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The Evaluation and Treatment of Metabolic Acidosis

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Abstract

Purpose of review Metabolic acidosis has a wide array of etiologies making the initial evaluation imperative in order to identify the proper treatment pathway. The clinical sequela of metabolic acidosis can often be vague and nonspecific. This underscores the importance of being able to comfortably recognize and evaluate acid-base disturbances.
Recent findings The diagnostic modalities used to evaluate metabolic acidosis have existed for quite some time, though the validity and usefulness of particular metrics have shown superior to others. Similarly, as our understanding of disease processes progresses, the conditions that warrant and respond to the use of base therapy are rare.
Summary Metabolic acidosis has potentially grave consequences to patient outcomes. As a result, timely diagnosis and recognition of treatment options is vital.

Introduction

Metabolic acidosis is a pathophysiologic state with a broad differential stemming from common and uncommon etiologies alike. In absolute terms, metabolic acidosis is an arterial pH less than 7.35 with a plasma bicarbonate concentration of less than 20 mmol/L in the absence of coexisting hypercapnia. The importance of understanding how to recognize metabolic acidosis from a laboratory standpoint is critical, as the clinical sequela, while potentially vital to patient outcome, is often vague and nonspecific. Physiological effects of metabolic acidosis are listed in Table 1 [1].

Table 1. Acute and chronic effects of metabolic acidosis

	Acute
GI effects	Nausea
	Emesis
Electrolyte abnormalities	Hyperkalemia
	Hyperglycemia
Neurologic effects	Confusion/altered mental status
	Headache
	Muscle weakness
	Cerebral vasodilation • Possibly secondary increased intracranial hypertension
Cardiovascular effects	Decreased myocardial contractility • Prominent when serum pH < 7.2
	Hypotension
	Tachycardia
	Increased right heart strain
Pulmonary effects	Tachypnea
	Increased pulmonary vascular resistance
	Right shift of oxyhemoglobin dissociation curve • Decreased affinity for oxygen
	Chronic
Musculoskeletal	Bone disease
	Growth retardation
	Muscle wasting
Metabolic	Hypoalbuminemia
	Decreased glucose tolerance
Renal	Progression of renal failure

Acid-base homeostasis

To understand metabolic acidosis pathophysiology, it is important to understand the mechanisms by which the body attempts to remain at an optimal pH for cellular function. Within the plasma, there is a free flowing reaction mediated by carbonic anhydrase that highlights the respiratory and metabolic interplay of acid-base homeostasis [2]:

$$CO_2 + H_2O > H_2CO_3 < -> H + HCO_3$$

This free flowing reaction has critical implications not only on means of compensation, but also on disease processes and treatment options.

In the most basic sense, metabolic acidosis occurs by three scenarios, whether in isolation or combined effect. They are as follows:

1) *An increase in net acid production*

Under typical metabolic and dietary conditions, infants and children produce between 1 and 3 mmol/kg of net acid each day [1]. In states of critical illness, such as in lactic acidosis, or after the ingestion of toxic substances like ethylene glycol, the production of nonvolatile acids can increase exponentially. In either of these scenarios, if severe enough, the increased acid production can overwhelm the body's ability to remain in acid-base homeostasis.

2) *An increase in bicarbonate loss*

The GI tract is the most common source for an increase in bicarbonate loss with diarrhea serving as one of the most common causes of metabolic acidosis in the pediatric population. The degree of bicarbonate loss depends on the severity and volume of diarrhea. The concern in severe gastroenteritis, as it relates to metabolic acidosis, is the potential for hypovolemia that may precipitate an exacerbating lactic acidosis.

3) *An impairment in the kidney's ability to reabsorb bicarbonate and/or properly excrete acid and synthesize bicarbonate*

The kidney plays a fundamental role in maintaining acid-base homeostasis through the reabsorption and synthesis of bicarbonate. In regard to the reabsorption of filtered bicarbonate, 90% occurs within the proximal convoluted tubule, and the remainder is largely absorbed through the thick ascending limb and distal nephron. Failure of the proximal convoluted tubule to reabsorb bicarbonate is the pathophysiologic defect noted in type II or proximal renal tubular acidosis and is responsible for the bicarbonate wasting that produces a normal anion gap metabolic acidosis [3]. In a more global sense, damage to the proximal convoluted tubule is what leads to the constellation of sequela in Fanconi syndrome, with loss of phosphate, glucose, amino acids, and other solutes in addition to bicarbonate. In regard to bicarbonate formation, bicarbonate synthesis occurs in the process of titratable acid excretion and ammoniagenesis. The ability of the kidney to upregulate acid excretion and, by default, generate bicarbonate occurs roughly 12 h after an inciting acidosis and can persist for up to 72 h [4].

Alveolar ventilation

When serum bicarbonate levels decrease, either due to primary loss or through depletion of intracellular and extracellular buffers, hydrogen ions will stimulate the peripheral and medullary chemoreceptors. The stimulation of these chemoreceptors by hydrogen ions leads to an increase in alveolar ventilation, which serves as a compensatory response to help maintain optimal pH for cellular function [2]:

$$CO_2 + H_2O <-> HCO_3 + H$$

Being able to recognize and appreciate this compensatory response in critically ill children is especially vital. Emerging hypercapnia in a critically ill child with metabolic acidosis may be a telling sign of impending respiratory failure secondary to muscle fatigue, or the onset of a mixed respiratory etiology.

In a child who is already in respiratory failure, especially if the child is on muscle relaxing agents, careful attention must be directed towards adjusting appropriate ventilator settings in order to allow for adequate respiratory compensation [5]. Understanding alveolar ventilation and its impact on metabolic acidosis is also critical when assessing for mixed acid-base disturbances. In children with isolated metabolic acidosis, CO_2 will decrease in a predictable way as follows, using Winter's formula [6••]:

$$PCO_2 = 1.5\ (HCO_3) + 8 \pm 2$$

If the PCO_2 is lower than predicted and respiratory compensation is not appropriate, there is likely a concurrent/isolated respiratory alkalosis. A PCO_2 that is greater than predicted indicates a concurrent respiratory acidosis.

Evaluation

More often than not, clinical context pinpoints the primary pathology leading to a consequent metabolic acidosis. For example, a child with profuse and severe diarrhea suggests the acute loss of bicarbonate through the GI tract while a child with new-onset polyuria, polydipsia, and weight loss with hyperglycemia suggests new-onset diabetes mellitus with ketoacidosis. As a result, a complete history and a physical exam are the first step in the encounter. However, in order to evaluate severity and chronicity properly, as well as to be able to consider treatment options further, a more detailed workup is required. Laboratory evaluation should begin with a metabolic panel and urinalysis. A metabolic panel provides serum bicarbonate, glucose, renal function, and the means to calculate an anion gap. A metabolic panel may also help to broaden the differential and expose pathology that may not be overtly obvious. For example, an elevated BUN to creatinine ratio in the presence of gastroenteritis or septic shock is suggestive of prerenal azotemia and may correlate to poor perfusion with a primary or coexisting lactic acidosis. Meanwhile, in regard to a urinalysis, while blood ketones are a more precise marker of ketoacidosis and should be obtained when clinical context deems it worthy [6••], a urinalysis is a fast, helpful, and often readily available diagnostic aid for the assessment of urinary ketones, glucose, and specific gravity.

When serum bicarbonate is low, an arterial blood gas should be obtained to eliminate the potential for a primary respiratory alkalosis with an appropriately decreased bicarbonate per a compensatory renal response [6••]. Equally, an arterial blood gas aids in assessing for a coexisting mixed acid-base disturbances through use of Winter's formula. Next, in order to stratify etiology further, it is important to calculate the anion gap. The anion gap subdivides patients into two groups: those with normal anion gap metabolic acidosis and those with increased anion gap metabolic acidosis. Particular disease states correspond to the aforementioned categories allowing an algorithmic approach to diagnosis.

Before particular pathologic states and their corresponding anion gaps may be discussed, it is important to understand the principles behind increased and normal anion gap metabolic acidosis. Within the blood, there is electrical neutrality between negatively charged anions and positively charged cations ($Na = Cl + HCO_3$ + unmeasured anions). Unmeasured anions, consisting

largely of charged proteins like albumin and phosphate, are often not included in routine laboratory screening. As a result, there is a cluster of unmeasured anions referred to as the anion gap [7]. While laboratories vary, a normal anion gap is typically between 8 and 12 ($AG = Na-(Cl+HCO_3)$).

It is important to consider the potential influence hypoalbuminemia has on this calculation, as charged proteins like albumin influence the anion gap. A decreased albumin concentration by 1 g/dL correlates with a decrease in the anion gap of roughly 2.5 mEq/L [8]. As a result, it is important to obtain an albumin level before calculating the anion gap. While we do not correct for unmeasured cations, we have to remain cognizant that the contrast, an increase in any unmeasured cation, such as calcium, potassium, or magnesium will ultimately decrease the anion gap. List of pathologies relating to normal or increase anion gap metabolic acidosis is presented in Table 2.

Increased gap metabolic acidosis

An increased gap metabolic acidosis occurs when there is an increase in the number of both unmeasured anions and hydrogen ions. In lactic acidosis, for example, lactic acid is composed of positively charged hydrogen ions and negatively charged lactate anions. Serum bicarbonate will buffer the hydrogen ions until reserves are exhausted. Upon exhaustion, the remaining hydrogen ions will decrease serum pH, while the lactate anions will increase the anion gap. In the same way, beta-hydroxybutyrate and acetoacetate are the unmeasured anions in diabetic ketoacidosis. In regard to presumed lactic acidosis, if there is high clinical suspicion, an arterial sample is more specific and therefore the more appropriate test to obtain. Venous samples are more appropriate to obtain when there is a lower likelihood of lactic acidosis. If the venous sample is negative for an elevated lactate level, it is adequate to rule out lactic acidosis,

Table 2. High and normal anion gap metabolic acidosis

High anion gap metabolic acidosis	Normal anion gap metabolic acidosis
Ingestion	Inability to regenerate bicarbonate
• Methanol	• Type I renal tubular acidosis
• Salicylate overdose	• Type IV renal tubular acidosis
• Phenformin	
• Ethylene glycol	
Inorganic acid build-up	Increased loss of bicarbonate
• Acute and chronic renal failure	• GI: diarrhea Small bowel and pancreatic drainage
Increased organic acid production	• Ureteral diversions
• Lactic acidosis	• Renal: type II renal tubular acidosis Carbonic anhydrase inhibitors
• Ketoacidosis: starvation ketoacidosis Alcoholic ketoacidosis Diabetic ketoacidosis	

though, if elevated, venous samples should be confirmed with an arterial measurement. Cases of ingestion warrant baseline toxicology screening. If salicylate testing returns negative, an increased osmolar gap (> 10) is suggestive of substances such as methanol or ethylene glycol [6••].

Normal or nonanion gap metabolic acidosis

Normal anion gap metabolic acidosis occurs when there is a decrease in serum bicarbonate without an increase in unmeasured anions. Gastrointestinal loss of bicarbonate due to significant diarrhea is a classic example of bicarbonate loss without an increase in unmeasured anions. Nonanion gap metabolic acidosis is sometimes referred to as hyperchloremic metabolic acidosis as chloride concentrations will increase or decrease, depending on the serum sodium concentration in order to satisfy electrical neutrality [7].

In the absence of acute or chronic renal disease, use of the urinary anion gap can better differentiate the etiology of normal anion gap metabolic acidosis [6••]. Due to electrical neutrality, chloride often accompanies ammonium as it is synthesized and excreted by the kidneys and therefore, a lack of ammoniagenesis means less chloride will pass into the urine. The concentrations of sodium and potassium, however, will remain largely the same. Therefore, if we use the equation [(Na + K)-Cl], we can conclude that a positive urinary gap is indicative of pathologies such as renal tubular acidosis. However, in properly functioning kidneys, with intact tubular capacities, such as in the case of increased stool output, the urinary anion gap will remain negative [9].

Renal failure in the pediatric population is more complex as it can span across the subgroups of both high anion gap and normal anion gap metabolic acidosis. Due to the higher incidence of renal dysplasia and obstructive uropathy in the pediatric population, renal failure is more commonly due to congenital and structural disorders. In cases of damage to the glomerulus and tubular structures, renal failure results in an increased anion gap metabolic acidosis. Conversely, if damage is largely due to the tubular structures, a normal anion gap metabolic acidosis may occur [10]. With damage to the renal tubules, the increase in bicarbonate wasting may outweigh the increase in unmeasured anions such as urate and phosphate that occur in renal insufficiency. As a result, in renal failure, the anion gap is a less predictable means of direction.

Treatment

The best treatment approach for patients with metabolic acidosis is correcting the inciting etiology. Restoring hemodynamic stability in a patient with hypovolemic shock or administering insulin to a patient in diabetic ketoacidosis remains the first-line therapy not only for the primary pathology, but also for the ensuing metabolic acidosis.

Bicarbonate replacement

In regard to replacement of bicarbonate, when metabolic acidosis occurs due to loss of intracellular and extracellular buffers, it is tempting to replenish bicarbonate stores to help to further buffer an ongoing acidosis. While this seems valid, the use of base therapy is not as unanimous as it would seem. In fact, the

use of base therapy in lactic acidosis, diabetic ketoacidosis, septic shock, and cardiac arrest has not yielded improved clinical outcomes or decreased mortality [11, 12, 13•]. This is controversial for multiple reasons. First, in pathologies where bicarbonate serves to buffer an increased acid load, such as DKA or lactic acidosis, the use of bicarbonate forms an anionic base known as potential bicarbonate [12, 13•, 14]. This potential can lead to a resultant overcorrection alkalosis that can produce dangerous levels of hypokalemia, hypophosphatemia, and ionized hypocalcemia. Equally concerning, through the carbonic anhydrase–mediated reaction, bicarbonate can freely convert to carbon dioxide. Carbon dioxide will freely diffuse across cell membranes, which can lead to a paradoxical intracellular acidosis that can cause impaired cellular function [14–16]. Beyond that, regular administration of sodium bicarbonate poses a risk for hypernatremia and/or fluid overload, which can further worsen cardiomyopathies and pulmonary edema. Careful consideration of the inherent risks of base therapy in the aforementioned etiologies must therefore be weighed against the potential consequences of unchecked acidemia.

Giving base therapy to a patient, who is bicarbonate deficient, such as those with gastroenteritis, is less controversial. Base therapy is available in both oral and intravenous forms. In the intravenous form, sodium bicarbonate infusions are typically prescribed in 1 to 2 mEq/kg. A less acute approach is to add sodium acetate or sodium bicarbonate to intravenous fluids. In this case, it is important to pay particular attention to the sodium load and titrate the desired concentration according to interval chemistries. When giving intravenous bicarbonate, the titration to CO_2 is not only relevant to intracellular diffusion, but also in cases of a mixed concurrent respiratory acidosis. In respiratory acidosis, an elevated CO_2 secondary to respiratory failure exacerbates the titration of bicarbonate to CO_2 if the CO_2 is not appropriately exhaled. In this case, the administration of sodium bicarbonate can cause worsening hypercapnia and contribute to the overall acidemia [16]. To avoid this potential pitfall, another option, which has become increasingly unavailable, is the administration of tris-hydroxymethyl aminomethane (THAM). THAM, restricted to IV formulation, has the ability to buffer acid by directly binding to protons without a consequent increase in CO_2 [17]. As a result, unlike sodium bicarbonate, which requires an open system (the ability to ventilate properly), THAM can be used in a closed system such as an ARDS where there is often a degree of permissive hypercapnia so to not induce drastic lung injury. THAM is also useful as it slowly diffuses intracellularly where it has the potential to optimize pH for cellular function [18]. The most significant adverse reactions of THAM include respiratory depression and hypoglycemia, secondary to the potential fast rate of infusion and increased insulin release, respectively. Use of THAM is contraindicated in children with renal failure as excretion is entirely through the kidneys [17, 19, 20].

Chronic scenarios

Use of long-term base therapy is reserved for children with conditions such as renal tubular acidosis or chronic renal failure. Here, oral options exist, either as sodium bicarbonate tablets or as citrate solutions. In regard to citrate solutions, citrate is actively metabolized in the liver to bicarbonate. The use of citrate solutions has been shown to improve the chronic ill effects of metabolic

acidosis, such as poor bone quality [21]. Specifically for children with type I and II renal tubular acidosis who are often hypokalemic, potassium citrate provides an added benefit. For those in renal failure, sodium citrate aides to prevent an additional potassium load.

Poisonings

In salicylate poisoning, the administration of base therapy will increase renal clearance and decrease the cognitive toxicity of salicylate ingestion. Creating an alkalotic environment makes it more difficult for hydrogen to bond with salicylate. As a result, salicylate remains as a charged anion unable to diffuse across the blood-brain barrier [22]. Use of base therapy in salicylate poisoning is therefore recommended regardless of arterial pH.

Similarly, base therapy is also indicated in order to maintain a pH of > 7.3 following the ingestion of ethylene glycol or methanol. Again, keeping the metabolites of these ingested substances in the charged form limits their ability to diffuse into end organs and ultimately reduces their toxic effects. In addition, as seen in salicylate poisoning, urinary alkalization helps to aid clearance [22].

Dialysis

Either hemodialysis or peritoneal dialysis offers an acute option for correcting metabolic acidosis. Concurrent electrolyte derangements, especially hyperkalemia, may lead to the decision to perform hemodialysis. Equally efficacious is the ability for hemodialysis to remove offending toxins such as ethylene glycol or methanol. Peritoneal dialysis is another option to correct metabolic acidosis in cases of renal insufficiency, though the use of lactate makes it incompatible in those with a concurrent lactic acidosis.

Conclusion

Metabolic acidosis has a wide array of causes, making the initial evaluation important in identifying the proper treatment pathway. While metabolic acidosis has potentially grave consequences, as our understanding of the pathophysiologic changes due to metabolic acidosis continues to evolve, so too does our ability to recognize when treatment is appropriate. In summary, when appropriate treatment and identification of etiology are ascertained, treatment of metabolic acidosis in children is very favorable and outcomes are generally survivable.

Compliance with Ethical Standards

Conflict of Interest

Dr. Melinda Carpenter declares no conflict of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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