8 Metabolic Acidosis

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Key Points

1. Normal acid–base balance is crucial for proper cell function and integrity.
2. Metabolic acidosis is due to either the loss of blood buffers, or the gain of non-volatile strong acids.
3. An organized, step-wise approach (the "ABCDE toolkit") is crucial in determining both the magnitude and the cause of a metabolic acidosis and deciding upon appropriate therapy.
4. Base excess is a measure of the *magnitude* (extent) of the deviation from normal acid–base balance.
5. Ion "gaps" give important clues as to the possible *cause* of the metabolic derangement.

Key Words: Metabolic acidosis; base excess; anion gap; strong ion gap; urine anion gap; renal tubular acidosis

1. INTRODUCTION

Acid–base balance is regulated carefully to maintain optimal cellular integrity and function. Metabolic acidosis may depress myocardial contractility, over-stimulate sympathetic activity, blunt the effect of catecholamines, and vasoconstrict pulmonary arteries. In the critically ill patient, the accumulation of "unmeasured anions" (lactic acid, keto acids, by-products of intermediate metabolism, and intoxicants) is associated with a poor outcome *(1)*. Therefore, extracellular pH is kept within a narrow physiologic range through the coordinated action of blood buffers and homeostatic mechanisms.

Acidosis, the addition of an acid load, is countered immediately by the buffering action of extracellular bicarbonate, intracellular proteins, and intracellular phosphorus (a total capacity of 12–15 mEq/kg body weight). Afterwards, the lungs and the kidneys act to restore normal homeostasis by excretion of the acid load and re-generation of the buffer stores. The most important excretion of acid occurs via the lungs, amounting to approximately 13,000 mEq/day of CO_2. The kidneys excrete an additional ~1 mEq/kg body weight per day in the form of titratable acid, in a process directly linked to the formation of "new" bicarbonate *(2)*. According to the law of electroneutrality, the gain and loss of plasma protons and buffers must be counter-balanced by a similar gain and losses

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of electrolytes. The electroneutrality principle is used to devise algebraic descriptions of plasma acid–base balance and also to provide an alternative explanation of acid–base physiology *(3)*.

When the defensive mechanisms become overwhelmed, the acid–base balance of the body is disturbed. The term "acidemia" refers to a plasma pH < 7.4, and the more general term "acidosis" refers to the imposition of an acid load. Conceptually, acidosis may be classified as either "respiratory" (arising from the retention of CO_2) or "metabolic" (arising from the net loss of buffer base or the gain of a strong acid). Although the definition of metabolic acidosis is based on plasma pH, in practice acidosis usually suspected based upon the discovery of a low plasma bicarbonate concentration.

2. CAUSES OF METABOLIC ACIDOSIS

Through metabolism, the liver generates ~1 mM per kg BW per day of endogenous acid and accompanying anion. In the growing infant and child, daily acid generation can reach up to 3 mM per kg BW. The kidneys play an important role in the maintenance of systemic acid–base balance due to their ability to regulate the ions involved. To defend against metabolic acidosis, the proximal renal tubule absorbs bicarbonate, while the distal tubule secretes protons and generates new bicarbonate ions. The latter replaces bicarbonate ions lost in the process of buffering the protons that have been generated during metabolism. The hydrogen ion secreted into the distal tubule combines with ammonium and titratable acids (TA), comprised mostly in the form of phosphates. As secretion of diet-dependent TA is more or less fixed, it is mostly ammonia secretion that increases during metabolic acidosis. The process requires several days to achieve its maximum ability. Although urine pH is an important factor in assessing acid–base balance and in some diseases like uric acid lithiasis where it plays an important pathophysiologic role, "free" urine hydrogen ion concentration represents only a miniscule amount of the total protons that are excreted.

Metabolic acidosis can arise from renal or extra-renal etiologies. The extra-renal causes may result from the addition of non-volatile acid (lactic anion acidosis) or from a loss of base (diarrhea). The renal causes may result from abnormalities in the structure and function of the kidneys (renal tubular acidosis) or from the physiologic response of the kidneys to excessive or insufficient extra-renal stimuli (hyperparathyroidism and hypoaldosteronism, respectively). An "ABCDE toolkit" compiles the information needed to unravel the different possible mechanisms.

3. ABCDE TOOLKIT

The diagnosis of metabolic acidosis can be made by application of an "ABCDE toolkit," a compendium of useful equations, rules of thumb, and physiological approximations:

A is "assessment"
B is "base excess" and "blood gas"
C is "creatinine" and "compensations"
D is "deltas" or gaps
E = "extras"

An explanation of the toolkit is as follows:

Assessment: The clinical setting, be it sepsis, shock, dehydration, stool losses, growth retardation, intoxication, or uremia, provides important clues that are necessary for arriving at a correct differential diagnosis.

Blood gas and Base Excess: A blood gas (arterial or venous) provides essential information for the evaluation of acid–base disorders, including the pH, pCO_2, bicarbonate concentration, and base excess (BE). The hallmark of metabolic acidosis is a low plasma bicarbonate concentration (in a child and adult <24 mEq/L; a low value in a newborn or infant is <20–22 mEq/L) in the setting of a low pCO_2 measurement (<40 mmHg). Base excess (BE), defined as the milli-equivalents of a strong acid or strong base that is needed to titrate 1 L of blood to pH 7.4 when pCO_2 is held constant at 40 mmHg, provides the magnitude of the metabolic (non-respiratory) portion of an acidosis. In general, the larger the negative BE, the more severe the disturbance.

Creatinine and Compensation: Renal failure is an important cause of metabolic acidosis and the plasma creatinine concentration is an important index of renal function. In the absence of a specific defect in renal tubular function, the plasma creatinine concentration is inversely proportional to the ability of the kidney to "handle" an acid load. *Teaching Point:* Patients in renal failure with hypocalcemia may develop tetany due to the shift in ionized calcium from free to albumin-bound with the change in blood pH when there is too rapid correction of the acidosis.

For any disturbance causing a metabolic acidosis, there is an expected renal and respiratory compensation. A simple test for the adequacy of the renal response in patients with normal renal function is the "urine anion gap" ($UAG = Na^+ + K^+ - Cl^-$), a misnomer for an indirect estimate of urine NH_4^+. In compensation of metabolic acidosis, the normal kidney increases its production of ammonia and secretion of H^+, thus increasing urine ammonium secretion and with that chloride secretion. Consequently urine Cl^- will exceed the sum of urine Na^+ plus K^+, thus creating a negative (–) gap. In patients with distal renal tubular acidosis, interstitial renal disease, or renal insufficiency, ammoniagenesis is inadequate, thus creating a positive (+) gap. It should be pointed out that the UAG gap test is invalid in dehydrated patients, such as children with gastroenteritis and a low urine $Na^+ < 20$ mEq/L. Avid reabsorption of Na^+ by the proximal renal tubular results in low delivery of Na^+ to the distal nephron and diminished Na^+–H^+ exchange.

The adequacy of the respiratory response is assessed by Winter's formula, a "rule of thumb" or pearl that relates the measured plasma bicarbonate concentration to the expected, "compensated" pCO_2:

$$pCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$$

The measurement of a pCO_2 greater than calculated from Winter′s formula indicates an inadequate ventilatory response, and the presence of a mixed metabolic-respiratory disorder.

Additional Pearls: For each 1 mM decrement in plasma bicarbonate (due to metabolic acidosis), respiratory compensation lowers the plasma pCO_2 by 1.25 mmHg.

As a rough guide, pCO_2 is equal approximately to the last 2 digits of the pH.

Example: Ammonium chloride is administered to normal volunteer, lowering the plasma bicarbonate from 24.25 mM to 14.25 mM. Using the "pearls," one would expect the plasma pCO_2 to decrease from 40 mmHg to ~29 mmHg, as the plasma pH decreases from 7.4 to ~7.29. Deviations from the expected compensation suggest presence of a second, concomitant acid–base process.

On the other hand, primary respiratory alkalosis blunts the reabsorption of bicarbonate by the proximal tubule, lowering the plasma pH by 0.008 units per mmHg change in pCO_2 acutely, and 0.003 units per mmHg change in pCO_2 chronically. In practice, compensation in mixed acid–base disorders may be difficult to interpret, as commingled processes may occur.

Deltas or Gaps: The plasma anion gap (AG) serves as a simple and effective tool in the evaluation of the etiology of metabolic acidosis. The anion gap indicates anions that are not routinely measured when plasma electrolytes are assessed. According to the law of electroneutrality, the sum of the charges of the plasma cations must equal the sum of the charges of the anions:

$$\text{Anion gap (AG, mEq/L)} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

The use of the term strong ion gap (SIG) improves upon the AG by accounting for the charge contribution of weak acids, such as albumin and phosphate *(4)*.

$$\text{SIG} = \text{AG} - [\text{albumin g/dl}](1.2 \times \text{pH} - 6.15) + [\text{phosphate mg/dl}]\,(0.097 \times \text{pH} - 0.13)$$

Under normal conditions, the AG is ~12 mEq/L $\pm$4, while the SIG is ~0. A high AG may be due to a low plasma albumin concentration or an "unmeasured" anion such as lactate, while a high SIG is always due to an "unmeasured" anion *(2, 5)*.

Metabolic acidosis may be divided conveniently into disorders that present with a normal AG/SIG (high plasma chloride) and those with an elevated AG/SIG (normal or low plasma chloride) (Table 1).

The osmol gap, the difference between the measured and calculated plasma osmolality, may be useful if intoxicants such as ethylene glycol are suspected. In normal subject the main constituents of plasma osmolality are sodium salts of chloride and bicarbonate, glucose, and blood urea nitrogen (BUN). Under normal circumstances, the measured plasma osmolality is equal to the calculated value:

$$\text{Calculated plasma osmolality (Posm, mOsm/kg)} = 2[Na^+] + [\text{Glucose in mg/dL}]/18 + [\text{BUN in mg/dL}]/2.8$$

In the above equation, plasma sodium concentration is doubled to account for its accompanying anions, and glucose and BUN are divided by 18 and 2.8, respectively, to convert their units from mg/dL to mOsm/kg. An exogenous substance may be present if the measured osmolality exceeds the calculated value by >10 mOsm/kg.

Extras: Alkaline urine per se does not necessarily indicate an impaired renal acidification mechanism, as it may result from dietary factors or physiological proton trapping of urinary ammonia/ammonium. Several tests have been devised to more effectively test

Table 1
Causes of Metabolic Acidosis by Type of Anion Gap

Normal anion gap (hyperchloremic)	*Elevated anion gap*	*Low anion gap*
Renal (loss of bicarbonate)	Renal failure – acute and chronic	Dilution
Renal tubular acidosis – Type 1 (distal) –, 2 (proximal) and 4 (mineralocorticoid) – (see Table 5 below)		Hypoalbuminemia
		Severe hypernatremia
		Hypercalcemia
		Hypermagnesemia
Renal failure (early)		Lithium
Carbonic anhydrase inhibitors – acetazolamide		
Potassium sparing diuretics		
Mineralocorticoid deficiency		
Gastrointestinal (loss of bicarbonate)	Poisoning – carbon monoxide or cyanide	
Diarrhea, drainage (small bowel, pancreatic, biliary, fistula, etc.), anion exchange resins		
Miscellaneous	Circulatory failure/tissue hypoxia	
Rapid intravenous expansion with bicarbonate or isotonic/hypertonic solutions		
Recovery from ketoacidosis		
Post-hypocapnia		
Exogenous chloride administration ($CaCl_2$, $MgCl_2$, arginine HCl, HCl)		
Hyperalimentation		
	Lactic acidosis – hypoxia, glycogen storage disease (type 1), pancreatitis, leukemia, seizures	
	Ingestions or overdose – ethanol, methanol, ethylene glycol, salicylate, isoniazid	
	Ketoacidosis – diabetes mellitus, starvation	
	Inborn errors in metabolism, organic acidosis	
	Paraldehyde – organic anions	

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the acidification capacity of the kidney. As an example, the administration of ammonium chloride acidifies the urine, except in patients with distal renal tubular acidosis who are unable to excrete the "acid load." These tests are quite cumbersome and currently used infrequently. A test developed recently is based on the simultaneous dosing of furosemide (to increase the delivery of sodium to the distal tubule) and fludrocortisone (to promote reabsorption of sodium by principal cells and the secretion of protons by alpha-intercalated cells) *(6)*. Patients with distal renal tubular acidosis fail to lower the urine pH < 5.8, indicating an abnormality in H^+ secretion. Another test assessing distal tubule H^+ secretion is to measure the (urine–blood) pCO_2. This elegant test (although difficult to obtain in most centers) is based on the fact that when bicarbonate reaches the distal tubule it combines with the secreted H^+ to form carbonic acid, which then splits to H_2O and CO_2. At this part of the nephron and all the way further down to the urethral meatus CO_2 cannot diffuse back, thus its tension in the urine is the same as in the distal tubule. In different laboratories normal values range between 20 and 30 mmHg. It is important to make sure that the urine is sufficiently alkaline (pH > 7.4) and contains sufficient HCO_3^- (>40 mEq/L) as substrate. To achieve that goal, most studies in adults use $NaHCO_3$ given orally or intravenously. Oral acetazolamide administration has several advantages including being more palatable, causing mild metabolic acidosis that stimulates H^+ secretion, and being a diuretic shortens the time of the test *(7)*. It is also recommended to analyze the second and third voids after the drug administration, with the venous blood sample to be obtained between these voids.

The fractional excretion of bicarbonate is extremely helpful for the diagnosis of proximal RTA (pRTA). The test should be conducted after serum bicarbonate concentration is corrected to its normal range with alkali treatment. Under such circumstances, patients with pRTA will have $FE_{HCO3} > 15\%$. In infants with distal RTA, there may be large quantities of bicarbonate in the urine due to the greater role of the distal tubule in bicarbonate reabsorption in this age group. Consequently treatment of these infants will require large doses of alkali that decreases over time when expressed in mg/kg body weight. The latter condition used to be called RTA type III, a condition now reserved for patients with carbonic anhydrase II deficiency (vide infra). Another reason for the need of higher doses of alkali in younger patients is the increased metabolic rate and build-up of bone (storing alkali), generating more non-volatile acids.

4. DIAGNOSIS OF METABOLIC ACIDOSIS: APPLICATION OF THE ABCDE TOOLKIT (TABLE 2, FIG. 1)

Table 2
Application of ABCDE Toolkit in Cases of Metabolic Acidosis (pH < 7.4, HCO_3^- < 24 mEq/L, BE > –3 mEq/L)

	Compensations	*Deltas*
Diarrhea	Urine anion gap negative	SIG/AG normal osmol gap normal
Renal tubular acidosis	Urine anion gap positive	SIG/AG normal osmol gap normal
Diabetic ketoacidosis	Urine anion gap negative	SIG/AG high osmol gap normal
Methanol ingestion	Urine anion gap negative	AG/SIG normal osmol gap high

5. HIGH AG/SIG

In the setting of normal renal and pulmonary function, these disorders are characterized by significant acidosis (pH < 7.4, HCO_3^- < 24 mEq/L, BE > –3 mEq/L), a high plasma SIG, and adequate renal (urine anion gap negative) and respiratory (pCO_2 < 40 mmHg, according to Winter's formula) responses. The differential diagnosis includes lactic anion acidosis, ketoacidosis, and a variety of intoxications (Table 1).

Lactic Anion Acidosis: Lactic anion acidosis occurs whenever production of lactic anion exceeds consumption or clearance. First, glucose enters the muscle cells by facilitative diffusion through the Glut-1 transporter and is then oxidized by a sequence of enzymatic reactions to form 2 molecules each of pyruvate, NADH, ATP and H^+. Pyruvate is then reduced by the cytosolic enzyme dehydrogenase (LDH) to form lactate anion. Lactate anion, along with H^+ derived from the hydrolysis of ATP, may enter the circulation by way of the membrane-bound lactate-H^+ co-transporter *(8)*.

Lactic Acidosis (plasma concentration > 1 mM) has been divided into 2 categories. Type A lactic anion acidosis caused by dysoxia, or the inability of cells to generate sufficient ATP to meet metabolic demand when mitochondrial P_{O2} is low. Dysoxia is most often due to hypoxia and ischemia secondary to pulmonary disease, cardiac disease, hemoglobin deficiency, or carbon monoxide poisoning. In turn, mitochondrial dysfunction results in the accumulation of pyruvate and lactic anion (often with a high plasma lactate/pyruvate ratio).

Type B lactic anion acidosis is due to *cytopathic* hypoxia, or the inability of pyruvate to enter the tricarboxylic acid cycle (TCA) or the electron transport chain (ETC). Cytopathic hypoxia may occur secondary to drugs (biguanides, isoniazid, salicylates, propofol, linezolid, nucleoside reverse transcriptase inhibitors), toxins (ethanol, methanol, ethylene glycol, propylene glycol, cyanide), or errors of metabolism (congenital lactic acidosis, thymine deficiency). In addition, *accelerated glycolysis* in well-oxygenated patients with sepsis may result in hyperlactemia due to a high production rate. *Poor lactate "shuttling"* in patients with severe liver and/or renal failure may result in hyperlactemia due to low consumption or clearance.

Other *endogenous* causes of metabolic acidosis with a high AG include inborn errors of metabolism and diabetic ketoacidosis. *Exogenous etiologies include* salicylate ingestion, pyroglutamic acidosis, D-lactic acidosis, propylene and ethylene glycol poisoning, methanol ingestion, alcoholic ketoacidosis, and arsenic poisoning *(2)*.

Salicylates stimulate respiratory drive, initiating a mixed metabolic acidosis and respiratory alkalosis. Patients present with vomiting, fever and central nervous system disturbance, which progresses to pulmonary edema and renal failure. Hypermetabolism results in an additional lactic anion acidosis, which increases the permeability of the blood–brain barrier to salicylates. Alkalinization of the urine greatly aids the renal excretion of salicylate and is the key to effective treatment. In some severe cases, hemodialysis may be indicated.

Pyroglutamic Acidosis. Pyroglutamic acidosis may occur in malnourished patients who have received acetaminophen or the antibiotic flucloxacillin. The diagnosis is confirmed by the finding of an elevated blood or urine 5-oxoproline level.

D-*Lactic Acidosis.* Patients with the short gut syndrome may develop encephalopathy. An associated D-lactic acidosis may arise due to the overgrowth of intestinal bacteria that ferment dietary carbohydrate. The diagnosis of D-lactic acidosis is made by a specific enzymatic test. Treatment consists of restriction of oral feeds while providing intravenous dextrose for calories.

Alcohols. In the early stages of propylene glycol, ethylene glycol or methanol poisoning, metabolic acidosis with a high AG is accompanied by a high plasma "osmol gap." Later in the clinical course, the osmol gap returns to normal as these active osmolytes are *metabolized by hepatic alcohol dehydrogenase* to osmotically – inactive but highly toxic by-products.

Propylene Glycol. A vehicle to deliver topical (e.g., silver sulfadiazine cream) and intravenous (e.g., diazepam) medications, propylene glycol that is not excreted by the kidneys is metabolized to lactic anion. Lactic anion acidosis may develop if the lactate–pyruvate–acetyl-CoA pathway is sluggish, as in thiamine deficiency.

Ethylene Glycol. Ethylene glycol, used commonly as an anti-freeze agent, is oxidized by the liver to glycolic acid and oxalate. Patients with ethylene glycol poisoning present with metabolic acidosis, flank pain, hypocalcemia, vomiting, ataxia, seizure and coma, progressing to cardiac, renal, and respiratory failure.

Unreliable indicators of ethylene glycol poisoning include a discrepancy between breath alcohol analyzer and ethanol blood levels, a high serum osmol gap, urinary calcium oxalate crystals, and urine that fluoresces under Wood's lamp. These non-specific tests cannot substitute for direct measurement of plasma ethylene glycol and glycolic acid.

Methanol. Methanol, used commonly in antifreeze, paint thinner, and rubbing alcohol, is metabolized to formaldehyde and formic acid. Formic acid accumulates in the optic nerve, and patients with methanol poisoning present with metabolic acidosis, blindness, cardiovascular instability, pancreatitis, and optic disc edema.

Treatment of all three poisonings centers on inhibition of alcohol dehydrogenase with either fomepizole or ethanol, and in some cases removal of toxins and their toxic-by-products with hemodialysis. As with other poisonings an important key to successful treatment is early diagnosis and intervention.

CASE SCENARIO 1

A 17-year-old girl is brought to the emergency department because of hyperpyrexia, vomiting, and confusion. Recently, she had been diagnosed with a hepatitis C infection but was otherwise well. On examination, the temperature is 40°C, the respirations are 32/min, and the pulse is 120/min. The lung examination is normal. The initial treatment consists of intravenous normal saline.

An arterial blood gas (analyzed at 37°C) is obtained. The pH and pCO_2 are 7.4 and 25 mmHg, respectively, and base excess (BE) is –11 mM. An additional blood sample has been sent to the laboratory for determination of plasma electrolytes.

What is the underlying acid–base disorder? What additional information is needed to make this determination? What is the diagnosis and proper treatment?

Case Scenario Discussion: A BE of –11 mM indicates a significant metabolic acidosis. The clinical examination and low pCO_2 suggest a compensatory respiratory alkalosis. The plasma electrolytes are reported: Na 140 mM, K 3.8 mM, chloride 115 mM, HCO_3^- 15 mM, and albumin 1.5 g/dL. The normal anion gap of 14 mM suggests a hyperchloremic, metabolic acidosis, perhaps due to the rapid infusion of crystalloids. However, the SIG (*SIG = AG – [albumin g/dL](1.2xpH–6.15) + [phosphate mg/dL](0.097xpH–0.13)*) of –9 mM reveals an "unmeasured" plasma anion as the major cause of the acidosis.

6. NORMAL AG/SIG

In the setting of normal renal and pulmonary function, these disorders are characterized by significant acidosis (pH < 7.4, HCO_3^- < 24 mEq/L, BE > –3 mEq/L), normal plasma SIG, and an adequate (urine anion gap negative) or inadequate (urine anion gap positive) renal response (Table 1, Fig. 1). The differential diagnosis includes diarrhea, dilutional acidosis, total parenteral nutrition, and renal tubular acidosis.

As an example, a positive urine anion gap in well-hydrated patient with normal renal function suggests the possibility of a renal tubular acidosis (Tables 3 and 4).

Proximal renal tubular acidosis. Proximal renal tubular acidosis (Type II) is characterized by a low threshold for bicarbonate reabsorption, due to a genetic defect in the SLC4A4 gene encoding NBC-1, a mutation in the CAII gene encoding carbonic anhydrase II or the use of carbonic anhydrase inhibitors such as acetazolamide or topiramate. SLC4A4 gene mutation is associated with cataracts and glaucoma, while CAII gene mutation is associated with osteopetrosis, as well as acidification defect in the distal tubule, making the latter the only true RTA type III.

Characterized by phosphaturia, aminoaciduria, glucosuria, and proximal renal tubular acidosis, Fanconi syndrome is a generalized defect in proximal tubular function that may be due to heavy metal poisoning, cystinosis, Lowe syndrome, Chinese Herb Nephropathy, mitochondrial disorder, Wilson disease, fructose intolerance, and monoclonal IgG light chain disease. Clinically only the phosphaturia and metabolic acidosis have metabolic consequences. In the young child with Fanconi syndrome the first potential diagnosis to be considered is cystinosis. Untreated children with Fanconi syndrome suffer from severe failure to thrive and rickets. The acidosis is often difficult to treatment as the treatment does not change the low bicarbonate threshold and the more bicarbonate is taken the more is found in the urine.

The finding of positive urinary anion gap (Cl^- < (Na^+ + K^+)), namely inappropriately low ammonium ion secretion automatically focuses the attention on the kidney (although positive anion gap is also observed in toluene ingestion due to the excretion of hippurate salts, but these conditions are not easily confused).

Distal Renal Tubular Acidosis. Distal renal tubular acidosis (Type I) is due to low net acid excretion in the distal nephron, and may be secondary to an autosomal dominant mutation in the SLC4A1 gene with aberrant trafficking of AE1 or an autosomal

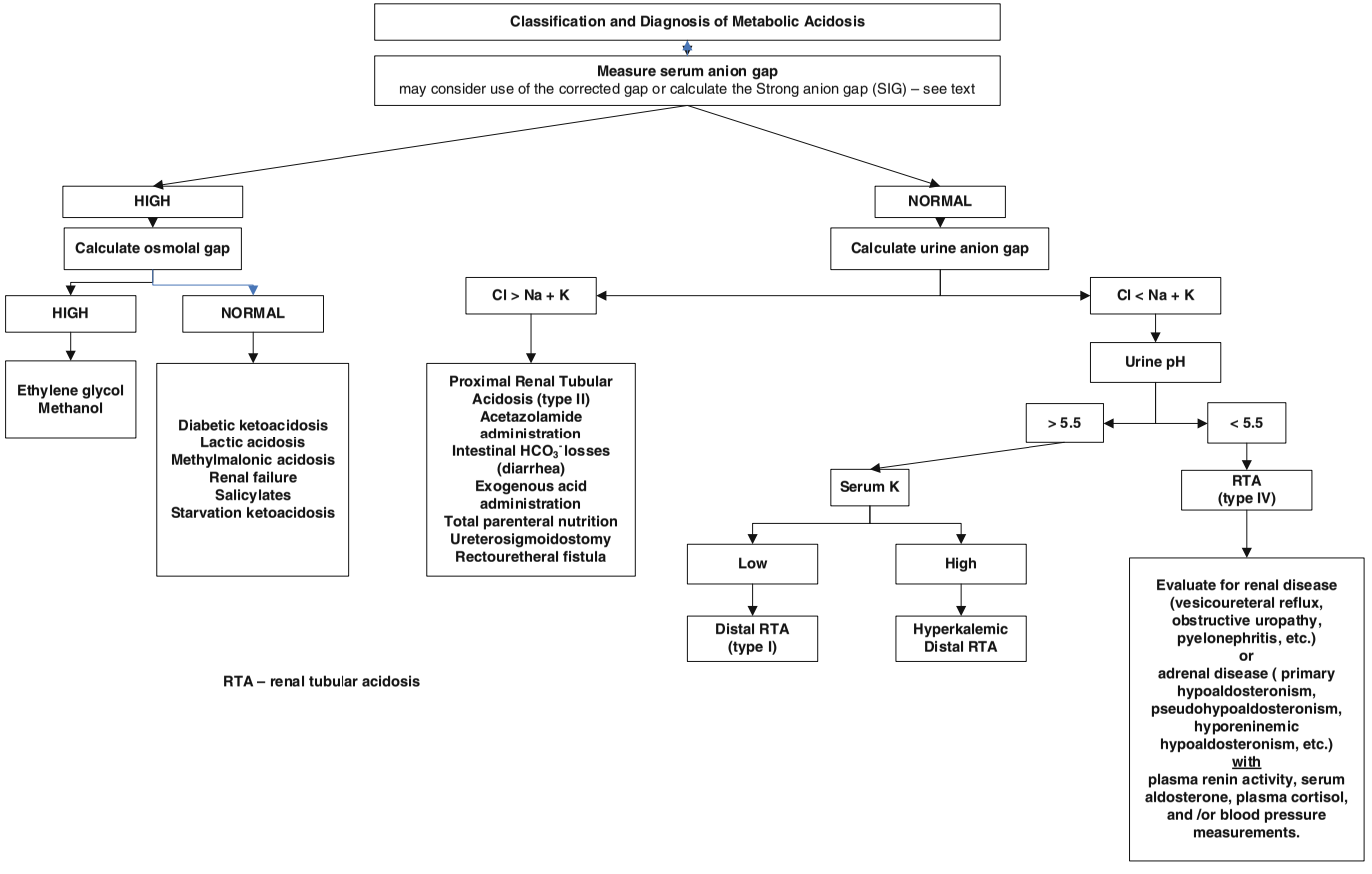

Fig. 1. Classification and diagnosis of metabolic acidosis.

Table 3
Selected Causes of Renal Tubular Acidosis (RTA)

Proximal RTA	*Distal RTA*	*Type IV RTA*
Isolated	*Primary*	*Mineralocorticoid deficiency*
Sporadic, transient in infancy	Transient in infancy	Aldosterone disorders
Hereditary	Persistent	Addison disease
	Adult type	Congenital adrenal hyperplasia
Fanconi syndrome	Incomplete	Primary hypoaldosteronism
	With bicarbonate wasting	Hyporeninemic hypoaldosteronism
Primary	With nerve deafness	
Secondary		*Other causes*
Inherited	*Secondary*	
Carbonic anhydrase II deficiency		Chloride shunt syndrome
Cystinosis	Interstitial nephritis	Diabetes mellitus
Galactosemia	Lupus nephritis	Idiopathic
Glycogen storage disease type I	Medullary sponge kidney	Interstitial nephritis
Hereditary fructose intolerance	Nephrocalcinosis	Nephrosclerosis
Leigh syndrome	Obstructive uropathy	Obstructive uropathy
Lowe syndrome	Pyelonephritis	Pseudohypoaldosteronism
Medullary cystic disease	Reflux nephropathy	Pyelonephritis
Metachromatic leukodystrophy	Sickle cell nephropathy	Transient in infancy
Mitochondrial cytopathies	Transplant rejection	Unilateral kidney diseases
Tyrosinemia		
Wilson disease	*Other causes*	
Acquired		
Cyclosporine	Carbonic anhydrase II deficiency	
Gentamicin	Chronic active hepatitis	
Heavy metals	Ehlers–Danlos syndrome	
Hyperparathyroidism	Elliptocytosis	
Interstitial nephritis		
Nephrotic syndrome	*Toxin or drug induced*	
Vitamin D deficiency rickets	Amphotericin B	
	Analgesics	
	Lithium	

Rodriquez Soriano *(10)*; Adrogue and Madias *(11)*.

Table 4
Features of Renal Tubular Acidosis in Childhood

Features	*Type I (distal)*	*Type II (proximal)*	*Type IV (hyperkalemic)*
Urine pH during acidosis	>5.5	<5.5	<5.5
Urine anion gap	Positive	Negative	Positive
$FEHCO_3^-$ at normal serum HCO_3	<15%*	>15%	<15%
(Urine–blood) pCO_2	<20 mmHg	>20 mmHg	?
Serum potassium	Normal or low	Normal or low	Increased
Calcium excretion	Increased	Normal or ↑	Normal (?)
Citrate excretion	Decreased	Normal	Normal
Nephrocalcinosis	Common	Rare	Absent
Associated tubular defects	Rare	Common	Rare
Rickets	Rare	Common	Absent
Daily alkali requirement (mEq/kg/day)	1–4*	10–15	2–3
Potassium supplementation	No	Yes	No

* Often higher in infants.
Modified with permission from Rodriquez-Soriano and Vallo *(12)*.

recessive mutation in the ATP6B1 gene encoding the B1 subunit of the vacuolar H^+-ATPase. The recessive form may be associated with growth retardation and hearing loss, whereas the dominant form is usually milder. Hypokalemia is common, and hypercalciuria and hypocitraturia predispose to nephrocalcinosis and nephrolithiasis. Distal renal tubular acidosis may also be observed with Sjogren's syndrome, hypergammaglobulinemia, amphotericin, and HIV infection.

Pathophysiologically, several mechanisms are responsible to dRTA. Among them (a) a secretory defect due to genetic or acquired abnormalities in the H^+-ATPase pump of the alpha intercalated cell (b) a gradient defect in which there is a backleak of luminal H^+ as seen in patients treated with amphotericin.

Renal Tubular Acidosis Type IV. This is the most common type of RTA. Contrary to RTA type II and most cases of RTA type I, which are associated with hypokalemia, RTA type IV is associated with hyperkalemia (Table 4). While the patients are able to lower their urine pH in response to systemic acidosis their ammonia generation is impaired. It is unclear to what extent it is the hyperkalemia itself causing the interference in ammonia metabolism. The hyperkalemia is due to either low serum aldosterone or to tubular defects. Based on the various abnormalities in the axis renin–aldosterone–kidney, RTA type IV is divided into 5 subtypes (Fig. 1). The rationale in this classification is in both in defining the pathophysiologic mechanism and the optimal treatment.

In order to identify the sub-type it is needed to assess the patient's blood pressure, obtain blood samples for renin, aldosterone, and cortisol and evaluate the urinary tract anatomy by ultrasound. Only pseudohypoaldosteronism type II is characterized by hypervolemia and hypertension. This autosomal dominant disorder is due to a genetic mutation resulting in increased NaCl reabsorption in the distal tubule. Secondary to the hypervolemia plasma renin activity and serum aldosterone are suppressed. In all other sub-types patients is hypo- or euvolemic and hypo- or normotensive. They result from either primary or secondary lack of aldosterone or decreased responsiveness of the renal tubule to aldosterone, namely end-organ resistance.

Chronic Renal Failure. In advanced chronic renal failure, low net acid excretion is due to global loss of functioning renal mass, resulting in progressive inability of the kidneys to clear phosphates, sulfate, and organic acids, combined with tubular damage lowering the ability to secrete H^+ lead to either normal anion gap (hyperchloremic) or high anion gap metabolic acidosis.

CASE SCENARIO 2

A 6-month-old Israeli boy is evaluated for failure to thrive, associated with vomiting, diarrhea, lethargy, and abdominal distention. He was the full-term product of a normal vaginal delivery, with height and weight initially at the 50th percentile. On examination, the weight is now 7 kg (9th percentile) and the height is 63 cm (2nd percentile). Laboratories revealed

Na 140 mmol/L; K 3.2 mmol/L, Cl 110 mmol/L; HCO_3 16 mmol/L, BUN 3 mg/dL, Pcr 0.3 mg/dL;
Venous pH 7.28; urine pH 8, ketones negative; anion gap 14 mmol/L

Suspecting renal tubular acidosis (RTA) on the basis of a normal anion gap and an alkaline urine pH, bicarbonate (Bicitra) 3 mEq/kg/day was prescribed. However, the infant deteriorated neurologically, developing ophthalmoplegia and upward gaze nystagmus. A head CT scan was normal.

Case Scenario Discussion:

1. Is the diagnosis of RTA correct?
   ANSWER: In this case, RTA may be an incorrect diagnosis. Urine pH is alkaline in many forms of chronic acidosis, due to "proton-trapping" by high concentrations of urinary ammonia. Furthermore, the anion gap may be misleading in patients with hypoalbuminemia.
2. What additional information do you need to make the diagnosis?
   ANSWER: The urine anion gap, the plasma osmol gap, and the plasma strong ion gap may be helpful to make diagnosis.

In this case, the urine anion gap (Na + K – Cl) is negative, suggesting a high concentration of urinary ammonium and pointing away from the diagnosis of RTA. The plasma albumin is 1.5 g/dL and the plasma osmolality is 285 mOsm/kg, so the plasma osmol gap is normal while the albumin-corrected anion gap is 21 nM and plasma strong ion gap (SIG) is also elevated at 11 mM.

3. What further diagnostic test lead to the correct diagnosis?
   The alkalinizing effect of hypoalbuminemia may "mask" the metabolic acidosis due to an "unmeasured" anion. In this case, the blood lactate level was found to be elevated. The differential diagnosis of lactate anion acidosis includes dysoxia (due to sepsis or shock), inborn errors of metabolism, a variety of drugs, and several intoxications.

On reviewing the history, the infant was fed a soy-based formula (Remedia Super Soya 1) that was specifically manufactured for the Israeli market. An erythrocyte transketolase activity assay revealed significant thiamine deficiency as the cause of the lactate anion acidosis.

Treatment with thiamine reversed the clinical symptoms and lead to a complete recovery.

7. TREATMENT

In general, treatment centers on the correction of the disordered pathophysiology (Table 5). For example, maneuvers that improve ventilation and perfusion will benefit critically ill patients with lactic anion acidosis due dysoxia. Bicarbonate therapy is helpful in children with renal tubular acidosis, but is of unclear benefit or harmful in patients with lactic anion or ketoacidosis. Hemodialysis may be indicated in severe intoxication and some of the metabolic disorders, but is of uncertain benefit in other conditions. Future investigations that link mitochondrial function, intracellular pH, and blood buffers may provide additional insight to the optimal treatment.

Table 5
Treatment of Some Forms of Metabolic Acidosis

Anion	*Cause*	*Treatment*	*Unclear benefit or possibly harmful*
Chloride	Acute diarrhea, renal tubular acidosis, acute, and chronic renal failure,	Bicarbonate (see Table 4)	Careful administration in hypocalcemic patients
Lactic anion	Dysoxia	Improve ventilation and perfusion	Hemodialysis/ hemofiltration
Keto acids	Diabetes mellitus	Insulin	Bicarbonate, Carbicarb
Salicylate	Ingestion	Alkalinization of urine	Over-aggressive fluid administration
Alcohols (propylene glycol, ethylene glycol, methanol)	Ingestion	Fomepizole, ethanol, hemodialysis	

The treatment of the various types of RTA type IV depends on the pathophysiology. In the case of chloride shunt, a thiazides diuretic is the drug of choice. In hypoaldosteronism, either primary or secondary, a mineralocorticoid will be the drug of choice. However in patients with chronic renal failure who are also hypertensive the drug should be replaced by furosemide. In patients with end-organ resistance a combination treatment with NaCl and $NaHCO_3$ is often required. In children with RTA type IV due to obstructive uropathy alleviation of the obstruction results in normalization of function of the tubule. A similar situation may be observed in patients with pyelonephritis especially when superimposed on an anatomic abnormality in the urinary tract.

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