test (type I).[69] For a complete list of the causes of RTA, the reader is referred to two reviews.[70,71] Hypomagnesaemia can also cause hypokalaemia likely because a low intracellular magnesium concentration activates the renal potassium transporter ROMK to secrete more potassium.[72] A cause of drug-induced hypomagnesaemia that was identified relatively recently are proton pump inhibitors.[73] Although the mechanism remains elusive, several reports suggest that proton pump inhibitors can cause severe hypomagnesaemia due to gastrointestinal magnesium loss that was often accompanied by secondary hypokalaemia and hypocalcaemia.[74,75] The treatment of hypokalaemia relies largely on potassium supplementation. Potassium chloride is the preferred compound, although potassium bicarbonate, citrate or acetate can be given if there is concurrent acidosis, and potassium phosphate can be given if there is concurrent hypophosphataemia. Potassium supplementation should be given with caution when there may be shift hypokalaemia because of the risk of rebound hyperkalaemia.[76] Symptomatic hypokalaemia should be treated intravenously and, in severe cases, may require a central venous catheter and continuous ECG monitoring. Less severe cases of hypokalaemia can be treated with oral potassium supplementation either as liquid or as tablet. When hypokalaemia is due to renal potassium loss, a potassium-sparing diuretic may be added as treatment such as amiloride or spironolactone. Importantly, the treatment of hypokalaemic periodic paralysis differs from other forms of hypokalaemia.[77] First, less potassium supplementation should be given (<10 mmol/hour not exceeding a total of 60 mmol) because of the risk of rebound *hyperkalaemia* when the shift has ceased.[78] Second, the shift of potassium into cells can be reversed by giving high doses of propranolol (3 mg/kg).[79] When hypomagnesemia is present, hypokalaemia usually does not respond to potassium supplementation until magnesium supplementation is also started.

CONCLUSIONS

Although electrolyte disorders are not often the primary reason for admission to hospital, they are common and may contribute to adverse outcomes. More specifically, all the electrolyte disorders reviewed here can cause an immediate threat to the patient that may require emergency treatment. At the same time, too aggressive treatment can also cause complications and therefore frequent monitoring is necessary. Diagnostically, the presence of one or more of these electrolyte disorders may be the first sign of an important underlying disease. Although little high-level evidence is available to guide the management of electrolyte disorders, we believe the revised guideline will help to harmonise the diagnosis and treatment of these disorders. We therefore recommend the use of this guideline in daily practice. We believe future revisions of the guideline should also be based on European guidelines, which are currently being developed. We welcome any suggestions for improvement of this guideline based on experiences with its use.

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REFERENCES

1. Hoorntje SJ, van Geelen JA, Geers AB, et al. NIV guideline: Electrolyte disorders 2005.
2. De Vries APJ, Gans ROB, Levi MM. Acute boekje: Richtlijnen voor de diagnostiek en behandeling van aandoeningen op het gebied van inwendige specialismen: Van Zuiden Communications B.V.; 2009; 4th edition.
3. Geers AB, Tuut MK, Hoorn EJ, Hoorntje SJ, Van Saase JL, Zietse R. NIV guideline: Electrolyte disorders 2012.
4. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342:1581-9.
5. Adrogue HJ, Madias NE. Hypernatremia. N Engl J Med. 2000;342:1493-9.
6. Elliott MJ, Ronksley PE, Clase CM, Ahmed SB, Hemmelgarn BR. Management of patients with acute hyperkalemia. CMAJ. 2010;182:1631-5.
7. Greenlee M, Wingo CS, McDonough AA, Youn JH, Kone BC. Narrative review: evolving concepts in potassium homeostasis and hypokalemia. Ann Intern Med. 2009;150:619-25.
8. Hoorn EJ, Zietse R. Hyponatremia revisited: translating physiology to practice. Nephron Physiol. 2008;108:46-59.
9. Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. Hyperkalaemia. BMJ. 2009;339:b4114.
10. Simmons MA, Adcock EW, 3rd, Bard H, Battaglia FC. Hypernatremia and intracranial hemorrhage in neonates. N Engl J Med. 1974;291:6-10.
11. Lindner G, Kneidinger N, Holzinger U, Druml W, Schwarz C. Tonicity balance in patients with hypernatremia acquired in the intensive care unit. Am J Kidney Dis. 2009;54:674-9.
12. Singer I, Oster JR, Fishman LM. The management of diabetes insipidus in adults. Arch Intern Med. 1997;157:1293-301.
13. Moritz ML. A water deprivation test is not indicated in the evaluation of hypernatremia. Am J Kidney Dis. 2005;46:1150-1; author reply 1.

14. Sands JM, Bichet DG, American College of P, American Physiological S. Nephrogenic diabetes insipidus. Ann Intern Med. 2006;144:186-94.

15. Liamis G, Kalogirou M, Saugos V, Elisaf M. Therapeutic approach in patients with dysnatraemias. Nephrol Dial Transplant. 2006;21:1564-9.

16. Bedford JJ, Weggery S, Ellis G, et al. Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. Clin J Am Soc Nephrol. 2008;3:1324-31.

17. Moritz ML, Manole MD, Bogen DL, Ayus JC. Breastfeeding-associated hypernatremia: are we missing the diagnosis? Pediatrics. 2005;116:e343-7.

18. Dmitrieva NI, Burg MB. Increased insensible water loss contributes to aging related dehydration. PLoS One. 2011;6:e20691.

19. Hoorn EJ, Betjes MG, Weigel J, Zietse R. Hypernatraemia in critically ill patients: too little water and too much salt. Nephrol Dial Transplant. 2008;23:1562-8.

20. Polderman KH, Schreuder WO, Strack van Schijndel RJ, Thijs LG. Hypernatremia in the intensive care unit: an indicator of quality of care? Crit Care Med. 1999;27:1105-8.

21. Nguyen MK, Kurtz I. Correction of hypervolaemic hypernatraemia by inducing negative Na+ and K+ balance in excess of negative water balance: a new quantitative approach. Nephrol Dial Transplant. 2008;23:2223-7.

22. Sterns RH. Hypernatremia in the intensive care unit: instant quality--just add water. Crit Care Med. 1999;27:1041-2.

23. Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med. 2010;36:304-11.

24. Lindner G, Funk GC, Schwarz C, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. Am J Kidney Dis. 2007;50:952-7.

25. Liamis G, Gianoutsos C, Elisaf MS. Hyperosmolar nonketotic syndrome with hypernatremia: how can we monitor treatment? Diabetes Metab. 2000;26:403-5.

26. Hoorn EJ, Carlotti AP, Costa LA, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. J Pediatr. 2007;150:467-73.

27. Haringhuizen A, Tjan DH, Grool A, van Vugt R, van Zante AR. Fatal cerebral oedema in adult diabetic ketoacidosis. Neth J Med. 2010;68:35-7.

28. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N Engl J Med. 1986;314:1529-35.

29. Kokko JP. Symptomatic hyponatremia with hypoxia is a medical emergency. Kidney Int. 2006;69:1291-3.

30. Moritz ML, Ayus JC. 100 cc 3% sodium chloride bolus: a novel treatment for hyponatremic encephalopathy. Metab Brain Dis. 2010;25:91-6.

31. Sterns RH, Riggs JE, Schochet SS, Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986;314:1535-42.

32. Lauriat SM, Berl T. The hyponatremic patient: practical focus on therapy. J Am Soc Nephrol. 1997;8:1599-607.

33. Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. Am J Kidn Dis. 2013; epub 3 Jan.

34. Chawla A, Sterns RH, Nigwekar SU, Cappuccio JD. Mortality and serum sodium: do patients die from or with hyponatremia? Clin J Am Soc Nephrol. 2011;6:960-5.

35. Hoorn EJ, Zietse R. Hyponatremia and mortality: how innocent is the bystander? Clin J Am Soc Nephrol. 2011;6:951-3.

36. Hoorn EJ, Hotho D, Hassing RJ, Zietse R. Unexplained hyponatremia: seek and you will find. Nephron Physiol. 2011;118:66-71.

37. Fenske W, Maier SK, Blechschmidt A, Allolio B, Stork S. Utility and limitations of the traditional diagnostic approach to hyponatremia: a diagnostic study. Am J Med. 2010;123:652-7.

38. Chung HM, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med. 1987;83:905-8.

39. Turchin A, Seifter JL, Seely EW. Clinical problem-solving. Mind the gap. N Engl J Med. 2003;349:1465-9.

40. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106:399-403.

41. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med. 2007;356:2064-72.

42. Raff H, Skelton MM, Cowley AW, Jr. Cortisol inhibition of vasopressin and ACTH responses to arterial hypotension in conscious dogs. Am J Physiol. 1990;258:R64-9.

43. van der Hoek J, Hoorn EJ, de Jong GM, Janssens EN, de Herder WW. Severe hyponatremia with high urine sodium and osmolality. Clin Chem. 2009;55:1905-8.

44. Soule S. Addison's disease in Africa--a teaching hospital experience. Clin Endocrinol (Oxf). 1999;50:115-20.

45. Curtis RH. Hyponatremia in primary myxedema. Ann Intern Med. 1956;44:376-85.

46. Warner MH, Holding S, Kilpatrick ES. The effect of newly diagnosed hypothyroidism on serum sodium concentrations: a retrospective study. Clin Endocrinol (Oxf). 2006;64:598-9.

47. Beukhof CM, Hoorn EJ, Lindemans J, Zietse R. Novel risk factors for hospital-acquired hyponatraemia: a matched case-control study. Clin Endocrinol (Oxf). 2007;66:367-72.

48. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. Nat Rev Nephrol. 2009;5:193-202.

49. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med. 2005;352:1884-90.

50. Singh S, Bohn D, Carlotti AP, Cusimano M, Rutka JT, Halperin ML. Cerebral salt wasting: truths, fallacies, theories, and challenges. Crit Care Med. 2002;30:2575-9.

51. Berendes E, Walter M, Cullen P, et al. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet. 1997;349:245-9.

52. Sherlock M, O'Sullivan E, Agha A, et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf). 2006;64:250-4.

53. Rozen-Zvi B, Yahav D, Gheorghiade M, Korzets A, Leibovici L, Gafter U. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. Am J Kidney Dis. 2010;56:325-37.

54. Konstam MA, Gheorghiade M, Burnett JC, Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297:1319-31.

55. Hoorn EJ, Zietse R. Tolvaptan for hyponatremia. N Engl J Med. 2007;356:961; author reply 2-3.

56. Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH. Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. Clin J Am Soc Nephrol. 2007;2:1110-7.

57. Sterns RH, Hix JK. Overcorrection of hyponatremia is a medical emergency. Kidney Int. 2009;76:587-9.

58. Perianayagam A, Sterns RH, Silver SM, et al. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin J Am Soc Nephrol. 2008;3:331-6.

59. Dosik H. Pseudohyperkalemia and leukocytosis. Blood. 1977;50:749-50.

60. Graber M, Subramani K, Corish D, Schwab A. Thrombocytosis elevates serum potassium. Am J Kidney Dis. 1988;12:116-20.

61. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med. 2004;351:585-92.

62. Furgeson SB, Linas S. Mechanisms of type I and type II pseudohypoaldosteronism. J Am Soc Nephrol. 2010;21:1842-5.

63. Ethier JH, Kamel KS, Magner PO, Lemann J, Jr., Halperin ML. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. Am J Kidney Dis. 1990;15:309-15.

64. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol. 2010;21:733-5.

65. Lin SH, Lin YF, Chen DT, Chu P, Hsu CW, Halperin ML. Laboratory tests to determine the cause of hypokalemia and paralysis. Arch Intern Med. 2004;164:1561-6.

66. Ahlawat SK, Sachdev A. Hypokalaemic paralysis. Postgrad Med J. 1999;75:193-7.

67. Matthews E, Labrum R, Sweeney MG, et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. Neurology. 2009;72:1544-7.

68. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. J Am Soc Nephrol. 2012;23:985-8.

69. Unwin RJ, Shirley DG, Capasso G. Urinary acidification and distal renal tubular acidosis. J Nephrol. 2002;15 Suppl 5:S142-50.

70. Smulders YM, Frissen PH, Slaats EH, Silberbusch J. Renal tubular acidosis. Pathophysiology and diagnosis. Arch Intern Med. 1996;156:1629-36.

71. Laing CM, Unwin RJ. Renal tubular acidosis. J Nephrol. 2006;19 Suppl 9:S46-52.

72. Yang L, Frindt G, Palmer LG. Magnesium modulates ROMK channel-mediated potassium secretion. J Am Soc Nephrol. 2010;21:2109-16.

73. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med. 2006;355:1834-6.

74. Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. Clin Endocrinol (Oxf). 2008;69:338-41.

75. Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis. 2010;56:112-6.

76. Crop MJ, Hoorn EJ, Lindemans J, Zietse R. Hypokalaemia and subsequent hyperkalaemia in hospitalized patients. Nephrol Dial Transplant. 2007;22:3471-7.

77. Lin SH, Chiu JS, Hsu CW, Chau T. A simple and rapid approach to hypokalemic paralysis. Am J Emerg Med. 2003;21:487-91.

78. Lu KC, Hsu YJ, Chiu JS, Hsu YD, Lin SH. Effects of potassium supplementation on the recovery of thyrotoxic periodic paralysis. Am J Emerg Med. 2004;22:544-7.

79. Lin SH, Lin YF. Propranolol rapidly reverses paralysis, hypokalemia, and hypophosphatemia in thyrotoxic periodic paralysis. Am J Kidney Dis. 2001;37:620-3.