

**Electrolyte disorders**

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Word count: 4064

## Synopsis

Electrolyte disorders can result in life threatening complications. The kidneys are tasked with maintaining electrolyte homeostasis, yet the low glomerular filtration rate of neonatal kidneys, tubular immaturity, and high extra-renal fluid losses contribute to an increased occurrence of electrolyte disorders in the newborn period.

Understanding the physiological basis of renal electrolyte handling is critical for identification of underlying causes and initiation of proper treatment.

Here we will review key aspects of renal physiology, the diagnostic work-up of disorders of plasma sodium and potassium and the appropriate treatment. In addition, we will review some inherited disorders associated with neonatal electrolyte disturbances that illuminate the physiology of renal electrolyte handling.

Key words: electrolyte disorders, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, newborn, renal physiology

### **Key points:**

- Electrolyte homeostasis is maintained by the kidneys
- Disorders of plasma sodium commonly reflect disorders of water
- Sodium handling by the kidneys is determined by volume homeostasis rather than plasma sodium
- Volume (i.e. sodium) homeostasis and potassium homeostasis are interdependent
- Low GFR and tubular immaturity contribute to an increased frequency of electrolyte abnormalities in the neonatal period

## **Introduction**

The evolution of life started in the sea, which contained a steady concentration of salts. The function of living cells is thus critically dependent on a constant electrolyte composition and the evolution of life on land was only possible due to the development of kidneys, which provided this constant “internal milieu”<sup>2</sup>. Disorders in the electrolyte composition of this milieu thus can have serious consequences and are associated with morbidity and mortality<sup>3</sup>. Abnormalities of plasma sodium and potassium are a frequent occurrence in neonates and especially in the neonatal intensive care unit (NICU). In order to provide adequate treatment, it is important to understand the underlying problem and physiology<sup>4</sup>. For instance, a common response to hyponatremia is to increase sodium supplementation. Yet, most patients with hyponatremia do not have a sodium deficiency, but water excess. Increasing sodium administration in these patients may correct the hyponatremia, but will result in volume overload, which has serious risks in the neonatal period, such as patent ductus arteriosus, bronchopulmonary dysplasia and necrotizing enterocolitis,<sup>5-7</sup>. We will review the physiology of renal water and electrolyte handling with respect to dysnatremias and dyskalemias in the context of the special circumstances of the transition from intra- to extrauterine life. In addition, we will discuss some rare inherited disorders associated with neonatal electrolyte abnormalities.

## **Basics of renal water and electrolyte handling**

In an average adult (surface area 1.73m<sup>2</sup>) with a glomerular filtration rate (GFR) of 100 ml/min, the kidneys produce 144 liters of primary filtrate a day. Assuming a sodium and potassium concentration of 140 and 4 mmol/l, respectively, these 144 liters contain approximately 20000 mmol of sodium and 500 mmol of potassium.

Whilst the vast majority (60-80%) of this is reabsorbed isototically in the proximal tubule, there is still a large volume of water, sodium and potassium delivered to the distal tubule, where decisions can then be made about either reabsorption or excretion. Urine osmolality can range from  $<50$  to  $>1000$  mosm/kg, so that, depending on intake and extrarenal losses, urine output can vary roughly between 500 ml to 20 litre a day. Similarly, tubular sodium reabsorption can be adjusted so that sodium excretion may range from  $< 10$  to  $>1000$  mmol per day<sup>8</sup>. Potassium can even be secreted, so that potassium excretion may exceed the filtered amount<sup>9</sup>. Thus, with normal kidney function, renal water, sodium and potassium excretion can be adjusted over a very wide range to provide homeostasis even under extreme circumstances. However, with decreased GFR, the ability of the kidneys to maintain volume and electrolyte homeostasis diminishes, so that abnormalities can occur more easily.

### **The special circumstances of the neonatal kidney**

Whilst the same physiological principles apply to neonatal and adult kidneys, there are some important differences in the ability to maintain water and electrolyte homeostasis:

- *Neonatal kidneys have a low GFR:* GFR measured by creatinine clearance in pre-term infants from 27-31 weeks of gestation without apparent kidney disease can be lower than  $10 \text{ ml/min/1.73m}^2$  in the first week of life and increases to only  $>15.5 \text{ ml/ min/1.73m}^2$  by 4 weeks of life<sup>10</sup>.

- *Urinary concentrating ability is not fully developed until about 1 year of age.*

In fact, all neonates have a degree of physiologic nephrogenic diabetes insipidus, so that maximal urine concentration may not exceed 300 mosm/kg, even in a term neonate<sup>11,12</sup>. It is because of this decreased urinary

concentrating capacity that normal saline, which is commonly recommended as the basic intravenous fluid solution in older children,<sup>13</sup> is not suitable in the NICU, as it typically will be hypertonic compared to the baby's urine and thus may lead to hypernatremia .

The impaired ability of the neonatal and especially premature kidneys to maintain electrolyte homeostasis is also reflected in the wider reference range for plasma electrolytes. For instance, plasma sodium between 125 and 150 mmol/l are usually considered normal in this age group<sup>14</sup>. This relative instability is further compounded by some factors specific to the transition from intra-to extrauterine life and the early neonatal period:

- *Extra-renal water losses are increased* due to the greater ratio of surface area to body mass, and will be further increased by the use of radiant heaters and UV therapy. Moreover, immature skin is more permeable to water, probably due to higher expression of water channels (aquaporins)<sup>15,16</sup>.
- *The composition and distribution of body water changes with gestation:* at 23-weeks, water makes up 90% of body weight, with two thirds in the extracellular fluid (ECF) and one third in the intracellular fluid (ICF). At term, 75% of body weight is water and this is now roughly equally distributed between ECF and ICF, whereas in an adult, water makes up approximately 60% of body weight with one third in ECF and two thirds in ICF<sup>17,18</sup>. Thus, there is quite a marked contraction of the ECF in the third trimester and the neonatal period, which is reflected in the physiologic weight loss, that newborns normally experience.

Considering all of these circumstances, it is easy to understand that electrolyte abnormalities can occur easily in the NICU.

### **Dysnatremias**

Abnormalities of plasma sodium are probably the most common electrolyte disorder encountered in neonates. Nevertheless, they are associated with serious morbidity, including a poorer long-term neurological outcome<sup>14</sup>.

There are technical obstacles to accurate measurement of the serum sodium. Most laboratories measure sodium using a so-called indirect ion-selective electrode<sup>4</sup>. Using this method, the sample is diluted in order to maximize sample volume and minimize interference from plasma proteins. The formula used to calculate plasma sodium concentration from the activity of sodium ions in the sample assumes that water comprises 93% of plasma volume, but this assumption fails in plasma samples with abnormal protein or lipid content, the so-called “ion exclusion” effect<sup>19</sup>. This leads to the well-recognized phenomenon of pseudohyponatremia in lipemic samples or those with excess protein content. But the converse is also true: in samples with low protein content, the sodium concentration is overestimated, leading to pseudonormo- or pseudohypernatremia<sup>20</sup>. In one study, hypoproteinemia was present in almost 60% of plasma samples obtained in the NICU and led to an overestimation of the sodium concentration by >3 mmol/l in about a third of all samples and in some occasions by more than 10 mmol/l, when compared to the measurement with a direct ion-selective electrode, which is not susceptible to this ion-exclusion effect<sup>21</sup>. This needs to be considered when assessing a plasma sodium result from a hypoproteinemic neonate and it is important to remember that the point-of-care analyzers often present in the NICU do not use the indirect method. Thus results from these analyzers are likely to

be more accurate in samples with abnormal protein content than those obtained in the main laboratory<sup>21</sup>.

## **Hyponatremia**

When faced with a low plasma sodium result, the first consideration should be the patient: if the patient is seizing and the sodium is substantially lower than previous results, then the result is likely real and emergency treatment with hypertonic saline should be instigated. If the patient is stable, there is time for a careful assessment:

- Is this true or pseudohyponatremia (see ion exclusion effect above)?
- What is the cause of the hyponatremia?

*How to assess the cause of true hyponatremia (see also figure 1)?*

The immediate first question should be:

- Is hyponatremia due to an excess of water or a deficiency of sodium?

Excess water is the most common cause. In this case, weight and blood pressure are either stable or increased and there is normal skin turgor and peripheral perfusion. Of course, due to the special circumstances of the perinatal period, the weight is more difficult to interpret. A weight loss of 5-10% of body weight is physiologic and expected in the first postnatal days. Thus, hyponatremia associated with this expected weight loss and otherwise clinically normal volume status does not indicate hypovolemia and salt loss. Once the assessment of water excess versus salt loss has been made, biochemical evaluation of the urine can help delineate the etiology.

A key point to remember is that kidneys regulate sodium reabsorption to maintain volume homeostasis, but not to maintain a normal sodium concentration. There are no sodium or osmosensors in the kidneys. Therefore, with excess water, the kidneys

will excrete sodium to restore euvolemia. For this reason, weight and blood pressure can be stable and not increased with water excess. Thus, an elevated urine sodium does not necessarily indicate primary renal salt loss, but may be the appropriate physiologic response to water overload.

Interpretation of biochemical urinary indices is again more difficult in the NICU. The physiologic contraction of the extracellular fluid volume in the first days of life is associated with excretion of sodium. Moreover, as discussed above, maximal urinary concentration is impaired in neonates. A urine osmolality isotonic to plasma thus may reflect appropriate maximal concentration of immature kidneys or may be pathologic. Therefore, making clear-cut isolated interpretations of urine biochemistries is difficult

**Box 1: Clinical parameters for the assessment of dysnatremias**

- weight
- blood pressure
- skin turgor
- peripheral perfusion
- type and volume of administered fluids
- insensible water losses (radiant warmer? UV therapy?)
- urine output
- renal ultrasound

and sometimes impossible. Biochemical and clinical data (see box 1) need to be integrated to generate a reasonable diagnosis.

*Treatment of hyponatremia*

Emergency treatment of hyponatremia in an acutely symptomatic child involves administration of salt, irrespective of the underlying cause. A commonly used protocol is a bolus of 2 ml/kg 3% NaCl, repeated as necessary<sup>22</sup>.

In the asymptomatic child, several options are available: in the case of water excess, the simplest treatment is to reduce the volume of water administered. The excess volume can be calculated: assuming a total body water content of 75% (this may be



higher in premature babies, see above), the excess volume is  $\text{weight [kg]} \times 0.75 \times (130 - \text{observed Na}) / 130$ . Thus, a euvolemic 3-kg neonate with a sodium of 120 would be estimated to have  $3 \times 0.75 \times 10 / 130 = 0.173$  l excess water and reduction of water administration by this amount over the next 24-48h would be expected to normalize plasma sodium to 130 mmol/l over the same time period, assuming that other factors, such as insensible water losses and urine output remain unchanged. It is clear from this last statement that close observation is important for successful management.

Recently, antagonists for the type 2 vasopressin receptor AVPR2 have been introduced for the treatment of patients with hyponatremia due to vasopressin excess<sup>23</sup>. However, no efficacy or toxicity data in neonates currently exist and given the ease of control over fluid administration in the NICU and the impaired concentrating capacity of neonates, these drugs are unlikely to be used commonly in this setting. For those patients presumed to have a sodium deficit, sodium supplementation is the correct treatment and the sodium deficit can be calculated similar to the water excess:  $\text{weight [kg]} \times 0.75 \times (130 - \text{observed Na})$ . Thus, a hypovolemic 3-kg neonate with a sodium of 120 would be estimated to have  $3 \times 0.75 \times 10 = 7.5$  mmol sodium deficit and administration of this amount over the next 24-48h would be expected to normalize plasma sodium to 130 mmol/l over the same time period, assuming that the other factors remain unchanged. In an asymptomatic child, slow correction of the plasma sodium concentration is generally advised due to concerns over osmotic demyelination, especially in chronic hyponatremia. An increase by not more than 10 mmol/l/d is generally considered safe<sup>24</sup>.

## **Hypernatremia**

The basic considerations in hypernatremia are the same as for hyponatremia. The sodium can be falsely high due to low protein content of the plasma and this can be verified by checking with a different method, not prone to the ion exclusion effect (see above). If true, the next question is whether the high sodium reflects a deficiency in water or an excess of salt and based on the clinical and biochemical data an underlying diagnosis can be made (see Figure 2). As with hyponatremia, the most common explanation for an abnormal plasma sodium is a disorder of water, rather than sodium, but there are many hidden sources of sodium, mostly from line flushes and bronchial lavage with normal saline, or from medications, which may add up sufficiently to exceed renal excretory capacity and thus cause hypernatremia<sup>25</sup>. A deficiency in water can occur for instance when insensible water losses are underestimated.

### *Treatment*

The main concern in the treatment of hypernatremia is the development of cell swelling as plasma sodium falls, resulting in cerebral edema. For this reason, a slow correction, not exceeding 10 mmol/l/d is generally advised. The same formulas listed under hyponatremia (see above) can be used to estimate the water deficit or sodium excess and water administration can be increased or sodium administration decreased accordingly.

### **Dyskalemias**

A few key facts on potassium:

- It is the most abundant intracellular ion and intracellular potassium concentration is usually between 100-150 mmol/l

- It is a critical component for many cellular functions, including cell growth and division, DNA and protein synthesis, as well as for many enzyme and transport processes <sup>26</sup>
- Approximately 98% of total body potassium is in the ICF, especially in skeletal muscle, and thus only 2% is in the ECF, where it is accessible to routine clinical measurements <sup>27</sup>
- The usual normal range in neonates is 4.0-6.5 mmol/l and thus somewhat higher than in older children and adults <sup>28,29</sup>
- The kidneys maintain potassium homeostasis by adjusting potassium excretion to intake. About 90% of ingested potassium is absorbed and only about 5 – 10% of this is excreted via extrarenal pathways, mainly the gut, although this can increase substantially in renal failure <sup>30</sup>
- Neonates and infants maintain positive potassium balance to allow incorporation into cells newly formed during the period of somatic growth <sup>31</sup>

### *Internal potassium balance*

An important concept for the understanding and management of dyskalemia is the so-called internal potassium balance, which describes the ability of potassium to shift between the ICF and ECF <sup>32</sup>. Several factors affect this balance, including:

- Acid-base status, as acidosis leads to a shift out of the cells and vice versa in alkalosis <sup>33</sup>. A whole range of different transport processes is involved in this shift, which results in buffering of the acid-base abnormality by the cells <sup>34</sup>. In one study, a pH shift by 0.1 led to a change in plasma potassium by approximately 0.6 mmol (range 0.2-1.7) <sup>35</sup>

- Hormones and medications that affect the activity of the cellular Na/K ATPase, such as insulin, adrenalin and drugs affecting the sympathetic nervous system and digitalis derivatives <sup>36</sup>

Consequently, an important first assessment of dyskalemia is whether it is due to a disturbed internal (potassium shift) or external balance (imbalance between intake and output).

### Hypokalaemia

#### *Clinical manifestations*

Patients with mild hypokalemia are usually asymptomatic, but symptoms may occur with potassium levels <3mmol/l. Symptoms may include muscle weakness, constipation and ileus. With severe hypokalemia, rhabdomyolysis, arrhythmias and even cardiac or respiratory arrest have been reported <sup>37 38</sup>.

#### *Clinical assessment*

As discussed above, an important consideration is whether the derangement reflects a change in the internal balance (and total body potassium is unaffected) or the external balance (altered intake or excretion). Clinical factors taken into this consideration are listed in box 2.

An important initial consideration is the medication list. Many drugs commonly used in the NICU affect the internal potassium balance [e.g. xanthines (theophylline, caffeine) and bronchodilators ( $\beta$ 2-sympathomimetics)]. Others increase urinary losses (e.g. loop diuretics, amphotericin). A list of commonly used medications affecting potassium levels is given in table 1.

**Box 2: Clinical parameters for the assessment of dyskalemias**

- ECG (T-waves, U-waves, QT interval)
- Acid-base status
- Plasma biochemistries (associated other electrolyte abnormality, kidney function, muscle enzymes in suspected rhabdomyolysis)
- Potassium intake (concentration in administered fluids and nutrition)
- Urinary potassium excretion (volume of urine and urinary potassium concentration)
- Extrarenal potassium losses (stool, NG or other drainage)
- Medications
- Renal ultrasound (nephrocalcinosis, obstruction)

In addition, there are some rare inherited disorders that can cause hypokalemia in the newborn, including neonatal Bartter syndrome (discussed below), congenital adrenal hyperplasia (with salt retention), apparent mineralocorticoid excess and congenital chloride losing diarrhea.

In cases with disturbed external potassium balance (potassium loss), biochemical analysis of plasma and urine can help distinguish between renal and extrarenal potassium loss. Commonly used is the fractional excretion of potassium (FEK) with an FEK of >15% usually considered suggestive of renal losses<sup>39</sup>. A more specific way to assess potassium secretion in the collecting duct (see Figure 4 for the molecular basis) is the transtubular potassium gradient TTKG<sup>40</sup> (see also box 3).

**Box 3: The transtubular potassium gradient TTKG**

Calculating the TTKG is based on the idea that potassium concentration in the collecting duct can change primarily due to two factors:

1. Secretion of potassium
2. Extraction of water

It is calculated as follows:  $(U_K / U_{osm}) / (P_K / P_{osm})$

With  $U_K$  and  $P_K$  = urinary and plasma potassium concentration, respectively and  $U_{osm}$  and  $P_{osm}$  = urinary and plasma osmolality.

The higher the TTKG, the more potassium is secreted in the collecting duct. A value of <2 is consistent with little to no secretion. Normal range for term newborns in one study was 5.65 – 18.22. TTKG in preterm neonates is usually lower, reflecting tubular immaturity<sup>1</sup>. The TTKG is valid only during antidiuresis. Thus, if  $U_{osm}$  is <  $P_{osm}$ , then the TTKG is not useful, limiting its applicability in the NICU, given the physiologic concentrating defect of neonates.

### *Treatment*

Treatment of hypokalemia depends on the symptoms and the underlying etiology. In patients with disturbed internal balance, removal of the underlying cause (e.g. discontinuation of medications causing potassium shift) will usually result in normalization of the plasma levels within hours.

In cases with disturbed external potassium balance and a true potassium deficit, potassium supplementation is usually commenced, ideally with removal of the underlying cause (e.g. discontinuation of medications causing potassium wasting).

Urgent supplementation, such as infusion of 0.3 mmol/kg of potassium-chloride over 1 hour is usually only given in cases of severe symptomatic hypokalemia (e.g. serious cardiac arrhythmias, respiratory depression). As rapid changes of plasma potassium concentration can lead to cardiac arrhythmias in itself, these patients should be monitored carefully. It is also important to recognize that potassium supplementation in a patient with hypokalemia due to a shift in the internal balance can experience rebound hyperkalemia, once the cause for the shift resolves.

### **Hyperkalemia**

Hyperkalemia is defined as a plasma potassium concentration  $> 6.5$  mmol/l in newborns. As with hypokalemia, a key concern is cardiac arrhythmia. In an asymptomatic patient, a first consideration should be whether this is true hyperkalemia or an artifact from hemolysis due to traumatic phlebotomy (i.e., from squeezing or prolonged application of a tourniquet)<sup>43</sup>. An ECG can help assess the severity, with peaked T waves indicating true hyperkalemia.

Otherwise, the same considerations apply as in hypokalemia: is it a disturbance of the internal or external potassium balance? Presence of a metabolic acidosis or administration of medications such as digitalis would suggest disturbance of the internal balance. If the external balance is affected, assessment of urinary potassium excretion (see box 3) can help distinguish between excess administration (FEK and TTKG high) and impaired elimination (FEK and TTKG low). An increased potassium load can also result from cellular lysis (e.g. after an internal bleed, such as gastrointestinal or intraventricular hemorrhage). Premature babies are especially at risk of hyperkalemia due to their impaired potassium secretory ability reflecting tubular immaturity. Indeed, hyperkalemia is seen in more than 50% of extremely premature babies with a birth weight of less than 1000g<sup>44</sup>.

Impaired kidney function is, of course, another important consideration in any patient with hyperkalemia. In addition, there are a few rare inherited diseases that can cause hyperkalemia, including pseudohypoaldosteronism type 1 (PHA1, discussed below) and congenital adrenal hyperplasia (salt-wasting forms).

### *Treatment*

Hyperkalemia-induced arrhythmias are a medical emergency. Treatment usually includes intravenous calcium salts to decrease myocyte excitability. In non-oliguric neonates, medications affecting internal potassium balance, including glucose with insulin and beta adrenergic agonists appear preferable to rectal exchange resins for the treatment of acute hyperkalemia<sup>29</sup>. However, these resins are the only choice in oliguric neonates for long-term potassium removal apart from dialysis, but obstruction and intestinal necrosis have been reported<sup>45 46</sup>.

Non-acute treatment depends on the underlying etiology. Correction of an underlying acidosis or discontinuation of the causative medication (see table 2) is the obvious solution in many cases. Administration of loop diuretics can increase renal potassium excretion to help eliminate an acute potassium load.

### **Inherited disorders associated with electrolyte abnormalities**

There are several inherited disorders that can affect electrolytes in the neonatal period, but two (Bartter syndrome and PHA1) will be discussed here briefly, as they illuminate the underlying renal physiology of renal electrolyte handling, the understanding of which is important for any electrolyte disorder. For a more detailed discussion of these disorders, the interested reader is referred to more specific reviews <sup>39,47,48</sup>.

#### *Bartter syndrome*

Bartter syndrome is primarily a disorder of salt reabsorption in the thick ascending loop of Henle <sup>39</sup>. Several genes have been associated with Bartter syndrome, but three are typically associated with antenatal presentation (see also figure 3): *SLC12A1*, encoding the target of loop diuretics, the  $\text{N}^+-\text{K}^+-2\text{Cl}^-$  cotransporter NKCC2 (Bartter syndrome type 1), *KCNJ1*, encoding the potassium channel ROMK (Bartter syndrome type 2) and *BSND*, encoding the chloride channel subunit Barttin (Bartter syndrome type 4). Whilst there is a huge spectrum of clinical severity with each of these types, typical antenatal presentation manifests in utero with polyhydramnios, often requiring multiple amniocentesis to relieve the fluid load. The polyhydramnios reflects the polyuria of the fetus, the high salt content of which can be used diagnostically <sup>49</sup>. These salt and water losses continue immediately postnatally and may necessitate



supplementation of fluid of > 250 ml/kg/d and sodium-chloride of >15 mmol/kg/d <sup>50</sup>.

Associated with the polyuria is typically a hypokalemic metabolic alkalosis. This is due to highly elevated renin and aldosterone levels, reflecting the kidneys attempt to salvage the salt not reabsorbed in the thick ascending limb by up-regulating sodium reabsorption in the collecting duct. As sodium uptake in this segment is balanced by potassium and proton secretion (see figure 4), the patient develops hypokalemia and metabolic alkalosis. Hyponatremia can also be present due to an often associated urinary concentrating defect <sup>51,52</sup>. Without adequate supplementation, affected neonates may develop severe dehydration and acute kidney injury, resulting in hyperkalemia and acidosis and confusing the diagnostic picture. A history of polyhydramnios, although rarely due to Bartter syndrome, should nevertheless alert the clinician to this diagnostic possibility so that severe dehydration can be avoided. Besides fluid and electrolyte supplementation, treatment of Bartter syndrome involves non-steroidal anti-inflammatory drugs, such as indomethacin <sup>53</sup>. Whilst in some cases, this has even been given antenatally, most neonatologists are hesitant to use this drug in the neonatal period due to concerns of serious side effects, such as intestinal perforation and bleeding <sup>54,55</sup>.

Bartter syndrome type 2 can be an especially challenging diagnosis in the neonatal period, as the underlying protein, the potassium channel ROMK, is not only important for salt reabsorption in the thick ascending limb, but also for potassium secretion in the collecting duct (figures 3 and 4). Thus, these patients typically experience hyperkalemia in the first weeks of life, which slowly converts to hypokalemia, as other potassium channels start compensating for the lack of ROMK in the collecting duct <sup>56</sup>. In some cases, patients initially resemble the phenotype of PHA1 (see below) with severe hyperkalemia, hyponatremia and acidosis <sup>57</sup>.

### **Pseudohypoaldosteronism type 1 (PHA1)**

PHA1 is primarily a disorder of salt reabsorption in the collecting duct, characterized by an inability of this segment to respond to aldosterone. We distinguish a recessive form, due to loss-of-function mutations in genes encoding the epithelial sodium channel ENaC (see Figure 4) from a dominant form, due to loss-of-function mutations in the gene encoding the mineralocorticoid receptor. The recessive form is more severe and can include extrarenal manifestation, such as cystic fibrosis-like lung disease, as well as skin problems, due to expression of ENaC in these organs. The dominant form is milder, restricted to the kidney, and often improves spontaneously over time<sup>58</sup>. For this review, the renal features are of relevance: patients present with severe volume depletion, potentially life-threatening hyperkalemia (sometimes >10 mmol/l), moderate hyponatremia and acidosis. This electrolyte constellation can be easily explained by the molecular characteristics of salt transport in the collecting duct (figure 4): reabsorption of sodium occurs via ENaC, expressed in the principal cells of the collecting duct, but needs to be electrically balanced. This can occur by potassium secretion through ROMK, or by proton secretion from the neighboring intercalated cells. Thus sodium (i.e. volume) homeostasis is molecularly coupled to potassium and acid-base homeostasis and disturbance of one pathway automatically affects the others, as well. Hyponatremia occurs from a combination of sodium loss and water retention, as hypovolemia leads to vasopressin-mediated urinary concentration.

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**Table 1: Medications associated with hypokalemia**

Modified from <sup>37</sup>

<b>Internal balance</b>	<b>Renal excretion</b>	<b>Extrarenal excretion</b>
insulin	Loop diuretics (e.g.furosemide)	laxatives
Xanthines (e.g.caffeine, theophylline)	Thiazide diuretics	exchange resins (e.g. sodium or calcium polystyrene sulfate)
$\beta$ 2-agonists (e.g.adrenalin, salbutamol)	Carbanhydrase inhibitors (e.g.acetazolamide)	
	amphotericin	
	foscarnet	
	cisplatin	
	aminoglycosides	
	mineralocorticoids	

**Table 2: Medications associated with hyperkalemia**

Modified from <sup>59</sup>

<b>Internal balance</b>	<b>Impaired Renal excretion</b>	<b>Increased potassium load</b>
Digitalis	Angiotensin Converting Enzyme inhibitors and Angiotensin receptor blockers	Penicillin K
$\beta$ 2-antagonists	Non-steroidal antiinflammatory drugs (indomethacin)	Stored packed red blood cells
E-Aminocaproic acid	ENaC blocker (amiloride, triamteren)	
	Spironolactone	
	Antifungals (e.g. Ketoconazole)	
	Calcineurin inhibitors (e.g.cyclosporine, tacrolimus)	
	Trimethoprim	
	Heparin	
	Pentamidine	

**Figure 1: Algorithm for the assessment of hyponatremia**

After establishing that the hyponatremia is true and not a measurement artifact, the most important step is to determine whether the cause is an excess of water or a deficiency of salt. Once that distinction is made, urinary indices can help delineate the etiology.

**Figure 2: Algorithm for the assessment of hypernatremia**

After establishing that the hypernatremia is true and not a measurement artifact, the most important step is to determine whether the cause is a deficiency of water or an excess of salt. Once that distinction is made, urinary indices can help delineate the etiology.

**Figure 3: Diagram of an epithelial cell in the thick ascending limb**

Sodium is reabsorbed together with potassium and chloride via the apical transporter NKCC2, the target of loop diuretics. Transport is facilitated by the action of the basolateral Na/K-ATPase, which creates the electrochemical gradient favoring sodium movement into the cell and also provides a basolateral exit for sodium. Chloride exits the cell via the basolateral chloride channels CLCKNA and B. Function of NKCC2 is critically dependent on the availability of potassium, which is ensured through recycling of potassium via the potassium channel ROMK. This recycling of potassium across the apical membrane contributes to a lumen-positive transepithelial voltage, which enables reabsorption of calcium, magnesium and sodium through a paracellular pathway lined by CLDN16 and 19. Modified from <sup>39</sup>.

**Figure 4: Diagram of a principal cell in the collecting duct**

Sodium is reabsorbed via the epithelial sodium channel ENaC, expressed on the apical side. Uptake is facilitated by the action of the basolateral Na/K-ATPase, which creates the electrochemical gradient favoring sodium movement into the cell and also provides a basolateral exit for sodium. Electrical balance for sodium uptake can be provided by potassium secretion through the apical potassium channel ROMK or by proton secretion from neighboring intercalated cells (not shown). Thus sodium (i.e. volume) homeostasis is molecularly linked with potassium and acid-base homeostasis in this nephron segment. Modified from <sup>39</sup>.