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EDUCATIONAL REVIEW

Renal aspects of metabolic acid–base disorders in neonates

Silvia Iacobelli[1,2] · Jean-Pierre Guignard[3]

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Abstract
Acid–base homeostasis is one of the most tightly regulated systems in the body. Maintaining the acid–base balance is particularly challenging for preterm infants and growing neonates. The kidney, which represents the crucial ultimate line of defense against disturbances of acid–base balance, undergoes a complex maturation process during the transition from a fetal to an extra-uterine environment. This review article summarizes the physiology of acid–base regulation by the immature human kidney and discusses disorders of acid–base balance, such as metabolic acidosis, respiratory acidosis, metabolic alkalosis, and respiratory alkalosis. In conditions of metabolic acidosis, the serum anion gap and the urinary anion gap can be useful tools to define the nature of the acidosis. Metabolic acidosis can reflect a decrease in glomerular filtration rate, or be the consequence of selective disorders of proximal or distal tubular function. Most tubulopathies associated with metabolic acidosis observed in neonates are primary, hereditary, isolated tubulopathies. Proximal renal tubular acidosis is characterized by bicarbonate wasting, while the distal types of renal tubular acidosis are secondary to distal acidification defects. All tubulopathies are associated with hypokalemia, with the exception of type 4 hyperkalemic distal renal tubular acidosis. The transporter defects in the various acid–base tubulopathies are now well defined. Treatment of the acidosis varies according to the site and mechanism of the defect. Chronic renal tubular acidosis or alkalosis severely impair growth and calcium metabolism. Early rational therapeutic intervention can prevent some of the consequences of the disorders and improves the prognosis.

Keywords Acidemia · Alkalemia · Anion gap · Physiological approach · Tubular function · Immaturity · Bicarbonate · Growth failure

Physiology of acid–base regulation

In a steady state, organic acids and proton generation are in balance with their excretion and with bicarbonate production, and this allows the maintenance of the systemic arterial pH between 7.35 and 7.45. The Henderson-Hasselbalch equation [1, 2] defines how the ratio of the major blood buffer, bicarbonate (HCO_3^-), to partial pressure of arterial carbon dioxide (PCO_2) maintains the pH at the physiological range:

$$pH = pK + \log_{10}\left(\text{bicarbonate}\ [HCO_3^-] \div [0.03 \times PCO_2]\right),$$

where 0.03 represents the solubility factor of CO_2 into the blood.

In the adult, the plasma pH is normally kept between 7.35 and 7.45. Any disorder tending to lower the pH < 7.35 is called acidosis, while a disorder tending to increase the pH > 7.45 is called alkalosis. The acid–base disorder is considered as metabolic when the primary change is due to a variation in the plasma bicarbonate concentration, and respiratory when the plasma PCO_2 is primarily modified [3]. The concept of base excess (BE) is used to estimate the amount of excess or deficit of bicarbonate in the system. A negative BE indicates a base deficit in the blood, and a positive BE an excess of base.

In case of acute changes of the extracellular pH, the respiratory system, stimulated by the central nervous system, induces variations in PCO_2 which act as an immediate compensatory response. The kidneys then modulate the final line of regulation by the tubular reabsorption of bicarbonate and the excretion of fixed hydrogen ions. The normal range of BE is − 5 to + 5 mmol/L.

✉ Silvia Iacobelli
silvia.iacobelli@chu-reunion.fr

[1] Néonatologie, Réanimation Néonatale et Pédiatrique, CHU La Réunion, Site Sud, Saint Pierre, France

[2] Centre d'Etudes Périnatales de l'Océan Indien, CHU La Réunion, Site Sud, EA 7388 Saint Pierre et Université de la Réunion, France

[3] Lausanne University Medical School, CHUV-1011 Lausanne, Switzerland

Acid–base regulation in the newborn infant

A tight control of pH is relatively efficient since birth. The compensatory mechanisms undergo, however, a maturation process during the transition from the fetal to the extra-uterine environment. This maturation may be limited in newborns by low gestational age, diseases, drugs, and therapeutic interventions. In the preterm infant, in particular, multiple factors may limit the ability to maintain acid–base homeostasis, such as decreased sensitivity to PCO_2, severe lung disease, immature glomerular filtration, and tubular function. The renal acidification capacity can be decreased by several factors during postnatal life, as summarized in Table 1 [4].

The renal bicarbonate threshold is low in newborn infants, thus maintaining the plasma bicarbonate concentration within the range of 20–22 mmol/L in the term infant and in the range of 18–20 mmol/L in preterm infants. Bicarbonate plasma concentrations as low as 14 mmol/L can be observed in extremely preterm infants [5]. Adult values are achieved during the first year of life. This "physiological acidosis" observed in neonates is neither due to impaired function of carbonic anhydrase enzymes, as their activity is comparable to that of healthy adults from the 26th week of gestation, nor to a limited renal capacity to excrete hydrogen ions. The state of relative expansion of the extracellular fluid volume, as well as the disparate maturity of nephrons in preterm neonates, is responsible for their difficulty to maintain higher levels of plasma bicarbonate.

In preterm infants, the urinary excretion of titratable acids and ammonium is lower than in term ones. It increases as a function of gestational age, with a rapid maturation process, that occurs within three postnatal weeks, whatever the gestational age at birth [6]. Human studies indeed show that the renal mechanisms for preserving bicarbonate are normally effective enough in preterm infants to compensate for the acid load delivered by milk intake [7].

Several drugs administered in neonatal intensive care units can also affect acid–base balance: (a) both dopamine [8] and carbonic-anhydrase inhibitors (acetazolamide) [9] lower the renal bicarbonate threshold by decreasing the apical sodium ion (Na^+–H^+) exchanger activity; (b) furosemide increases urinary excretion of titratable acids by direct stimulation of the collecting tubule; and (c) K^+-sparing diuretics decrease the excretion of H^+ into distal tubular fluid [10]. Finally, a recent study on very low birth weight (VLBW) infants receiving early parenteral nutrition according to new recent guidelines demonstrated that these babies were exposed to substantial acid–base disequilibrium during the first week of life, with a risk of developing significant metabolic acidosis secondary to amino acid and lipid intake [11].

Metabolic acidosis

Definition: BE ≤ 5 mmol/L, PCO_2 = 35–45 mmHg, and pH < 7.35.

The serum anion gap

Calculation of the serum anion gap should be used to precisely characterize metabolic acidosis:

$$\text{Serum anion gap} = Na^+ - [Cl^- + HCO_3^-] \text{ (normal value : 10–12 mEq/L)}$$

In metabolic acidosis with normal serum anion gap, hyperchloremia compensates for the loss of bicarbonate by the gastrointestinal tract (diarrhea, fistula or external drains, short bowel syndrome) or by the kidneys (deficient urinary acidification by the renal tubules). Hyperchloremic metabolic acidosis with normal serum anion gap can also be induced by infusion of large volumes of normal saline and, as recently described in VLBW infants, after inadvertently administering excessive chloride by parenteral nutrition [12, 13].

Increased serum anion gap metabolic acidosis points to a rise in the serum of an unmeasured anion, either endogenous (lactate, ketone bodies, organic acid) or exogenous. The most frequent case during the neonatal period is that of lactic acidosis due to perinatal hypoxia–ischemia, hemodynamic disturbances during adaptation, septic shock, severe respiratory distress syndrome, hypovolemia, or severe anemia. Metabolic acidosis with increased anion gap is usually

Table 1 Renal factors and determinant mechanisms which limit the acidification capacity during adaptation to extra-uterine life

Proximal nephron	Determinant mechanisms
Low glomerular filtration rate	Reduced filtered load of $HCO3^-$
Extracellular volume expansion	Low renal HCO3 threshold
Proximal tubule immaturity	Apical Na^+–H^+ exchangers immaturity
	Na^+,K^+–ATPase pumps immaturity
Distal nephron	
Distal and collecting tubule immaturity	Low excretion of titratable acids and ammonium salts

present in acute and chronic renal failure, due to accumulation of fixed acids in the blood.

As noted above, preterm infants frequently develop a transient normal anion gap metabolic acidosis in early postnatal life, due to a combination of increased urinary bicarbonate loss and reduced ability to excrete ammonium [9]. A tubular immaturity has been considered as responsible for the "late metabolic acidosis of prematurity" in preterm infants receiving an excessive acid load from high protein formula.

Finally, severe lactic acidosis has been described in newborn infants due to acute thiamine deficiency following prolonged total parenteral nutrition [14].

Prolonged positive anion gap metabolic acidosis in neonates suggests the diagnosis of an inborn error of metabolism.

The urinary anion gap

In normal plasma anion gap metabolic acidosis, the assessment of the urinary excretion of ammonium can be used as an index of the distal acidification and thus points to the renal origin of the acidosis. The measurement of ammonium in the urine is not easily available in all medical centers. Information on urinary ammonium excretion can be obtained by measuring the urinary anion gap:

$$\text{Urinary anion gap} = (Na^+ + K^+ - Cl^-).$$

This concept assumes that during metabolic acidosis, the major cations in the urine are Na^+, K^+, and $NH4^+$ and that the major anion is Cl^-. Consequently, a negative urine anion gap indicates that adequate amounts of $NH4^+$ are being excreted. The presence of a positive value of urine anion gap indicates a defect in the production and urinary excretion of $NH4^+$ by the kidney. Such is, for instance, the case in distal renal tubular acidosis (Fig. 1).

Respiratory acidosis

Definition: $PCO_2 > 45$ mmHg and pH < 7.35. BE depends on the effectiveness of renal compensation.

Primary respiratory acidosis is a common problem in newborn infants and failure to achieve adequate gas exchange occurs in several neonatal morbidities: respiratory distress syndrome, meconium aspiration syndrome, bronchopulmonary dysplasia, pneumonia, leaky lung syndromes, pulmonary hemorrhage, atelectasis, congenital diaphragmatic hernia, tracheomalacia, and apnea of prematurity.

Metabolic alkalosis

Definition: BE > 5 mmol/l and pH > 7.45. PCO_2 depends on the effectiveness of respiratory compensation.

This disorder often results from excessive renal hydrogen ion loss due to prolonged diuretic use (furosemide), where it is usually associated with hypokalemia. Other causes of metabolic alkalosis with hypokalemia and hypochloremia are losses of gastric fluid from vomiting or diarrhea. In the absence of these two etiologies, further investigation is needed. Bartter syndrome should be suspected when severe metabolic

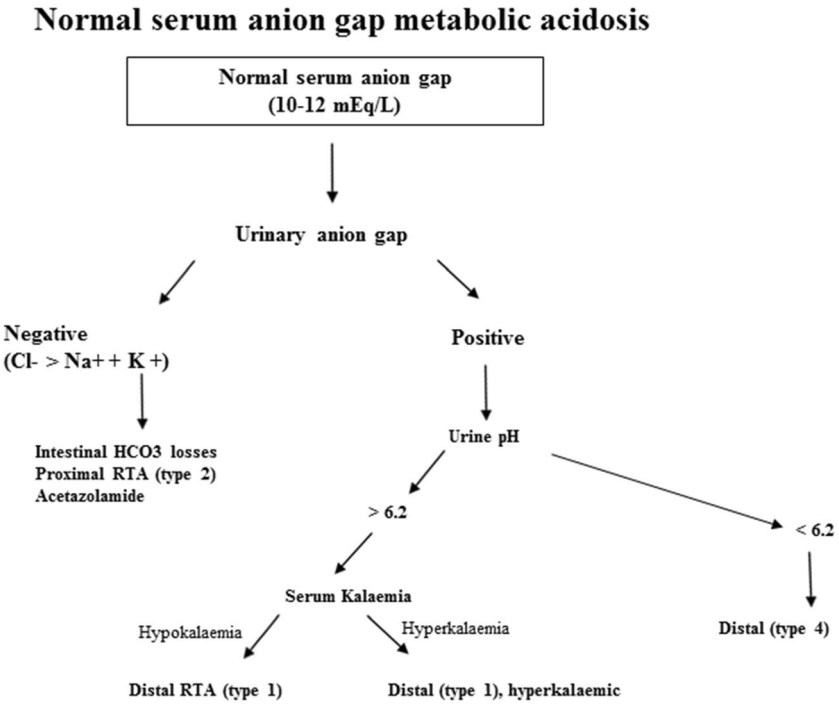

Fig. 1 Usefulness of urinary anion gap and pH measurement in the assessment of normal serum anion gap metabolic acidosis. Special care should be used when measuring urinary pH. For the best precision, urinary pH should be measured in a sample of urine collected by bladder puncture. If bladder puncture is not possible, a sample collected in a bag can be used, if urinary pH is measured immediately after collection.

alkalosis, dehydration, preterm birth, and polyhydramnios are associated (see section below).

Respiratory alkalosis

Definition: $PCO_2 < 35$ mmHg and pH > 7.45. BE depends on the effectiveness of renal compensation. Hyperventilation is the mechanism responsible for the lowered arterial pCO_2 in all cases of respiratory alkalosis. It can be iatrogenic in mechanically ventilated infants or due to severe encephalopathy (neurological injuries, infectious diseases, anoxic encephalopathy). The presence of respiratory alkalosis is very common in disorders of urea cycle due to hyperammonemia.

Disturbances of acid–base regulation of renal origin

Glomerular acidosis: causes–consequences–laboratory investigations–treatment

Glomerular acidosis is uncommon in the neonate and it occurs when chronic renal insufficiency is established and glomerular filtration rate persistently falls below 15 mL/min per 1.73 m^2. The major defect responsible for the acidosis is impaired net acid excretion, which is proportional to the reduction of functional renal mass. In the initial phase of renal failure, normal anion gap acidosis is usually present. When renal function further decreases, the retention of acids generated by the metabolism of proteins leads to elevated anion gap acidosis. Moreover, hyperkalemia can impair the distal H^+ secretory capacity by increasing intracellular pH and by inhibiting glutaminase and thus ammoniagenesis.

Chronic retention of fixed acids alters protein metabolism, growth, and bone mineralization and may accelerate the progressive loss of renal function. These consequences can be lessened by alkali therapy [15], starting soon after birth. It is recommended to keep the bicarbonate level above 20 mmol/L in infants with chronic kidney disease [16]. Base administration in the form of sodium bicarbonate is the starting treatment, drawing attention to potential complications (worsened hypertension, volume overload, and congestive heart failure). Alternative treatments are calcium carbonate or calcium acetate, the former also acting as a phosphate binder.

Renal tubular acidosis: causes–consequences–laboratory investigations–treatment

The entire renal tubular system plays a key role in maintaining acid–base homeostasis by two main mechanisms: (1) reabsorption of the filtered bicarbonate load in the proximal and distal tubule and (2) net acid excretion in the distal nephron.

Various tubular transporters and exchangers are involved in the regulation of acid–base balance. Mutations of these transporters affect the acid–base homeostasis. The defects observed in various acid–base tubulopathies are described in Table 2 [4, 17–19].

Generally, tubular transport disorders can be classified as acquired or hereditary. Children with hereditary tubulopathies can present with early onset of the disease during the first months of life or somewhat later. In this review, we will discuss proximal renal tubule acidosis (*pRTA*), distal renal tubule acidosis (*dRTA*) with hypo- or hyperkalemia, combined proximal and distal RTA (RTA type 3), and briefly mention the Bartter syndrome.

Proximal RTA

Proximal tubular acidosis (*pRTA*) (RTA type 2) is characterized by a low renal threshold of bicarbonate, leading to a state of metabolic hyperchloremic acidosis with normal serum anion gap. Initially, at normal plasma HCO_3^- concentration, the large amount of bicarbonate escaping proximal reabsorption reaches the distal tubule and is lost in urine, thus producing an alkaline urine. Once the plasma bicarbonate level has lowered below the renal threshold, the urine pH decreases to less than 6.2 (Table 3), as the HCO_3^- lost by the proximal tubule can be reabsorbed by the distal tubule. In *pRTA* the bicarbonate escaping reabsorption by the proximal tubule is delivered to the collecting duct as sodium bicarbonate, where some of the sodium is exchanged for potassium, thus inducing significant hypokalemia. Proximal RTA may occur as a primary isolated entity, either inherited and present from birth, or as a transient phenomenon disappearing during infancy (secondary to tubular immaturity, which resolves with development) [20, 21]. Primary, isolated *pRTA* is rare.

In the inherited recessive form of *pRTA*, the implicated gene is the *SLC4A4*, encoding the membrane Na^+–HCO_3^- cotransporter NBC1 (Table 2). This mutation is transmitted as an autosomal recessive trait and should be suspected in the presence of band keratopathy, glaucoma, or cataracts [22].

pRTA more often occurs as the manifestation of a generalized proximal tubule dysfunction (Fanconi syndrome) which leads to acidosis, hypokalemia, hypophosphatemia, glycosuria, and aminoaciduria. Fanconi syndrome is usually associated with hereditary disorders, such as cystinosis, galactosemia, fructosemia, and mitochondrial cytopathies.

The treatment of *pRTA* comprises administration of large amounts of oral alkali in the form of sodium salts (bicarbonate, citrate, or lactate), correction of water depletion, and potassium supplementation. Noteworthy is the fact that, due to the failure of proximal bicarbonate reabsorption, administered alkali is immediately lost in the urine, thus requiring repeated

Table 2 Inherited renal tubular acidosis (RTA). Defective genes, involved cotransporters and exchangers, cell type involvement, and localization

Disorder	Mode of inheritance	Gene	Defective protein	Cell type involvement, localization
pRTA (type 2)	AR	*SLC4A4*	Na^+–$HCO3^-$ cotransporter NBC1	Proximal, basolateral
dRTA (type 1)	AR (with deafness)	*ATP6V1B1*	B_1 subunit of H^+–ATPase	α-intercalated, luminal
	AR (without deafness)	*ATP6V014*	A^4 subunit of H^+–ATPase	α-intercalated, luminal
	AR	*FOXI1*	*	α-intercalated
	AR/AD	*SLC4A1*	AE1	α-intercalated, basolateral
dRTA (type 4)	AD pseudohypoaldosteronism type 1	*MR*	Mineralcorticoid receptor	
	AR pseudohypoaldosteronism type 1	*SCNN1A* *SCNN1B* *SCNN1C*	Na^+channel ENaC subunit α Na^+channel ENaC subunit β Na^+channel ENaC subunit γ	
Combined p/*dRTA* (type 3)	AR	*CA2*	CAII	PT and α-intercalated, cytoplasm

pRTA proximal renal tubular acidosis, *dRTA* distal renal tubular acidosis, *p/dRTA* mixed proximal and distal renal tubular acidosis, *AR* autosomal recessive, *AD* autosomal dominant, *PT* proximal tubule, *AE1* anion exchanger 1, *ENaC* epithelial Na^+ channel, *CAII* carbonic-anhydrase II

*Membrane transport proteins which require FOXI1 interactions for proper expression are defective

administration in order to reach and sustain constant normal or near-normal levels of plasma bicarbonate. This is in contrast with *dRTA* (see below) where the retained hydrogen ions can be buffered adequately by alkali supplementation.

Distal RTA

– Distal renal tubular acidosis

Distal renal tubular acidosis (*dRTA*) (RTA type 1) is the "classical" form of RTA, the first form that was described. The implicated defect is failure of hydrogen ion secretion by the intercalated cells of the cortical collecting duct (Table 2) that leads to a normal serum anion gap hyperchloremic acidosis. Urinary pH remains always higher than 6.2, even in the presence of severe metabolic acidosis (Table 3).

Severe hypokalemia is present, due to urinary potassium loss, and the clinical manifestations are polyuria, dehydration, and nephrocalcinosis. The mutation is transmitted as a dominant or recessive trait, with or without early-onset sensorineural deafness.

– Hyperkalemic distal renal tubular acidosis

In hyperkalemic distal renal tubular acidosis (*dRTA*) (RTA type 4), the hyperkalemia due to aldosterone deficiency (hypoaldosteronism) or resistance (pseudohypoaldosteronism secondary to defective activity of the epithelial Na^+ channel, ENaC) results in a reduced ammoniagenesis, thus a diminished

Table 3 Clinical and laboratory findings of various types of renal tubular acidosis (RTA)

	pRTA (type 2)	*dRTA* (type 1)	*dRTA* (type 4)	Combined *p/dRTA* (type 3)
Primary defect	Impaired capacity of PT to reabsorb $HCO3^-$	Failure of H^+ ion secretion in the CD	Impaired urinary ammoniagenesis and net acid excretion in the CD	Impaired capacity of PT to reabsorb $HCO3^-$ and impaired urinary acidification (CD)
Associated clinical features	Fanconi syndrome	Deafness	Failure to thrive	Failure to thrive Osteopetrosis Cerebral calcifications
Bone involvement	Frequent	Rare	Absent	Frequent
Serum anion gap	Normal Hyperchloremic acidosis	Normal Hyperchloremic acidosis	Normal Hyperchloremic acidosis	Normal Hyperchloremic acidosis
Urinary anion gap	Negative	Positive	Positive	Positive
Serum K^+	Low	Low	High	Normal or low
Urinary pH	< 6.2 (during acidemia)	> 6.2	> 6.2	> 6.2

pRTA proximal renal tubular acidosis, *dRTA* distal renal tubular acidosis, *p/dRTA* mixed proximal and distal renal tubular acidosis, *PT* proximal tubule, *CD* collecting duct

net acid excretion. ENaC plays a crucial role in controlling Na^+ and fluid reabsorption in several organs, and among those the principal cells of the collecting duct (Table 2). *dRTA* type 4 thus induces a metabolic, hyperchloremic normal serum anion gap acidosis, with associated severe hyperkalemia (as opposed to hypokalemia in RTA type 1 and 2), hyponatremia, salt wasting, and hypotension.

– Congenital pseudohypoaldosteronism type 1

In congenital pseudohypoaldosteronism type 1 (autosomal dominant, recessive trait, or spontaneous mutation) the above symptoms and biological disturbances may appear early in the newborn infant. They are systematically associated with elevated plasma renin activity and aldosterone concentration and excretion. In the autosomal dominant form as in spontaneous mutation, the lack of response to mineralocorticoid affects only the kidneys, while the recessive form leads to severe Na^+ transport defects in several aldosterone target tissues (kidneys, lungs, colon, salivary, and sweat glands).

– Transient pseudohypoaldosteronism

Transient pseudohypoaldosteronism may also occur due to urinary tract infection in infants with or without urinary tract malformations, and after renal vein thrombosis; it usually resolves after recovery from the underlying disease [23].

Combined proximal and distal RTA

This pattern has been described in very rare cases of congenital deficit of carbonic anhydrase. It associates impaired renal bicarbonate reabsorption with the inability to acidify the urine (decreased $NH4^+$ excretion). Urinary pH remains always higher than 6.2 and serum potassium is low, as in RTA type 1 (Table 3).

This variant of RTA has an autosomal recessive transmission and the mutated gene (*CAII*) is expressed in the kidney, bone, and brain (Table 2). The acidosis of mixed type is thus associated with additional clinical signs: osteopetrosis, cerebral calcifications, and mental retardation. Other clinical features include bone fractures (due to increased bone fragility) and growth failure. Excessive facial bone growth leads to facial dysmorphism, conductive hearing loss and blindness due to nerve compression [24].

Treatment or RTA

For dRTA type 1, treatment by alkali is advised and the amount of bases is modulated according to a patient's weight and needs. Bases are given in the form of sodium and potassium salts. The correction of the hypercalciuria is also mandatory and potassium citrate is the preferred treatment as it reduces calcium excretion. The treatment of dRTA type 4 depends on underlying diseases and generally requires alkali supplementation as well.

Bartter syndrome

This syndrome is composed of several inherited salt-losing tubulopathies, due to numerous gene defects affecting electrolyte transport in the thick ascending limb of Henle's loop or distal convoluted tubule. Sodium wasting is always present, with metabolic hypokalemic alkalosis, hyperreninemic hyperaldosteronism, hyperplasia of the juxtaglomerular apparatus, and normal blood pressure. Among the different subtypes of Bartter syndrome that will not be further discussed in this review, the antenatal form (also called hyperprostaglandin E syndrome) is particularly severe. In this condition polyhydramnios is the first symptom, present in 90% of cases, leading to preterm birth. Significant sodium and water losses and metabolic hypokalemic alkalosis are present in association with hypercalciuria and nephrocalcinosis.

Treatment of all forms of Bartter syndrome relies on the systematic correction of sodium and water losses and hypokalemia. Infants with antenatal Bartter syndrome often require rapid and very large fluid and sodium supplementations. Amiloride and spironolactone can be added for the treatment of hypokalemia as they will also improve the metabolic alkalosis [25]. Potassium-sparing diuretics should however be administered with caution because they carry the risk of inducing hypovolemia. Finally, in these infants, the early introduction of indomethacin or COX2 inhibitor treatment to achieve adequate weight gain during the early postnatal period can be considered [26].

Long-term consequences of metabolic acid–base disorders of renal origin

Chronic acidosis

Chronic acidosis of renal origin can have substantial adverse effects, including altered protein synthesis, increased muscle wasting, development or exacerbation of bone disease, and chronic hypokalemia. The associated clinical complications (anorexia, vomiting, growth retardation) may be absent during neonatal life and during the early stage of the disease, but they should be anticipated as soon as the diagnosis is made. The nutritional issue is a major challenge in infants suffering from chronic metabolic acidosis. Actually, current nutritional guidelines in children with chronic kidney disease, including *pRTA* or *dRTA*, recommend measurement and monitoring of the serum bicarbonate level and advocate measures to keep the bicarbonate level above 22 mmol/l for the neonate and young infant below 2 years of age, in order to improve bone histology

and linear growth [16]. Further investigations are clearly warranted with regard to the long-term effects of alkali therapy and the optimal type of alkali supplement in the different diseases.

Chronic alkalosis

Clinical effects of long-term chronic alkalosis are not very well known.

In animal models, chronic hypochloremic metabolic alkalosis has been proven responsible for failure to thrive and severe catabolism, by retarding cell growth and RNA synthesis [27]. In preterm infants with bronchopulmonary dysplasia, chronic hypochloremic metabolic alkalosis due to prolonged administration of furosemide is an important contributing factor of the poor outcome, as it affects head and body growth [28]. Finally, as described by Rodriguez-Soriano et al. [29], chronic metabolic alkalosis induced by low-chloride milk formula in newborn infants was associated with a significant elevation in the serum concentrations of calcium and phosphate and in the urinary excretion of calcium and magnesium, with a major risk of nephrocalcinosis.

Key summary points

1. Acid–base regulation undergoes a maturational process after birth and renal acidification capacity can be impaired by low GFR and tubule immaturity, especially at low gestational ages.
2. Hereditary and acquired tubular disorders accompanied by acid–base derangements can present with early onset during the first months of life.
3. Two main mechanisms are impaired in tubular acid–base disorders: (i) the reabsorption of the filtered bicarbonate load by the proximal tubule and/or (ii) the net acid excretion in the distal nephron. Electrolytes and mineral disturbances are often associated.
4. Serum anion gap is normal in RTA. Urinary pH and anion gap are useful tools for the characterization of RTA.
5. Chronic acidosis of renal origin has adverse effects on growth and bone development and should be corrected as soon as detected.

Multiple-choice questions (answers are provided following the reference list)

1. The mechanisms responsible for reduced renal acidification capacity in newborn infants are:

   a Low excretion of titratable acids
   b Low renal $HCO3^-$ threshold
   c Low glomerular filtration rate
   d Low excretion of ammonium salts
   e All of the above

2. Metabolic acidosis with high serum anion gap can be observed in:

   a Severe dehydration
   b Drug-induced hypokalemia
   c Established chronic renal failure
   d *dRTA* (type 4)
   e Excessive chloride intake following resuscitation or parenteral nutrition

3. Which of the following statements about *pRTA* is false?

   a The serum anion gap is normal
   b Severe hypokalemia is present
   c Urinary pH remains always higher than 6.2
   d Can be associated with a number of various diseases
   e It is caused by an impairment of $HCO3^-$ reabsorption with intact distal acidification

4. Which of the following statements about *dRTA* is true?

   a The treatment of hyperkalemia is mandatory
   b Urinary pH may decrease below 6.2 following severe metabolic acidosis
   c Dehydration and salt wasting are very common
   d It is associated with juxtaglomerular apparatus hyperplasia
   e Treatment by alkali should be administered by caution, due to the risk of hypertension

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Answers to questions:

1. e;2. c;3. c;4. c