Renal Tubular Acidosis

Helena Gil-Peña, PhD[1,2], Natalia Mejía, MD[3,*], and Fernando Santos, MD, PhD[1,2]

In this article, we discuss the current views on the renal regulation of acid-base metabolism and the diagnostic approach to children with metabolic acidosis, including the major characteristics of the different types of renal tubular acidosis (RTA), focusing on distal RTA (dRTA). We update progress in identifying the underlying defective transporters and gene mutations responsible for the primary forms, suggest candidate genes possibly involved in some cases, discuss the mechanisms causing growth retardation and disordered mineral metabolism, and provide the basis for differential diagnosis with other types of primary RTA.

Physiology of Renal Acid-Base Homeostasis

The majority of acid produced in the body is excreted as CO_2 by the lungs. The kidneys regulate acid-base balance by reabsorbing filtered HCO_3^- and excreting nonvolatile acids, a process linked to regeneration of the HCO_3^- consumed in buffering these fixed acids. In the most distal segments of the nephron, urinary acidification is accomplished by reclamation of 10%-15% of the filtered HCO_3^- that is not reabsorbed in proximal tubule and by secretion of H^+. Secreted H^+ is eliminated as titratable acid and NH_4^+, as well as free ions that determine the urine pH.

The intercalated cells of the collecting duct modify urine pH according to the acid-base status. The α-intercalated cells (AICs), identified by a vacuolar H^+ATPase (adenosine triphosphatase) located on the luminal membrane and a basolateral anion exchanger (anion exchanger type 1 [AE1]), are the largest contributors to net acid excretion (**Figure 1**; available at www.jpeds.com).[1]

AICs are dispersed from the late distal convoluted tubule to the initial inner medullary collecting duct.[2] β-intercalated cells have a H^+ATPase in either cytoplasmic or basolateral distribution and a Cl^-/HCO_3^- exchanger, pendrin, in the apical membrane responsible for the secretion of net base.[3] A controversial subtype, "non-α, non-β" or C-intercalated cells, express pendrin, H^+ATPase, the ammonia transporter Rhcg in the apical pole, and glycoprotein Rhbg in the basolateral membrane.[4,5] Simultaneous luminal expression of H^+ATPase and pendrin in β- and non-α, non-β intercalated cells might cause the parallel secretion of H^+ and HCO_3^- without affecting acid-base homeostasis.

AE1	Anion exchanger type 1
AG	Anion gap
AIC	α-intercalated cell
ATPase	Adenosine triphosphatase
CA	Carbonic anhydrase
dRTA	Distal renal tubular acidosis
GFR	Glomerular filtration rate
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
kAE1	Kidney anion exchanger type 1
RTA	Renal tubular acidosis

Diagnostic Approach to the Child with Metabolic Acidosis

Metabolic acidosis, identified by low plasma HCO_3^- concentration (<22-24 mEq/L in children and <20-22 mEq/L in infants) and low blood pCO_2 (<40 mm Hg in children and <35 mm in infants), is usually classified according to the plasma or serum anion gap (AG; in mEq/L). AG is calculated in the clinical setting as $(Na^+ + K^+) - (Cl^- + HCO_3^-)$. Elevated AG metabolic acidosis results from the retention of acid containing an anion other than Cl^- in such conditions as advanced renal failure, intoxication, ketoacidosis, lactic acidosis, and inborn errors of metabolism. Normal AG metabolic acidosis is hyperchloremic, because the drop in serum HCO_3^- is matched by an equivalent increment in serum Cl^-. Hyperchloremia results from gastrointestinal loss of HCO_3^- (eg, diarrhea), decreased renal reabsorption of HCO_3^-, and/or reduced urinary NH_4^+ excretion (eg, RTA).

Although calculating serum AG is useful for the differential diagnosis of metabolic acidosis (**Figure 2**), there may be overlap between the causes of normal and high AG metabolic acidosis. Thus, 20%-30% of patients with diabetic ketoacidosis have normal AG acidosis at presentation or develop it during recovery. This normal AG acidosis may be explained by the high urinary loss of ketone anions when the glomerular filtration rate (GFR) is normal, the administration of sodium chloride–containing solutions, cellular phosphate depletion, and insulin-induced hypophosphatemia.

Proper assessment of AG requires that each laboratory determine its own normal range, because the values of Na^+ and Cl^- concentrations may vary according to measurement technique. Moreover, whenever possible, for a more accurate interpretation of the AG change in a given individual, baseline AG should be used rather than the average normal value.[6] It is also important to note that the venous

From the [1]Division of Pediatric Nephrology, Hospital Universitario Central de Asturias; [2]Department of Medicine, University of Oviedo, Oviedo, Spain; and [3]Department of Pediatrics, University of Los Andes, Bogotá, Colombia

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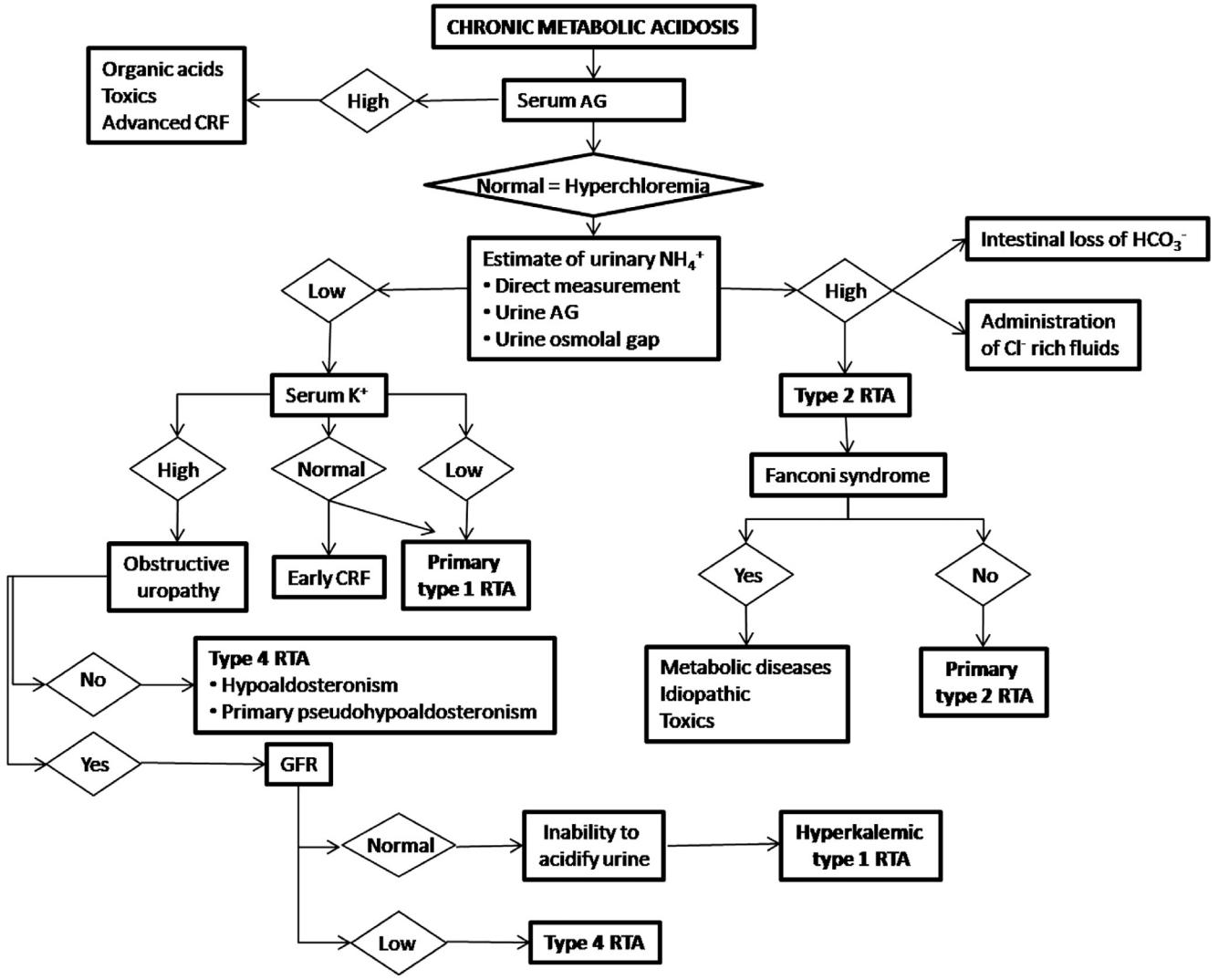

Figure 2. Diagnostic approach to metabolic acidosis and RTA. *CRF*, chronic renal failure.

HCO_3^- concentration must be measured using a blood gas analyzer. Assessing serum HCO_3^- with a typical biochemical analyzer is less accurate and has been shown to yield values up to 5.6 mEq/L lower than those measured by a blood gas analyzer.[7]

Some clinicians do not include K^+ in the calculation of AG; however, the measurement of serum K^+ is usually available, and there may be significant differences in concentration in patients with kidney disease, and thus its determination seems justified. Because the AG reflects the difference between unmeasured anions and cations other than Na^+ and K^+, modifications in the circulating concentrations of albumin and phosphate, which account for the majority of unmeasured anions, as well as in concentrations of calcium and magnesium, affect the AG value. The AG drops approximately 0.5 mEq/L for every 1 mg/dL reduction in serum phosphate[8] and 2.3 mEq/L for every 1 g/dL reduction in serum albumin.[9] Without the correction for hypoalbuminemia, high AG acidosis may be overlooked in malnourished or critically ill children.

Types of RTA

RTA is biochemically characterized by persistent, normal AG metabolic acidosis. Four types of RTA can be distinguished on the basis of clinical, pathophysiological, and molecular criteria (Figure 2). Primary RTA results from specific genetic defects in transporters or enzymes involved in renal HCO_3^- reabsorption or H^+ secretion. Primary RTA usually presents in infancy or early childhood. Forms of RTA secondary to exposure to drugs or toxins or as an aspect of systemic disease are more common in adults.

Type 1 dRTA is caused by impaired distal tubular acidification. Most pediatric cases are primary. In the secondary forms, the mechanism responsible for the defective urinary acidification is usually not well understood, although cases