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REVIEW

Na^+, K^+, Cl^-, acid–base or H_2O homeostasis in children with urinary tract infections: a narrative review

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Abstract Guidelines on the diagnosis and management of urinary tract infections in childhood do not address the issue of abnormalities in Na^+, K^+, Cl^- and acid–base balance. We have conducted a narrative review of the literature with the aim to describe the underlying mechanisms of these abnormalities and to suggest therapeutic maneuvers. Abnormalities in Na^+, K^+, Cl^- and acid–base balance are common in newborns and infants and uncommon in children of more than 3 years of age. Such abnormalities may result from factitious laboratory results, from signs and symptoms (such as excessive sweating, poor fluid intake, vomiting and passage of loose stools) of the infection itself, from a renal dysfunction, from improper parenteral fluid management or from the prescribed antimicrobials. In addition, two transient renal tubular dysfunctions may occur in infants with infectious renal parenchymal involvement: a reduced capacity to concentrate urine and pseudohypoaldosteronism secondary to renal tubular unresponsiveness to aldosterone that presents with hyponatremia, hyperkalemia and acidosis. In addition to antimicrobials, volume resuscitation with an isotonic solution is required in these children. In secondary pseudohypoaldosteronism, isotonic solutions (such as 0.9 % saline or lactated Ringer) correct not only the volume depletion but also the hyperkalemia and acidosis. In conclusion, our review suggests that in infants with infectious renal parenchymal involvement, non-renal and renal causes concur to cause fluid volume depletion and abnormalities in electrolyte and acid–base balance, most frequently hyponatremia.

Keywords Acidosis · Childhood · Electrolytes · Hyperkalemia · Hyponatremia · Pseudohypoaldosteronism · Urinary tract infection

Introduction

Several reports suggest that abnormalities in Na^+, K^+, Cl^-, acid–base or H_2O homeostasis often occur among pediatric inpatients with a febrile urinary tract infection (UTI), especially in newborns and infants concurrently affected by a dilating urinary tract malformation [1–5] (see Table 1). These abnormalities may result from factitious laboratory results, from the signs and symptoms of the infection, from renal dysfunction, from improper fluid management and/or from the prescribed drugs. The aim of this narrative review is to describe the underlying mechanisms and suggest therapeutic maneuvers.

Laboratory techniques and factitious results

The laboratory testing [6] process begins with the order of the physician, includes the pre-analytical (activities occurring prior to insertion of the sample in the analytical instrument), analytical (processes occurring in the analytic platform) and post-analytical phase (events occurring after the generation of the test results, such as data entry, transport of the results

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Table 1 Rough estimate of frequency of disturbances in Na^+, K^+ or acid–base balance in infants with acute febrile urinary tract infections [1–5]

Abnormality	Frequency (%)
Hyponatremia	≥50
Hyperkalemia	10-25
Metabolic acidosis	10-25
Hypernatremia	5-10
Hypokalemia	5-10
Metabolic alkalosis	≤5
Two or more concomitant abnormalities	10-25

through information systems and interpretation of the results). Laboratory practice has improved over the years and, consequently, error rates in laboratory medicine are currently far lower than those seen in clinical healthcare settings. Regrettably, the pre-analytical process remains error-prone [6].

It is currently recommended to determine Na^+, Cl^-, K^+, pH and the partial pressure of carbon dioxide (pCO_2) in undiluted blood samples by means of ion-selective electrodes [7]. The Na^+, Cl^- and K^+ values obtained using such electrodes, referred to as ionized (or free) Na^+, Cl^- or K^+, are more relevant than those obtained in diluted samples (or by flame photometry). In addition, the use of ion-selective electrodes almost completely circumvents the problem of pseudohyponatremia that occurs when Na^+ is determined in diluted samples or by flame photometry [7]. The bicarbonate (HCO_3^-) level is either calculated from the pH and pCO_2 or is measured by means of an enzymatic assay [8].

Clinicians must be alert to common spurious pre-analytical abnormalities when faced with the determination of Na^+, Cl^-, K^+ and blood gas testing, as shown in Table 2. Due to hemolysis, capillary Na^+ and Cl^- values are lower than venous values by 2–3 mmol/L [9]. A tourniquet, traumatic venipuncture, capillary blood or a delay in specimen transport or processing may cause K^+ to be released from cells [10]. However, the most usual cause of hemolysis in capillary samples is the alcohol that is used to clean the skin (if alcohol is allowed to dry, hemolysis is negligible) [10]. While the gold standard method for blood gas testing is generally arterial blood, pH, pCO_2 and HCO_3^- values in arterial, venous and capillary samples correlate fairly well because of the low arteriovenous gradient of these analytes. However, relevant pre-analytical errors are common in testing for pH, pCO_2 and HCO_3^- [11].

Non-renal causes of disturbed Na^+, K^+, Cl^-, acid–base or H_2O homeostasis

Conditions such as meningitis, gastroenteritis and respiratory tract infections often present with a disturbed Na^+, K^+, Cl^-, acid–base or H_2O homeostasis. Since UTIs and these conditions share a tendency for the patient to experience eating disorders (poor feeding), increased sweating, vomiting or loose stools, it is speculated that in childhood UTIs, electrolyte abnormalities result at least in part from these symptoms and signs.

In a prospective Spanish study, the frequency of hyponatremia (<135 mmol/L) was similar (approx. 50 %) in

Table 2 Common factitious laboratory results secondary to pre-analytical laboratory errors in the determination of Na^+, Cl^-, K^+ and in blood gas testing [6, 9–11]

Parameter affected	Cause	Direction of change[a]	Comment
Na^+ (Cl^-)	Capillary blood collection	↓	Clinically not relevant
K^+	Capillary blood collection (especially if alcohol is not allowed to dry), tourniquet applied for prolonged period, traumatic venipuncture, excessive force with syringe draws, delay in specimen transport or processing	↑	K^+ release from cells
pCO_2	Low temperature (plastic syringes on ice after collection)	↓	Gas permeability of plastic syringes increases at lower temperatures
	Air bubbles in blood sample	↓	Room air having a pCO_2 of basically zero; air bubbles lower pCO_2
pCO_2, HCO_3^-	Excess of heparin solution in the sampling syringe	↓	pH of heparin being near 7.0, and pCO_2 of heparin solution near room air values, excess of heparin decreases pCO_2 and HCO_3^-
pCO_2 pH	Delay (>20 minutes) in estimation	↑ ↓	pCO_2 increases by 1 mmHg, pH decreases by 0.02–0.03 pH units hourly at 22 °C

pCO_2, Partial pressure of carbon dioxide in blood; HCO_3^-, bicarbonate

[a] ↓, Decrease in level; ↑, increase in level

113 bacteriuric and 75 non-bacteriuric febrile infants aged ≤30 months, highlighting the possibility that common non-renal pathways, such as poor fluid intake, vomiting, passage of loose stools or excessive sweating, explain, at least in part, this dyselectrolytemia. On the contrary, in another study, hyperkalemia was more frequent ($P<0.05$) in patients with bacteriuria ($N=24$; 21 %) than in those without ($N=7$; 9.3 %) [3]. In a retrospective case–control study, 24 Japanese infants aged ≤7 months affected by an acute pyelonephritis were compared with 20 febrile infants without acute pyelonephritis [2]. The circulating K^+ level was higher ($P<0.003$) by 0.6 mmol/L and that of Na^+ was lower ($P<0.002$) by 5 mmol/L in the group of infants with pyelonephritis [2]. In addition, exploratory observations suggest that hyponatremia might be especially prevalent in infants with pyelonephritis associated with vesico-ureteral reflux [5]. Finally, in a cohort of 140 South Korean children with a febrile UTI, hyponatremia (sometimes associated with metabolic acidosis) was more frequent ($P<0.01$) in those with scintigraphic abnormalities (74 %) than in those without (45 %) and more pronounced in those with an elevated white cell count or increased C-reactive protein ($P<0.01$), while a tendency ($P<0.01$) to hyperkalemia was observed during the first year of life [4]. These data suggest that, compared with infants affected by a non-bacteriuric febrile infection (Table 3), infants with severe UTIs present with a distinct pathophysiological pathway that is responsible for hyperkalemia during the first 3 years of life and for hyponatremia during the first 6 months of life.

Finally, severe urosepsis is hallmarked by anion gap metabolic acidosis secondary to increased lactate production [12].

Renal causes of disturbed Na^+, K^+, Cl^- or acid–base or H_2O homeostasis

Three mechanisms possibly underlying disturbances in Na^+, K^+, Cl^-, acid–base or H_2O homeostasis have been investigated in infants with acute infectious renal parenchymal involvement: (1) an impaired renal acid excretion [13], (2) a reduced capacity to concentrate urine [14–21] and (3) a secondary transient pseudohypoaldosteronism [22–27].

Impaired renal acid excretion Over 30 years ago, Tulassay et al. observed a reduced urinary pCO_2, which is a marker of altered distal H^+ secretion, in maximally alkaline urine of Hungarian children affected with an acute febrile UTI [13]. Regrettably, this association was not investigated further in subsequent research.

Reduced maximal capacity to concentrate urine In infants with acute bacteriuria, there is a well-recognized association, first documented more than 50 years ago [15, 16], between involvement of the renal parenchyma in acute UTI and a mild impairment of the maximal urinary concentrating ability, which is traditionally considered to be the first evidence of bacterial invasion of the renal medulla [17–21]. These children normally present with a normal or at most high-normal circulating Na^+ level. The reduced maximal urinary concentrating ability, if challenged by H_2O restriction or by desmopressin, a synthetic analog of antidiuretic hormone, reverts to normal within 4–6 weeks after treatment initiation of the infection [18–21]. A number of findings [17–21] have been identified in these patients (Table 4).

It is assumed, but not proven, that the reduced capacity of infants with infectious renal parenchymal involvement to concentrate urine might be the consequence of an increased renal medullary blood flow, which decreases the outer–inner medullar osmotic gradient. Alternatively, the reduced capacity to concentrate urine might result from an impairment of H_2O reabsorption in nephron segments upstream of the collecting duct. Marra et al. [28] observed an impaired urinary concentrating ability for up to 3 years after surgical correction for infantile congenital hydronephrosis.

Secondary transient pseudohypoaldosteronism Since the initial 80s, it has been recognized that transient renal Na^+ wasting, hyponatremia, hyperkalemia, inappropriately low

Table 3 Rough estimate of the frequency of hyponatremia and hyperkalemia in infants with a severe urinary tract infection and in infants affected by a non-bacteriuric febrile infection [3–6]

Age (months)	Analyte	Febrile urinary tract infection[b]	Febrile non-urinary infection
≤6	Na^+	↓↓	↓
	K^+	↑↑	→
7–36	Na^+	↓	↓
	K^+	↑	→

[a] In infants affected by a severe urinary tract infection, the data suggest the existence of a distinct pathophysiological pathway responsible for hyperkalemia during the first 3 years of life and for hyponatremia during the first 6 months of life

[b] ↓↓, Decreased Na^+ is a very frequent abnormality; ↑↑, increased K^+ is a very frequent abnormality; ↓, decreased Na^+ is a frequent abnormality; ↑, increased K^+ is a frequent abnormality; →, an infrequent abnormality

Table 4 Findings identified in patients with acute infectious renal parenchymal involvement and transient impaired renal concentrating ability [17–21]

- Unimpaired urine diluting ability
- Capacity to concentrate urine better in non-infected than in infected side
- Urinary osmolality lower in children with bilateral renal parenchymal involvement than in those with unilateral renal parenchymal involvement
- Slightly increased glomerular filtration rate and renal plasma flow
- Increased circulating vasopressin level
- Increased urinary excretion of the specific protein H_2O channel aquaporin-2, the renal target for antidiuretic hormone

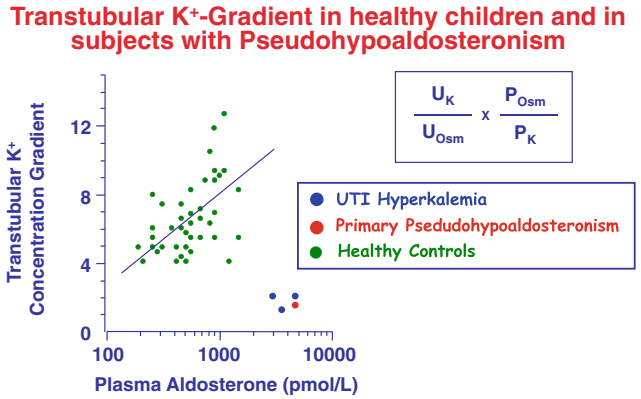

Fig. 1 Relationship between circulating aldosterone and the transtubular K^+ gradient, a simple biochemical index of renal aldosterone bioactivity, in 41 healthy (*green circles*) subjects (26 boys, 15 girls, ranging in age from 9 to 19 years; y=-8.16+5.43 log x; r=0.56), three male infants (aged 2, 5 and 6 weeks, respectively) with hyperkalemic urinary tract infection (*blue circles*) and an 8-week-old boy with primary Na^+ wasting pseudohypoaldosteronism secondary to a mutation in the mineralocorticoid receptor (*red circle*). The transtubular K^+ gradient is calculated as shown in *box* using the following parameters: U_K Urine K^+ (mmol/L), U_{Osm} urine osmolality (mOsmol/kg), P_{Osm} plasma osmolality (mOsmol/kg), P_K plasma K^+ (mmol/L). Data on these patients were collected between 1989 and 2002 at the Pediatric Department of Southern Switzerland, Bellinzona, Switzerland, and are reported here for the first time

urinary K^+ excretion and non-anion gap metabolic acidosis (we avoid using the term hyperchloremic acidosis and recommend that of non-anion gap or normal anion gap acidosis because if there is an associated hyponatremia, as in most cases of pseudohypoaldosteronism, the Cl^- concentration is often normal) characteristically associated with a moderately reduced glomerular filtration rate, occasionally develop in infants between 6 and 12 months of age with acute UTIs, urinary tract malformations or both [22–24]. In these cases, the renin–angiotensin II–aldosterone system is highly activated, denoting an apparent renal tubular unresponsiveness to aldosterone, which reverts to normal following antimicrobial treatment of bacteriuria (or repair of the underlying urinary tract malformation). A less severe form of pseudohypoaldosteronism occurs almost exclusively in infants with UTIs aged ≥12 months. These patients present with Na^+ wasting but without hyponatremia, hyperkalemia or acidosis [25].

The transtubular K^+ gradient is a biochemical index of renal aldosterone bioactivity [25]. Therefore, there is normally a highly significant relationship between the level of circulating aldosterone and the transtubular K^+ gradient. This relationship is blunted in infants with bacteriuria presenting with Na^+ wasting, hyponatremia, hyperkalemia and metabolic acidosis and in the context of primary pseudohypoaldosteronism, a rare salt-wasting syndrome caused by congenital renal resistance to aldosterone (Fig. 1). The mechanisms underlying secondary pseudohypoaldosteronism are poorly understood. However, the severity of salt wasting is inversely correlated with age, supporting a role for renal tubular immaturity [25–27, 29]. Signs of pseudohypoaldosteronism have been reported to persist for up to 3 years after surgery in infants with congenital hydronephrosis [28].

Classic Na^+-losing congenital adrenal hyperplasia characteristically manifests at 1–2 weeks of age with hyponatremia, hyperkalemia and acidosis [30]. These laboratory features are often associated with ambiguous genitalia and clitoral enlargement in girls and with phallic enlargement and scrotal hyperpigmentation in boys [30]. With the advent of neonatal screening, affected newborns are typically diagnosed before they develop Na^+-losing syndrome. Consequently, nowadays it is assumed that infections and malformations of the urinary tract are the most common cause of hyponatremia, hyperkalemia and metabolic acidosis in infants aged ≤2 months [30].

Iatrogenic causes

Intravenous maintenance fluids are designed to provide H_2O and electrolyte requirements in a fasting patient. In young children with a febrile UTI, the administration of low Na^+ maintenance fluid therapy, which has been the standard of care for many years and unfortunately still is everyday practice, may result in hospital-acquired hyponatremia [31–33].

In addition, some children are at risk of developing Na^+, K^+, Cl^- and acid–base disturbances induced by antimicrobial agents that are often prescribed to treat UTIs, such as the β-lactams, aminoglycosides and trimethoprim (alone or, more frequently, combined with sulfamethoxazole in a fixed 1:5 ratio), as shown in Table 5 [34, 35]. Finally, nonsteroidal anti-inflammatory drugs, such as ibuprofen, which are often prescribed to treat fever, can occasionally be nephrotoxic and subsequently may cause H_2O, Na^+ or K^+ retention.

Table 5 Disturbances in Na^+, Cl^-, K^+ and acid–base balance that have been frequently associated with antimicrobials commonly used to treat infants with a febrile urinary tract infection [34, 35]

Antimicrobial	Abnormality	Underlying mechanisms
β-lactam preparations containing large amounts of Na^+[a]	Hypernatremia, hypokalemia, often associated with metabolic alkalosis and sometimes also with hypomagnesemia	-β-lactams are non-reabsorbable anions that result in large-scale Na^+ reabsorption in exchange for K^+ and H^+ -Large amounts of Na^+ (administered with lactams) cause solute diuresis and subsequently K^+–H^+ excretion
Aminoglycosides	Hypokalemia, sometimes associated with metabolic alkalosis	Activation of the calcium-sensing receptor in the thick ascending loop of Henle
Trimethoprim[b]	Hyperkalemia, normal anion gap hyperchloremic acidosis	Blockade of luminal Na^+-channels

[a] Exclusively patients managed with very high doses (which contain large amounts of Na^+)

[b] Mostly combined with sulfamethoxazole at a fixed 1:5 ratio as cotrimoxazole, a sulfonamide

Mechanisms underlying hyponatremia

Hyponatremia (Fig. 2) is classified as "hypovolemic" (= depletional) or "normo-hypervolemic" (= dilutional). Antidiuretic hormone plays a pivotal role in hyponatremia. In depletional hyponatremia, release is triggered by a low effective blood volume; in dilutional hyponatremia, the primary defect is euvolemic increase in circulating antidiuretic hormone (or activation of its renal receptor).

The causes of hyponatremia in childhood UTIs remain controversial. The standard tenet is that excessive sweating, poor fluid intake, vomiting, loose stools or unresponsiveness to aldosterone predispose to depletional hyponatremia [32, 36]. On the contrary, preliminary observations suggest that pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β or -6, might result in dilutional hyponatremia by directly causing the release of antidiuretic hormone or increasing the function of its renal receptor [4, 37].

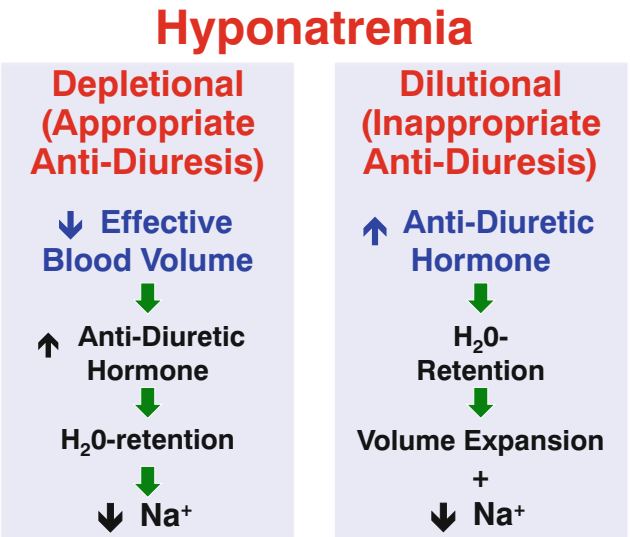

Fig. 2 Hyponatremia is classified according to the fluid volume status as either hypovolemic (= depletional) or normo-hypervolemic (= dilutional). Depletional hyponatremia results from a low effective arterial blood volume and is referred to as hypovolemic hyponatremia (the term syndrome of appropriate antidiuresis is occasionally used in this situation). Dilutional hyponatremia results from persistently high levels of antidiuretic hormone or, less frequently, from activation of its renal receptor (the term syndrome of inappropriate antidiuresis is used to denote this situation)

Clinical and laboratory assessment

Infants with a severe febrile UTI are susceptible to fluid volume depletion and, consequently, the initial assessment should include the identification of acute changes in weight from baseline (regrettably, previous recent weight measurements are often unavailable) and signs such as dry mucous membranes, sunken dry eyes and open fontanelle, decreased skin elasticity, delayed capillary refill and abnormal heart and respiratory rate [32]. Surprisingly, clinicians tend to underestimate fluid-volume depletion in these children [38]. In children with acute diarrhea, overestimation of volume depletion is much more common than underestimation [38].

In addition to urinalysis, urine and blood culture, blood cell count and C-reactive protein (and perhaps procalcitonin as well [39]), recommended laboratory studies in these cases are Na^+, Cl^-, K^+, blood gas profile, glucose, creatinine and urea as well as renal and bladder ultrasonography.

A careful examination of the external genitalia is advised in infants with hyponatremia, hyperkalemia and acidosis.

Fluid and salt therapy

The data summarized in this narrative review suggest that many infants with infectious renal parenchymal involvement require, in addition to antimicrobial treatment [40], volume therapy with an isotonic solution such as 0.9 % saline or lactated Ringer [31, 33]. In patients with secondary pseudohypoaldosteronism, as in those affected by primary

Na^+-losing pseudohypoaldosteronism, isotonic solutions correct not only volume depletion but also hyperkalemia, acidosis and reduced glomerular filtration rate [26, 27]. It is generally assumed that 0.9 % saline is the more efficacious solution for repairing hyponatremia, whereas lactated Ringer is the better choice to repair acidosis. Management of hyperkalemia with insulin, $ß_2$-adrenergic agonists, $NaHCO_3$ or fludrocortisone [41] is mostly unnecessary.

Reduced renal sensitivity to aldosterone sometimes persists for months after treatment of the UTI, repair of the urinary malformation or both [26, 27]. This persistence implies that Na^+ supplementation [26, 27] can sometimes be required for months (the youngest patients may require a long-lasting supplementation, whereas older ones have lower salt requirements).

Everyday clinical practice [28] and experimental data [42] indicate that many children with reduced capacity to concentrate urine are concomitantly affected by secondary pseudohypoaldosteronism. As a consequence, rehydration with an isotonic solution is mostly prescribed in this setting as well.

Conclusions

In infants with a febrile non-urinary infection, poor fluid intake, vomiting, passage of loose stools or excessive sweating predispose to fluid volume depletion and abnormalities in electrolyte and acid–base balance. Nonetheless, in these cases, undamaged kidneys partly protect against this tendency. In infants with an acute renal parenchymal infection, non-renal and renal causes concur to cause fluid volume depletion and abnormalities in electrolyte and acid–base balance, most frequently manifesting as hyponatremia. Surprisingly, none of the guidelines on the diagnosis and management of UTIs in young children published between 2007 and 2015 address this issue [43–46].

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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