Approach to the adult with metabolic acidosis

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INTRODUCTION

On a typical Western diet, approximately 15,000 mmol of carbon dioxide (which can generate carbonic acid as it combines with water) and 50 to 100 mEq of nonvolatile acid (mostly sulfuric acid derived from the metabolism of sulfur-containing amino acids) are produced each day. Acid-base balance is maintained by pulmonary and renal excretion of carbon dioxide and nonvolatile acid, respectively.

Renal excretion of acid involves the combination of hydrogen ions with urinary titratable acids, particularly phosphate ($HPO_4^{2-} + H^+ \rightarrow H_2PO_4^-$), and ammonia to form ammonium ($NH_3 + H^+ \rightarrow NH_4^+$) [1]. The latter is the primary adaptive response since ammonia production from the metabolism of glutamine can be appropriately increased in response to an acid load [2].

Acid-base balance is usually assessed in terms of the bicarbonate-carbon dioxide buffer system:

$$\text{Dissolved } CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

The ratio between these reactants can be expressed by the Henderson-Hasselbalch equation. By convention, the pKa of 6.10 is used when the denominator is the concentration of dissolved CO_2, and this is proportional to the pCO_2 (the actual concentration of the acid H_2CO_3 is very low):

$$pH = 6.10 + \log \frac{[HCO_3]}{[0.03 \times pCO_2]}$$

In this equation, the pH is equal to (-log[H^+]), 6.10 is the pKa (equal to the -log of the dissociation constant for the reaction), 0.03 is equal to the solubility constant for CO_2 in the extracellular fluid, and pCO_2 is equal to the partial pressure of carbon dioxide in the extracellular fluid [3].

The definition, pathogenesis, and approach to the adult with metabolic acidosis will be reviewed here. An overview of simple and mixed acid-base disorders and the approach in children with metabolic acidosis are discussed separately. (See "Simple and mixed acid-base disorders" and "Approach to the child with metabolic acidosis".)

DEFINITION AND PATHOGENESIS

Definition — Metabolic acidosis is defined as a pathologic process that, when unopposed, increases the concentration of hydrogen ions in the body and reduces the HCO_3 concentration. Acidemia (as opposed to acidosis) is defined as a low arterial pH (<7.35), which can result from a metabolic acidosis, respiratory acidosis, or both. Not all patients with metabolic acidosis have a low arterial pH; the pH and hydrogen ion concentration also depend upon the coexistence of other acid-base disorders. Thus, the pH in a patient with metabolic acidosis may be low, high, or normal.

Pathogenesis — Metabolic acidosis can be produced by three major mechanisms. The most important individual etiologies are discussed in detail elsewhere (table 1):

- Increased acid generation
- Loss of bicarbonate
- Diminished renal acid excretion

In addition to classifying metabolic acidosis by the primary pathogenic mechanism, the serum anion gap can be used to categorize the metabolic acidoses into two groups: high anion gap metabolic acidosis and normal anion gap metabolic acidosis (table 1). The normal anion gap metabolic acidoses must, by definition, manifest relative hyperchloremia (a high chloride relative to the sodium concentration). Thus, the two groups can also be labeled high anion gap metabolic acidosis and hyperchloremic metabolic acidosis. (See 'Physiologic interpretation of the serum anion gap' below.)

Increased acid generation — Increased acid generation leading to metabolic acidosis occurs in a variety of clinical settings, which are discussed in detail in separate topics dealing with each of these specific disorders (links to those topics are provided throughout this review).

- Lactic acidosis (see "Causes of lactic acidosis")
- Ketoacidosis due to uncontrolled diabetes mellitus, excess alcohol intake (generally in a malnourished patient), or fasting (see "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis" and "Fasting ketosis and alcoholic ketoacidosis")
- Ingestions or infusions
  - Methanol, ethylene glycol, diethylene glycol, or propylene glycol (see "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis")
  - Aspirin poisoning (see "Salicylate (aspirin) poisoning: Clinical manifestations and evaluation")
  - Chronic acetaminophen ingestion, especially in malnourished women
  - D-lactic acid, generated from carbohydrates by gastrointestinal bacteria
  - Toluene (see "Inhalant misuse in children and adolescents" and "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis")

Loss of bicarbonate — Metabolic acidosis due to loss of bicarbonate occurs in the following settings:

- Severe diarrhea (see "Acid-base and electrolyte abnormalities with diarrhea")
- When urine is exposed to gastrointestinal mucosa, which occurs after ureteral implantation into the sigmoid colon or the creation of replacement urinary bladder using a segment of the gastrointestinal tract (see "Acid-base and electrolyte abnormalities with diarrhea")
- Proximal (type 2) renal tubular acidosis (RTA), in which proximal bicarbonate reabsorption is impaired (see "Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance", section on 'Proximal (type 2) RTA')

In addition, in several conditions, such as ketoacidosis, which would be expected to generate an anion gap acidosis, the renal excretion of organic acid anions (for example, ketoacid anions) in

the urine with sodium or potassium represents the loss of "potential bicarbonate" and the anion gap shrinks or normalizes. With the onset of ketoacidosis, bicarbonate levels fall and ketoacid anion concentrations increase. As ketoacidosis resolves, metabolism of the ketoacid anions results in regeneration of the bicarbonate that was lost in the initial buffering reaction. However, if these ketoacid anions are lost into the urine before they can be metabolized (as sodium or potassium salts), this represents lost "potential bicarbonate." The net effect of these urinary losses is that most patients with diabetic ketoacidosis develop a normal anion gap metabolic acidosis during their recovery phase. Similarly, the loss of sodium and potassium lactate into the urine also represents loss of potential bicarbonate and partially converts an anion gap acidosis to a hyperchloremic acidosis. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

Diminished renal acid excretion — A regular Western diet generates a daily nonvolatile metabolic acid load of approximately 50 to 100 mEq/day that must be excreted by the kidneys. Acid-base balance is maintained by excreting the hydrogen ions and the acid anions in the urine. Metabolic acidosis due to diminished renal acid excretion can be divided into two general types of disorders:

- Reduced acid excretion that occurs in conjunction with a reduction in glomerular filtration rate (ie, the acidosis of kidney failure) (see "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease", section on 'Development of metabolic acidosis')

- Distal (type 1) RTA and type 4 RTA, in which tubular dysfunction is the primary problem and glomerular filtration is initially preserved (see "Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance", section on 'Distal (type 1) RTA')

Dilution acidosis — Dilution acidosis refers to a fall in serum bicarbonate concentration that is primarily due to rapid infusion of large volumes of normal saline, which contains neither bicarbonate nor the sodium salts of organic anions that can be metabolized to bicarbonate (such as lactate or acetate) [4]. The degree of metabolic acidosis is generally quite moderate. However, concern has been raised that hyperchloremia and metabolic acidosis generated by volume expansion with normal saline may contribute to acute kidney injury and affect patient outcomes [5]. Although initial studies did not confirm any clinical benefit of "balanced solutions" (eg, Lactated Ringer) compared with normal saline [6], subsequent studies have suggested a modest potential survival benefit of balanced solutions in both critically ill and noncritically ill patients [7,8].

DIAGNOSIS AND EVALUATION

Diagnosis — A metabolic acidosis is diagnosed when the serum pH is reduced and the serum bicarbonate concentration is abnormally low (often defined as <23 mEq/L, but the threshold may vary across clinical laboratories) [9].

When a simple metabolic acidosis exists, both the serum pH and bicarbonate concentration will both be reduced. Although both measurements may be needed, in most patients, the diagnosis can be made on the basis of a reduced bicarbonate concentration alone (provided that chronic respiratory alkalosis can be ruled out on clinical grounds).

However, if metabolic acidosis coexists with respiratory acidosis or metabolic alkalosis, then the serum bicarbonate may be normal or elevated. The bicarbonate concentration, serum pH, and other electrolyte measurements will be required to correctly diagnose such complicated mixed acid-base disorders. In such patients, a metabolic acidosis is diagnosed when the serum bicarbonate is lower than it should be, even if the value falls within the normal range. This issue is discussed in detail elsewhere but can be illustrated here. An example is a patient with chronic respiratory acidosis, characterized by hypercapnia and a compensatory rise in the serum bicarbonate concentration, develops watery diarrhea. The loss of alkali in the stool will lower the serum bicarbonate concentration and produce a metabolic acidosis, but the serum bicarbonate concentration may still be within or above the "normal" range since the baseline value may have been very high (figure 1). (See "Simple and mixed acid-base disorders", section on 'Response to respiratory acidosis'.)

It is important to recognize that the evaluation of an acid-base disorder often occurs at a single point in time. If the previous (or "baseline") acid-base parameters are not known, then the single set of values can be misinterpreted. Whenever a series of laboratory results are available, the analysis should consider the changes that occurred over time. (See "Simple and mixed acid-base disorders".)

Evaluation — Serum or plasma electrolytes, calculation of the anion gap, and a detailed history and physical examination are usually sufficient to determine the cause of the metabolic acidosis and guide therapy. However, in complicated patients, a definitive evaluation of metabolic acidosis usually requires the following:

- Measurement of the arterial pH and pCO_2. (See 'Measurement of the arterial pH and pCO2' below.)

- Determine whether respiratory compensation is appropriate. (See 'Determination of whether respiratory compensation is appropriate' below.)

- Assessment of the serum anion gap to help identify the clinical etiology of the acidosis (table 1) and calculation of the delta anion gap/delta HCO_3 ratio in patients who have an elevated anion gap. (See 'Assessment of the serum anion gap' below.)

  The strong ion difference analysis is a complex alternative to the serum anion gap methodology for analyzing acid-base disorders [10]. Although some believe that this analysis may be helpful in certain unusual settings, we and others prefer an approach based upon the serum pH, HCO_3, pCO_2, and anion gap (corrected for albumin concentration) because we believe it is much simpler to understand and utilize and it generates the correct clinical diagnosis in the vast majority of circumstances [11]. (See "Strong ions and the analysis of acid-base disturbances (Stewart approach)".)

  Although the serum anion gap is most often utilized in the evaluation of metabolic acidosis, an abnormally high or low anion gap may be a valuable clue to the presence of many conditions other than metabolic acidosis. These issues are discussed elsewhere. (See "Serum anion gap in conditions other than metabolic acidosis".)

Measurement of the arterial pH and pCO2 — Measurement of the serum bicarbonate concentration alone may not be sufficient to establish a clinical diagnosis since a low serum bicarbonate concentration can be generated by metabolic acidosis or, alternatively, reflect the compensatory response to a primary respiratory alkalosis. If the patient has a simple metabolic acidosis, then the arterial pH should be low. If the patient has respiratory alkalosis, the pH should be elevated. If the patient has a mixed disorder consisting of a metabolic acidosis plus a respiratory alkalosis, metabolic alkalosis, or all three disorders, then the arterial pH can be low, normal, or high.

However, blood gas measurement is not mandatory in all cases. The diagnosis of metabolic acidosis may be readily apparent clinically (ie, lactic acidosis with shock, hyperchloremic acidosis with diarrhea, ketoacidosis with uncontrolled type 1 diabetes, etc). If a blood gas measurement is needed, then a venous pH may often be adequate (see "Venous blood gases and other alternatives to arterial blood gases"). However, an arterial blood gas is necessary to determine the presence of a primary respiratory disorder or to accurately determine the degree of respiratory compensation for metabolic disorders. (See "Simple and mixed acid-base disorders".)

Determination of whether respiratory compensation is appropriate — The complete evaluation of a patient with metabolic acidosis requires determination of the appropriateness of

the compensatory response.

Metabolic acidosis should generate a compensatory respiratory response. The reduction in the serum bicarbonate and pH caused by the metabolic acidosis is expected to increase ventilation and reduce the pCO_2. The Henderson-Hasselbalch equation displayed above shows that a fall in pCO_2 will mitigate the fall in pH caused by a reduced HCO_3.

In all **simple** acid-base disorders, the primary abnormality generates a compensatory response that results in both the HCO_3 concentration and pCO_2 moving in the same direction (either both will increase or both will decrease). These directional changes always push the pH toward the normal range [3,12,13]. The compensatory responses are mediated, at least in part, by parallel alterations in pH within cells of the renal tubules or respiratory center [14]. (See "Simple and mixed acid-base disorders".)

The respiratory compensation for metabolic acidosis generates a reproducible and relatively linear relationship between the arterial pCO_2 and bicarbonate concentration. This respiratory response to metabolic acidosis begins within 30 minutes and is complete by 12 to 24 hours. Respiratory compensation for metabolic acidosis is very similar across all forms of metabolic acidosis (eg, lactic acidosis, ketoacidosis, hyperchloremic acidosis caused by diarrhea, etc). In order to determine whether an appropriate compensatory response exists, a variety of acid-base diagrams, charts, nomograms, and mathematical relations have been published. These are discussed in greater detail elsewhere. (See "Simple and mixed acid-base disorders", section on 'Response to metabolic acidosis'.)

Several relatively simple acid-base "rules" for metabolic acidosis are acceptable for clinical use. They include:

- $pCO_2 = 1.5 \times HCO_3 + 8 \pm 2$. This equation, which is called Winter's formula, was derived in children (many less than 2 years of age).
- $pCO_2 = HCO_3 + 15$.
- The pCO_2 should approximate the decimal digits of the arterial pH. As an example, if the pH is 7.25, then the pCO_2 should be approximately 25 mmHg [15].

These rules work well for mild to moderately severe metabolic acidosis (HCO_3 between 7 and 22 mEq/L). For more severe metabolic acidosis (HCO_3 less than 7 mEq/L), the pCO_2 should be maximally reduced to the 8 to 12 mmHg range. As an example, assume the following results are obtained in a patient with metabolic acidosis: pH = 7.30; pCO_2 = 30 mmHg (4.0 kPa); HCO_3 = 15 mEq/L. This is consistent with a simple metabolic acidosis with appropriate respiratory

compensation; all three of the compensation rules presented above are satisfied. It should be noted that these rules should not be used for determining the compensatory response for other acid-base disorders. The pCO_2 cannot be reduced to less than 8 to 12 mmHg. (See "Simple and mixed acid-base disorders", section on 'Response to metabolic acidosis'.)

An inability to generate an appropriate hyperventilatory response is generally indicative of a significant underlying neurologic or respiratory disorder and represents a mixed acid-base disorder: metabolic acidosis and respiratory acidosis. Conversely, excessive hyperventilation, which reduces the pCO_2 below the expected range, is indicative of mixed metabolic acidosis and respiratory alkalosis. (See "Simple and mixed acid-base disorders".)

Assessment of the serum anion gap — Disorders that produce metabolic acidosis by increasing organic acid generation and advanced chronic kidney disease, which leads to the accumulation of multiple acids such as phosphoric and sulfuric acid, usually result in an increased serum anion gap. Other disorders typically result in a hyperchloremic metabolic acidosis. Thus, the serum anion gap helps narrow the differential diagnosis in a patient with metabolic acidosis (table 1). (See 'Physiologic interpretation of the serum anion gap' below.)

In patients with an elevated serum anion gap metabolic acidosis, the rise in anion gap is generally similar to the fall in bicarbonate. This relationship can be defined as the delta anion gap/delta HCO_3. However, the expected 1:1 relationship between the decrease in HCO_3 and the increase in anion gap is not always observed in some forms of anion gap acidosis, such as ketoacidosis and D-lactic acidosis. The reasons for the disruption of the 1:1 relationship are discussed elsewhere. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

Physiologic interpretation of the serum anion gap — The serum anion gap can be helpful in narrowing the differential diagnosis in patients with metabolic acidosis (table 1) [1,3,12,13,16]. For purposes of the following discussion about the anion gap, all non-sodium cations will be referred to as "unmeasured cations," and all anions other than chloride and bicarbonate will be designated "unmeasured anions." Of course, all of these ions can be and often are "measured," but they are not utilized for these anion gap calculations. (The issue related to potassium is discussed below.)

The serum anion gap is typically calculated using the following formula:

$$\text{Serum anion gap} = Na - (Cl + HCO_3)$$

In some countries other than the United States, the serum potassium is also included in the formula; when this formula is used, the normal range for the anion gap increases by approximately 4 mEq/L:

$$\text{Serum anion gap} = (Na + K) - (Cl + HCO_3)$$

The normal value of the serum anion gap is dependent upon the specific chemical analyzers used to measure each analyte and therefore will vary from laboratory to laboratory and over time. In general the normal range is approximately 4 to 12 mEq/L [14,16], but it is best for each laboratory to determine its own local normal range.

Interpretation of the serum anion gap is most helpful when an individual's usual, or baseline, anion gap is known and serial measurements are available from the same laboratory. As an example, if a patient's baseline anion gap is 4 mEq/L and is found to be 12 mEq/L, then this 8 mEq/L increase in the anion gap is probably clinically significant despite the fact that the anion gap is still within the "normal" range. Unfortunately, baseline data are often unavailable.

When all ions in any solution are measured in units of electric charge, or valence (ie, mEq/L), then:

$$\text{The sum of all anions} = \text{The sum of all cations}$$

This relationship allows the derivation of another formulation for the anion gap, as follows:

$$\text{Total serum anions} = \text{Total serum cations}$$

Therefore:

$$Na + \text{All unmeasured cations} = Cl + HCO_3 + \text{All unmeasured anions}$$

Re-arranging:

$$Na - (Cl + HCO_3) = \text{All unmeasured anions} - \text{All unmeasured cations} = \text{Serum anion gap}$$

This formulation indicates that the anion gap will increase if unmeasured anions increase or unmeasured cations decrease. Conversely, the anion gap will decrease if unmeasured anions decrease or unmeasured cations increase.

In normal individuals, the major unmeasured anion responsible for the existence of a serum anion gap is albumin. This circulating protein has a significant net negative charge in the physiologic pH range. As a result, the expected baseline value for the anion gap must be adjusted downward in patients with hypoalbuminemia. The serum anion gap falls by approximately 2.5 mEq/L for every 1 g/dL (10 g/L) reduction below normal (4.5 g/dL) in the serum albumin concentration [1,16,17]:

Corrected serum anion gap = (Serum anion gap measured) + (2.5 x [4.5 - Observed serum albumin])

In addition to hypoalbuminemia, marked hyperkalemia may affect the interpretation of the anion gap. Potassium is an "unmeasured" cation when the anion gap equation that does not include the serum potassium is utilized. Thus, a serum potassium of 6 mEq/L will reduce the anion gap by 2 mEq/L. Marked hypercalcemia and/or hypermagnesemia can similarly reduce the anion gap. Another cause of a reduced or negative anion gap is immunoglobulin G (IgG) multiple myeloma. Many of these abnormal proteins circulate as cations. Other monoclonal proteins such as immunoglobulin A (IgA) are anions and therefore can raise the anion gap [16,18]. (See "Serum anion gap in conditions other than metabolic acidosis".)

An anion gap metabolic acidosis develops when an accumulating acid is any strong acid other than hydrogen chloride. Under these conditions, the bicarbonate concentration falls; the chloride concentration, the other "measured" anion, remains relatively unchanged; and the acid anion increases, raising the anion gap. As an example, when lactic acidosis develops, the following reaction occurs:

$$HLactate + NaHCO_3 \rightarrow NaLactate + H_2CO_3 \rightarrow CO_2 + H_2O$$

Note that, in this oversimplified schema, the magnitude of decrease in HCO_3 matches the magnitude of increase in the lactate concentration and the anion gap. However, this 1:1 relationship between the fall in HCO_3 and rise in serum anion gap is not always found; the reasons for this are discussed elsewhere. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis", section on 'Determinants'.)

Although the specific organic acid anions responsible for anion gap metabolic acidosis can often be characterized using a variety of analytic techniques, a significant component sometimes remains unidentified. These unidentified anions may include a number of organic acids generated by the Krebs cycle (citrate, isocitrate, alpha-ketoglutarate, succinate, and malate) [19-22].

Normal anion gap (hyperchloremic) metabolic acidoses are caused by loss of bicarbonate or a disorder that reduces renal acid excretion in the setting of a relatively normal glomerular filtration rate (ie, type 1, 3, or 4 renal tubular acidosis) [RTA]. A rare form of normal anion gap metabolic acidosis is due to the ingestion or infusion of hydrogen chloride or compounds which generate hydrogen chloride (NH_4Cl, arginine HCl, $CaCl_2$). (See 'Definition and pathogenesis' above.)

When hydrogen chloride is added to the extracellular fluid space, bicarbonate is replaced on an equimolar basis by chloride. Thus, there is no change in the serum anion gap. The terms "normal anion gap metabolic acidosis" and "hyperchloremic metabolic acidosis" are therefore interchangeable names for this disorder.

Loss of sodium bicarbonate, or other potential alkali salts (such as sodium acetate and sodium butyrate), from the body generates hyperchloremia because the lost fluid has a relatively high HCO_3, or alkali, concentration and a relatively low chloride concentration. The loss of such fluid (urine, pancreatic secretions, stool) will contract the extracellular fluid volume "around" a relatively stable quantity of chloride. Also, the hypovolemia that develops will favor retention of any chloride that is ingested or infused (eg, isotonic saline).

Causes of elevated anion gap metabolic acidosis — The major causes of a high anion gap metabolic acidosis include (table 1) [1,3,16]:

- Lactic acidosis – There are numerous conditions that cause L-lactic acidosis (L-lactate is the dominant mammalian isomer of lactate). Lactic acidosis commonly occurs with tissue hypoperfusion that may be secondary to systemic hypotension. Microcirculatory hypoperfusion without overt systemic hypotension, called "cryptogenic shock," can also generate lactic acidosis. In addition, numerous medications may cause an increase in the production of lactic acid. (See "Causes of lactic acidosis".)

- Ketoacidosis – Ketoacidosis results from uncontrolled diabetes mellitus or in association with chronic alcohol abuse. (See "Fasting ketosis and alcoholic ketoacidosis" and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Anion gap metabolic acidosis'.)

- Acute or chronic kidney disease – Patients with severe kidney failure may develop a high anion gap acidosis, resulting from the retention of both hydrogen ions and anions such as sulfate, phosphate, and urate [3,23]. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

- Toxic alcohol ingestion – Ingestion of methanol or ethylene glycol produces high anion gap metabolic acidosis. These alcohols are metabolized to various organic acids; methanol is metabolized to formic acid, and ethylene glycol to glycolic and oxalic acid. Diethylene and propylene glycol may also produce an elevated anion gap acidosis. (See "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis".)

- Salicylate (aspirin) poisoning – Salicylate poisoning impairs oxidative phosphorylation and causes the accumulation of multiple acids including lactic acid and ketoacids. (See "Salicylate (aspirin) poisoning: Clinical manifestations and evaluation".)

- Acetaminophen – Chronic acetaminophen use at therapeutic doses can result in an elevated anion gap metabolic acidosis [24-29]. The accumulating acid is pyroglutamic acid (also called 5-oxoproline). Affected patients are usually women with chronic illness and malnutrition. The pathogenesis is probably related to chronic glutathione and cysteine deficiency. This disorder is distinct from acute acetaminophen overdose, which can generate severe acute liver disease and, in some cases, lactic acidosis.

- D-lactic acidosis – D-lactic acid is generated by bacterial fermentation of ingested, but unabsorbed, carbohydrates. D-lactic acidosis results from excessive absorption of D-lactic acid from the lumen of the gastrointestinal tract, usually in patients with jejunoileal bypass or short bowel syndrome. Several other causes of D-lactic acidosis have been described. The metabolism of propylene glycol (which is used as the solvent for intravenous preparations of several medications, such as lorazepam, and as a less toxic alternative to ethylene glycol in automotive antifreeze) can generate D-lactic acid. Elevated D-lactate acid levels have also been identified in some patients with diabetic ketoacidosis [30,31]. (See "D-lactic acidosis".)

There are other, much less common causes of a high anion gap acidosis. As an example, inherited glutathione synthetase deficiency may result in an acidosis caused by the accumulation of pyroglutamic acid (5-oxoproline), a metabolic product of gamma-glutamylcysteine. This is discussed separately. (See "Rare RBC enzyme disorders", section on 'Glutathione synthetase (GSS) deficiency'.)

In both ketoacidosis and lactic acidosis, the unmeasured anions that accumulate in the body represent "potential bicarbonate" because metabolism of these anions generates bicarbonate. This occurs when the underlying abnormality is corrected (eg, restoration of tissue perfusion in lactic acidosis and volume expansion and insulin therapy in diabetic ketoacidosis). However, the accumulation of unmeasured "potential bicarbonate" anions in these two disorders differs in the following way:

- In patients with ketoacidosis, a large amount of the potential bicarbonate is excreted in the urine as sodium and potassium beta-hydroxybutyrate and acetoacetate. The renal loss of ketoacids increases during therapy because volume expansion with intravenous saline restores the extracellular fluid volume and improves kidney function. This increases the renal loss of potential bicarbonate. The net effect is that most patients with diabetic ketoacidosis convert their anion gap acidosis into a normal anion gap (hyperchloremic) acidosis in response to successful therapy [32]. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Anion gap metabolic acidosis' and "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

- By contrast, in patients with hypoperfusion-induced lactic acidosis, the renal loss of potential bicarbonate is much less marked because kidney function is typically reduced. Thus, lactate anions are not excreted, and, after adequate perfusion is restored, a normal anion gap acidosis does not usually develop.

Causes of hyperchloremic (normal anion gap) metabolic acidosis — As noted above, normal anion gap (hyperchloremic) metabolic acidoses usually result from a loss of bicarbonate or an isolated reduction in renal acid excretion. Loss of bicarbonate-rich fluid can occur in several clinical settings including:

- Diarrhea (see "Acid-base and electrolyte abnormalities with diarrhea", section on 'Acid-base, electrolyte, and volume abnormalities associated with diarrhea')

- Prolonged exposure of urine to colonic or ileal mucosa (in patients who have had ureteral implants into the colon or have a malfunctioning ileal loop bladder) (see "Acid-base and electrolyte abnormalities with diarrhea")

- Proximal (type 2) RTA (table 1) (see "Etiology and diagnosis of distal (type 1) and proximal (type 2) renal tubular acidosis", section on 'Proximal (type 2) RTA')

Impairment of renal acid excretion also produces a normal anion gap metabolic acidosis. The daily metabolism of dietary proteins generates 50 to 100 mEq of acid, mainly sulfuric acid and phosphoric acid [3]. Excretion of these acids can be considered a two-step process. The anions (sulfate and phosphate) are filtered by the glomeruli and excreted as sodium salts. The hydrogen ions are excreted by the distal nephron via the acid secretory process (figure 2). When kidney function is intact, these two processes successfully excrete both the anions and the hydrogen ions of sulfuric and phosphoric acid. However, impaired acid excretion, and therefore metabolic acidosis, can develop in the following settings:

- Acute or chronic kidney disease can, if severe, produce an elevated anion gap metabolic acidosis. Tubular dysfunction decreases hydrogen ion excretion while a pronounced reduction in glomerular filtration rate results in accumulation of anions (such as sulfate and phosphate) that elevate the anion gap. However, a normal anion gap acidosis may develop in patients with mild or moderate kidney function impairment whose defect in distal tubular function is considerably worse than the reduction in glomerular filtration rate. In such patients, glomerular filtration is adequate to permit excretion of the anions as sodium or potassium salts, but the tubular defect impairs acid excretion, and a hyperchloremic acidosis ensues [23,33]. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

- Similar considerations apply when hydrogen ions are retained because of impaired renal acid excretion due to distal (type 1) or type 4 RTA or hypoaldosteronism. In these conditions, a normal anion gap acidosis develops since there is no retention of unmeasured anions [1,3]. (See "Etiology and diagnosis of distal (type 1) and proximal (type 2) renal tubular acidosis" and "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)".)

Combined elevated anion gap and hyperchloremic acidoses — Normal and high anion gap metabolic acidosis can coexist. Three settings in which this can occur are:

- Diarrhea – Diarrhea typically generates a normal anion gap acidosis. However, with severe diarrhea (as can occur in cholera), the development of marked hypovolemia can generate an anion gap metabolic acidosis. This is due to hypoperfusion-induced lactic acidosis, hyperalbuminemia (albumin is negatively charged and accounts for most of the anion gap in normal individuals), and a reduced glomerular filtration rate, which generates hyperphosphatemia and retention of other organic ions [34]. (See "Overview of the causes and treatment of hyperphosphatemia", section on 'Acute extracellular shift of phosphate' and "Acid-base and electrolyte abnormalities with diarrhea", section on 'Serum anion gap in patients with metabolic acidosis due to diarrhea'.)

- Ketoacidosis – The reasons why ketoacidosis can produce both a high anion gap and normal anion gap acidosis are presented above. (See 'Causes of elevated anion gap metabolic acidosis' above.)

- Progression of kidney disease – Early kidney disease generates a nonanion gap, hyperchloremic metabolic acidosis, and this may gradually evolve into an anion gap uremic acidosis [33]. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

Similar considerations apply to D-lactic acidosis and toluene-induced metabolic acidosis. These conditions will increase the anion gap if the acid anions (D-lactate or hippurate) are retained, but a normal anion gap acidosis will evolve if these anions are excreted. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

OVERVIEW OF THERAPY

The treatment of metabolic acidosis varies depending upon the underlying disorder. The general principles of treatment of metabolic acidosis will be reviewed here, including issues related to estimation of the bicarbonate deficit.

The specific approaches to therapy in the most common causes of metabolic acidosis are discussed in detail separately. These include:

- Diabetic ketoacidosis (see "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment")
- Lactic acidosis (see "Bicarbonate therapy in lactic acidosis")
- Chronic kidney disease (see "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease")
- Diarrhea (see "Acid-base and electrolyte abnormalities with diarrhea")
- Renal tubular acidosis (RTA) (see "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis")
- Ingestions, such as aspirin, methanol, and ethylene glycol (see "Salicylate (aspirin) poisoning: Clinical manifestations and evaluation" and "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis")

General approach and rationale — First, whenever possible, the primary focus of therapy for metabolic acidosis should be directed at reversing the underlying pathophysiologic process (see above). Second, it is important to consider acute and chronic forms of metabolic acidosis separately:

Acute metabolic acidosis — We initiate bicarbonate therapy when acute metabolic acidosis has generated severe acidemia (ie, pH less than 7.1). We also generally suggest bicarbonate therapy for patients with less severe acidemia (eg, pH 7.1 to 7.2) who have severe acute kidney

injury (ie, a twofold or greater increase in serum creatinine or oliguria); bicarbonate therapy in such patients can potentially prevent the need for dialysis and may improve survival [35].

The clinical impact and treatment of severe acute metabolic acidosis remain controversial. Experts disagree about the indications for the use of sodium bicarbonate or other buffering agents. Some studies indicate that myocardial depression, decreased catecholamine efficacy, and arrhythmias develop when the pH falls below 7.1. However, these data come mainly from animal or tissue experiments. Human studies of the cardiovascular effects of severe acidemia have generally **not** supported the animal or tissue experimental results. As an example, transient decreases in pH to 6.8 in individuals with diabetic ketoacidosis are not associated with depressed cardiac function [36]. In addition, raising the pH may have adverse consequences including a paradoxical fall in intracellular pH, increased lactate production, and myocardial depression. It is, however, important to recognize that, at a pH below 7.1, small changes in pCO_2 or HCO_3 can have very large pH effects. Thus, many clinicians initiate treatment of metabolic acidosis when the bicarbonate level is very low (eg, <5 mEq/L) and the pH is below 7.1.

We do **not** generally use bicarbonate therapy in patients with less severe acidosis (pH 7.1 or greater), unless the patient also has severe acute kidney injury. The best data come from a randomized trial of critically ill patients with severe metabolic acidosis (most patients had lactic acidosis, and the mean arterial pH was 7.15) [35]. In this trial, bicarbonate therapy (to maintain a pH >7.3) had no overall effect on mortality or organ failure, but, among the subgroup of patients with severe acute kidney injury (defined as a twofold or greater increase in serum creatinine or oliguria), bicarbonate therapy reduced 28-day mortality and the need for dialysis. (See "Bicarbonate therapy in lactic acidosis", section on 'Which patients should receive bicarbonate therapy'.)

Severe and symptomatic acute acidemia can most rapidly be treated by the intravenous administration of sodium bicarbonate. Despite its potential adverse effects, sodium bicarbonate remains the most frequently used alkalinizing agent. Less severe acute metabolic acidosis does not usually require bicarbonate treatment. This is especially the case when "potential" bicarbonate (ie, lactate, ketoacid anions) has been retained and can be converted to bicarbonate when the underlying pathologic derangement has been alleviated or eliminated. Even if the "potential bicarbonate" has been excreted (and a hyperchloremic metabolic acidosis exists), a patient with relatively intact kidney function can restore normal acid-base status in several days by excreting ammonium chloride into the urine.

An alternative alkalinizing agent is tris-hydroxymethyl aminomethane (tromethamine, or THAM), although this drug is not continuously available for use. The potential advantages and disadvantages of this agent are discussed below. (See 'Alternative agent' below.)

Chronic metabolic acidosis — The most common causes of chronic metabolic acidosis are diarrhea, advanced chronic kidney disease, and the various forms of RTA. The indications for treating these disorders are fully discussed in the sections devoted to these disorders. (See "Acid-base and electrolyte abnormalities with diarrhea" and "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease" and "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis".)

Generally, if more normal acid-base parameters can be achieved with exogenous alkali (eg, sodium or potassium bicarbonate, citrate, or analogous salts) without creating other difficulties (such as potassium wasting in disorders such as type 2 or proximal RTA), then such treatment may be helpful. The rational for alkali therapy is summarized here:

- Increasing the bicarbonate concentration reduces or eliminates the need for compensatory hyperventilation and can alleviate the dyspnea experienced by some patients.
- Chronic metabolic acidosis may have adverse effects on muscle function and metabolism, skeletal integrity, hormone levels, and other physiologic parameters. In children, for example, correction of chronic metabolic acidosis restores skeletal growth. (See "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis" and "Approach to the child with metabolic acidosis".)
- Patients with chronic distal (type 1) RTA are likely to develop nephrocalcinosis and calcium-containing kidney stones. This defect can be reversed with adequate bicarbonate replacement. (See "Nephrocalcinosis".)
- Chronic metabolic acidosis in patients with kidney dysfunction may accelerate the progression of their kidney damage, and reversal of the acidosis can slow this process. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

Dosing of alkali therapy (when given)

Bicarbonate — In general, the dose of bicarbonate to be administered is determined empirically. We typically do **not** calculate the virtual bicarbonate distribution space. Although intravenous bicarbonate is sometimes administered to patients with severe acute metabolic acidosis, the therapeutic focus should be on **slowing the rate of acid generation** (ie, correcting the cause of acidosis) rather than administering large amounts of intravenous sodium bicarbonate.

Ampules of hypertonic sodium bicarbonate are available as 8.4 percent (50 mEq/50 mL), 7.5 percent (44.6 mEq/50 mL), and 4.2 percent solutions (25 mEq/50 mL). A variety of oral bicarbonate (or bicarbonate equivalent) preparations are available for use in stable patients with chronic metabolic acidosis (table 2).

- **Acute metabolic acidosis** – In patients with acute metabolic acidosis, intravenous bicarbonate is given if the blood pH is <7.1 or, in some patients, <7.2. The initial goal is a pH >7.2 and/or serum bicarbonate concentration >16 mEq/L. Because of the difficulty in predicting the impact of hypertonic sodium bicarbonate infusions on serum bicarbonate concentrations, we use the following empiric approach:

  - Infuse 2 ampules (100 mL) of 7.5 percent sodium bicarbonate (44.6 mEq/50 mL) over 1 to 2 minutes and remeasure the blood pH and serum bicarbonate concentration (eg, after two hours). If the distribution space is approximately 55 percent of the body weight (as it is in healthy individuals), the serum bicarbonate level should increase by approximately 2 to 3 mEq/L.

  - If the bicarbonate concentration does not increase by this level, then ongoing acid generation is probably expanding the apparent bicarbonate distribution space. Another infusion of 1 to 2 ampules of 7.5 percent sodium bicarbonate can be administered to determine if the bicarbonate concentration can be raised. However, it is important to note that this solution is hypertonic (50 mEq sodium bicarbonate/50 mL = 2000 mOsm/L). Thus, the infusion of this hypertonic sodium bicarbonate will raise the serum sodium concentration and cause movement of water from the intracellular to the extracellular space. If more than two vials are needed, infusion of electrolyte free water should be used to avoid marked hypernatremia. An alternative approach to administering two additional ampules of hypertonic sodium bicarbonate is to add three ampules of 8.4 percent sodium bicarbonate to 1 liter of 5 percent dextrose to generate an intravenous solution containing approximately 150 mEq/L of sodium bicarbonate; this is typically administered over 2 to 4 hours, and further treatment is determined based upon reassessment of the pH and serum bicarbonate.

- **Chronic metabolic acidosis** – When chronic alkali treatment is required, options include the sodium or potassium salts of either bicarbonate or a metabolizable anion such as citrate or lactate (table 2). The potassium salts are indicated when hypokalemia and total body potassium deficits exist. In general, the initial dose is 50 to 100 mEq per day, which is then titrated up, or down, as required. If ongoing bicarbonate losses persist or accelerate, the dose will need to be adjusted accordingly.

When sodium bicarbonate is infused intravenously into the intravascular space, it rapidly distributes throughout the extracellular fluid space. Some bicarbonate will enter the intracellular fluid space, some will be titrated by hydrogen ions released from a variety of body acid-base buffers, and some will be titrated by organic acids that can be produced both as a part of the original pathologic process and in response to the bicarbonate load and increase of pH. Together, the physical distribution of the bicarbonate into these spaces and the disappearance of some bicarbonate as a result of its titration with hydrogen ions can be considered a virtual "space" into which the infused HCO_3 load distributes [37,38]. If the bicarbonate distribution space could be determined, then the quantity of bicarbonate required to elevate the serum bicarbonate concentration by any given amount can be estimated from the bicarbonate deficit:

$$HCO_3 \text{ deficit} = HCO_3 \text{ space} \times HCO_3 \text{ deficit per liter}$$

When the serum bicarbonate concentration is normal or only moderately reduced, the apparent bicarbonate space is approximately 55 percent of lean body weight. Thus, in a healthy 70 kg individual, the infusion of one vial of 8.4 percent sodium bicarbonate will raise the serum bicarbonate concentration by approximately 1.5 mEq/L.

However, for a number of complex reasons related to the body's bicarbonate buffering mechanisms, and because the bicarbonate-carbon dioxide acid-base pair is an "open" system (ie, carbon dioxide can be added or removed in great quantities through ventilation), the bicarbonate space is not fixed; rather, it varies markedly with the initial bicarbonate concentration and the size and potency of the other buffer pools with which it equilibrates. When severe metabolic acidosis exists, the apparent bicarbonate buffer space enlarges markedly, reaching approximately 70 percent of lean body weight when the serum bicarbonate falls below 10 mEq/L and exceeding total body weight when the serum bicarbonate falls below 5 mEq/L [38,39].

Alternative agent — Tromethamine (tris-hydroxymethyl aminomethane; also called THAM, TRIS, and trometamol) is an alternative to sodium bicarbonate. The manufacturer of THAM has not continuously produced the drug, and therefore it is not always available. Although used by some clinicians, the authors of this topic do not administer THAM.

THAM is an amino alcohol that buffers hydrogen ions by virtue of its amine (NH_2) moiety (pKa = 7.7) via the following reactions [40]:

$$THAM\text{-}NH_2 + H^+ = THAM\text{-}NH_3^+$$

or

$$THAM\text{-}NH_2 + H_2O + CO_2 = THAM\text{-}NH_3^+ + HCO_3^-$$

Unlike bicarbonate, which generates carbon dioxide (CO_2) when it reacts with hydrogen ions (H^+), THAM consumes carbon dioxide.

In addition, unlike sodium bicarbonate, THAM is not a sodium salt and therefore does not provide a sodium load.

Renal clearance of protonated THAM salts is slightly greater than renal clearance of creatinine. Thus, THAM can buffer hydrogen ions without generating carbon dioxide but can accumulate when kidney function is reduced. Toxicities include hyperkalemia, hypoglycemia, and respiratory depression; the latter may be due to rapid alkalization of the central nervous system.

THAM has been used to treat severe acidemia due to sepsis, permissive hypercapnia, diabetic ketoacidosis, RTA, gastroenteritis, and drug intoxications [40-43]. However, THAM has **not** been evaluated in clinical trials involving patients with lactic acidosis.

Because of its ability to decrease pCO_2, THAM is an alternative to bicarbonate that may be the preferred buffer in critically ill patients with mixed metabolic and respiratory acidosis. THAM is also used to correct the acidity of acid-citrate-dextrose (ACD) blood in cardiac bypass surgery. THAM is dosed using the following formula:

$$0.3\ M\ THAM\ (mL) = Body\ dry\ weight\ (kg) \times (Desired\ HCO_3 - Actual\ HCO_3) \times 1.1$$

Each 100 mL of THAM contains 3.6 g (30 mEq) in water, and the solution is hypertonic at 389 mosmol/L.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute kidney injury in adults" and "Society guideline links: Toxic alcohol poisoning".)

SUMMARY AND RECOMMENDATIONS

- **Definition** – Metabolic acidosis is defined as a pathologic process that, when unopposed, increases the concentration of hydrogen ions in the body and reduces the HCO_3 concentration. Acidemia (as opposed to acidosis) is defined as a low arterial pH (<7.35), which can result from a metabolic acidosis, respiratory acidosis, or both. Not all patients with metabolic acidosis have a low arterial pH; the pH and hydrogen ion concentration also depend upon the coexistence of other acid-base disorders. Thus, the pH in a patient with metabolic acidosis may be low, high, or normal. (See 'Definition' above.)

- **Etiology** – Metabolic acidosis can be produced by three major mechanisms (table 1) (see 'Pathogenesis' above):

  - Increased acid generation due, for example, to lactic acidosis or ketoacidosis (see 'Increased acid generation' above)

  - Loss of bicarbonate due, for example, to diarrhea (see 'Loss of bicarbonate' above)

  - Diminished renal acid excretion due, for example, to renal tubular acidosis (RTA) (see 'Diminished renal acid excretion' above)

- **Diagnosis** – A metabolic acidosis is diagnosed when the serum pH is reduced and the serum bicarbonate concentration is abnormally low (often defined as <22 mEq/L, but the threshold may vary across clinical laboratories). When a simple metabolic acidosis exists, the serum pH and bicarbonate concentration will both be reduced. Although both measurements may be needed, under many clinical circumstances the diagnosis can be made on the basis of a reduced bicarbonate concentration alone (provided that chronic respiratory alkalosis can be ruled out on clinical grounds). The lower normal range limit for a peripheral venous bicarbonate measurement is generally 22 mEq/L, but this may vary in different laboratories. However, if metabolic acidosis coexists with respiratory acidosis or metabolic alkalosis, then the serum bicarbonate may be normal or elevated. The bicarbonate concentration, serum pH, and other electrolyte measurements will often be required to correctly diagnose such complicated mixed acid-base disorders. In such patients, a metabolic acidosis is diagnosed when the serum bicarbonate is lower than it should be, even if the value falls within the normal range. (See 'Diagnosis' above.)

- **Evaluation** – Serum or plasma electrolytes, calculation of the anion gap, and a detailed history and physical examination are frequently sufficient to determine the cause of the metabolic acidosis and guide therapy. However, in complicated patients, a definitive evaluation of metabolic acidosis usually requires the following (see 'Evaluation' above):

- Measurement of the arterial pH and pCO_2 (see 'Measurement of the arterial pH and pCO2' above)
- Determining whether respiratory compensation is appropriate (see 'Determination of whether respiratory compensation is appropriate' above)
- Assessment of the serum anion gap to help identify the cause of acidosis (table 1) and calculation of the delta anion gap/delta HCO_3 ratio in patients who have an elevated anion gap (see 'Assessment of the serum anion gap' above)

- **Management** – The treatment of metabolic acidosis varies depending upon the underlying disorder. The specific approaches to therapy in the most common causes of metabolic acidosis are discussed in detail separately. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment" and "Bicarbonate therapy in lactic acidosis" and "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease" and "Acid-base and electrolyte abnormalities with diarrhea" and "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis" and "Salicylate (aspirin) poisoning: Clinical manifestations and evaluation" and "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis".)

  After addressing the underlying pathophysiologic process, the general approach to treatment of adults with metabolic acidosis depends upon whether or not the metabolic acidosis is acute or chronic (see 'General approach and rationale' above):

  - Acute metabolic acidosis – The appropriate treatment of severe acute metabolic acidosis is controversial, and experts disagree about the indications for the use of sodium bicarbonate or other buffering agents. Our general approach is as follows (see 'Acute metabolic acidosis' above):

    - In patients with acute metabolic acidosis that has generated severe acidemia (arterial pH less than 7.1), we suggest sodium bicarbonate therapy rather than no alkali therapy (**Grade 2C**). The goal of bicarbonate therapy is to maintain the arterial pH above 7.1 until the primary process causing the metabolic acidosis can be reversed.

    - In patients with acute metabolic acidosis that has generated less severe acidemia (ie, arterial pH 7.1 to 7.2), we suggest sodium bicarbonate therapy, rather than no alkali therapy, if severe acute kidney injury is also present (defined as a twofold or greater increase in serum creatinine or oliguria) (**Grade 2B**). We generally target a pH of 7.3 or higher in such patients. We do **not** typically give sodium bicarbonate

to patients with arterial pH 7.1 or higher if they do not have severe acute kidney injury.

- Chronic metabolic acidosis – The most common causes of chronic metabolic acidosis are diarrhea, advanced chronic kidney disease, and the various forms of RTA. The indications for treating these disorders are fully discussed in the sections devoted to these disorders. However, if more normal acid-base parameters can be achieved with exogenous alkali (eg, sodium or potassium bicarbonate or citrate) without creating other difficulties (such as potassium wasting in disorders such as type 2 or proximal RTA), then such treatment may be helpful. (See "Acid-base and electrolyte abnormalities with diarrhea" and "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease" and "Treatment of distal (type 1) and proximal (type 2) renal tubular acidosis".)

- **Dosing of alkali therapy (when given)**

  - Acute severe metabolic acidosis – When the decision to administer sodium bicarbonate is made for a patient with severe acute metabolic acidosis, it is usually accomplished with 50 mL ampules of hypertonic sodium bicarbonate. The blood pH and bicarbonate concentration are monitored to determine if additional bicarbonate is needed. (See 'Bicarbonate' above.)

  - Chronic alkali therapy – When chronic alkali treatment is required, options include the sodium or potassium salts of either bicarbonate or a metabolizable anion such as citrate or lactate (table 2). The potassium salts are indicated when hypokalemia and total body potassium deficits exist. In general, the initial dose is 50 to 100 mEq per day, which is then titrated up or down as required. If ongoing bicarbonate losses persist or accelerate, the dose will need to be adjusted accordingly. (See 'Bicarbonate' above.)

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Topic 2291 Version 45.0

GRAPHICS

Major causes of metabolic acidosis

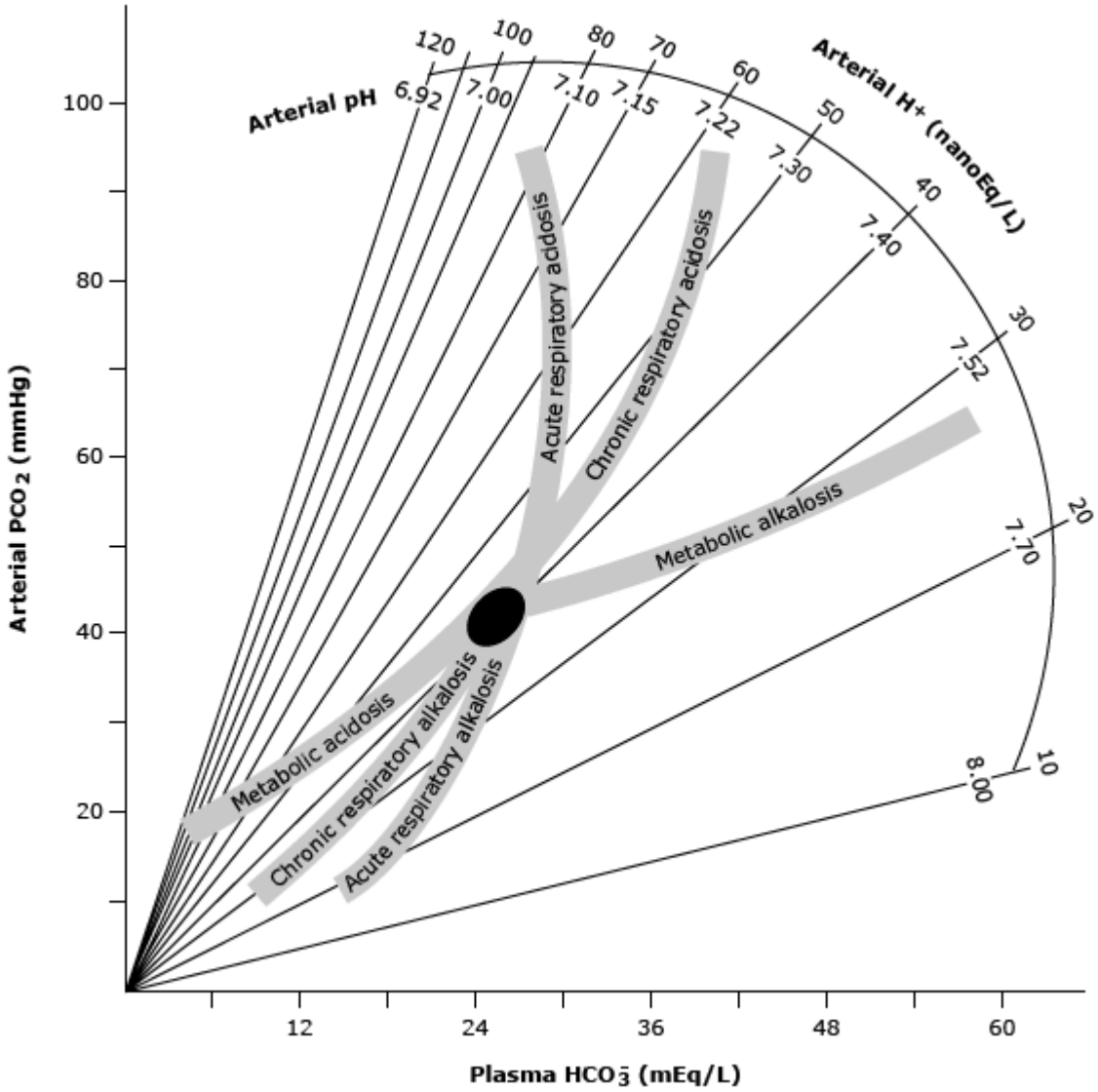
Mechanism of acidosis	Increased AG	Normal AG
Increased acid production	Lactic acidosis	
	Ketoacidosis	
	Diabetes mellitus	
	Starvation	
	Alcohol associated	
	Ingestions	
	Methanol	
	Ethylene glycol	
	Salicylates	
	Toluene (if early or if kidney function is impaired)	Toluene ingestion (if late and if kidney function is preserved; due to excretion of sodium and potassium hippurate in the urine
	Diethylene glycol	
	Propylene glycol	
	D-lactic acidosis	A component of non-AG metabolic acidosis may coexist due to urinary excretion of D-lactate as Na and K salts (which represents potential HCO_3)
	Pyroglutamic acid (5-oxoproline)	
Loss of bicarbonate or bicarbonate precursors		Diarrhea or other intestinal losses (eg, tube drainage)
		Type 2 (proximal) RTA
		Posttreatment of ketoacidosis
		Carbonic anhydrase inhibitors
		Ureteral diversion (eg, ileal loop)
Decreased renal acid excretion	Severe kidney dysfunction (eGFR <15 to 20 mL/min/1.73 m^2)	Moderate kidney dysfunction (eGFR >15 to 20 mL/min/1.73 m^2
		Type 1 (distal) RTA (hypokalemic)

		Hyperkalemic RTA
		Type 4 RTA (hypoaldosteronism)
		Voltage defect
Large volume infusion of normal saline		Diffusion acidosis

AG: anion gap; RTA: renal tubular acidosis.

Graphic 77464 Version 15.0

Expected compensation ranges for simple acid-base disorders



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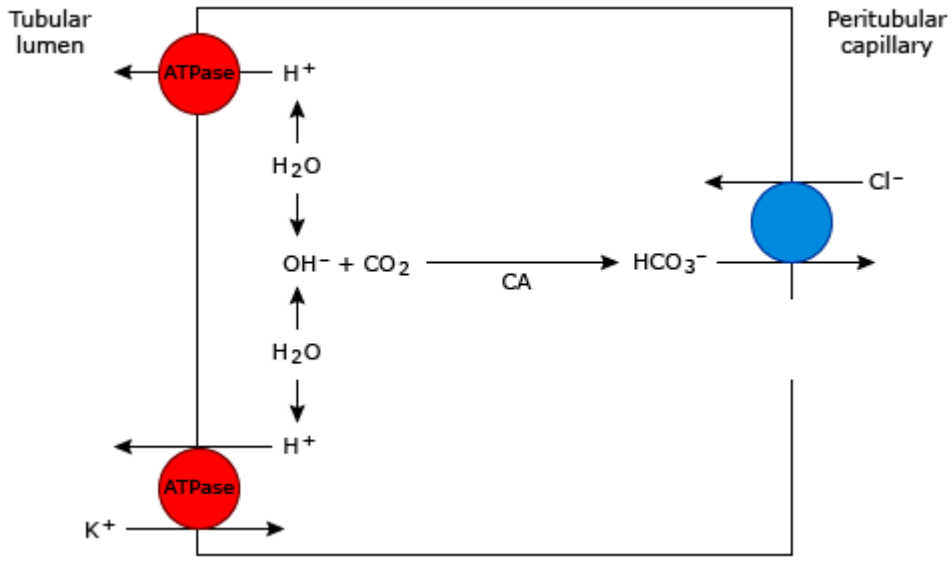
Graphic 79833 Version 9.0

Acid-secreting type A intercalated cells



Transport mechanisms involved in hydrogen secretion and HCO_3^- and K^+ reabsorption in type A intercalated cells, which are present from the late distal convoluted tubule to the initial portion of the inner medullary collecting duct. Water within the cell dissociates into H^+ and OH^- ions. The former are secreted into the lumen by H-ATPase pumps in the luminal membrane, where they combine with urinary buffers to generate titratable acid (eg, convert HPO_4^{-2} to $H_2PO_4^-$) and convert NH_3 to NH_4^+. The OH^- ions in the cell combine with CO_2 to form HCO_3^- in a reaction catalyzed by carbonic anhydrase (CA). Driven by their electrochemical concentration gradients, cellular bicarbonate enters the peritubular capillaries in exchange for extracellular chloride via Cl-HCO_3 exchangers on the basolateral membrane. H-K-ATPase pumps, which secrete H^+ and reabsorb K^+, are also present in the luminal membrane of the type A intercalated cells. The number and activity of these pumps are increased by K^+ depletion, suggesting that they may be important for K^+ conservation.

Graphic 51361 Version 9.0

Oral bicarbonate and bicarbonate equivalent salts used for systemic and/or urinary alkalinization

Generic name	Common brand names (US) and form	Electrolyte and bicarbonate content*
Potassium citrate	Urocit-K (tablet, controlled release)	Tablet: Each pill contains 5, 10, or 15 mE potassium and delivers the equivalent o 5, 10, or 15 mEq bicarbonate.
Potassium citrate-citric acid	Polycitra K, Cytra-K (powder or solution)	Powder: Each packet contains 30 mEq potassium and delivers the equivalent o 30 mEq of bicarbonate. Solution: Each 5 mL contains 10 mEq potassium and delivers the equivalent o 10 mEq bicarbonate.
Sodium citrate-citric acid	Bicitra, Cytra-2, Oracit, Shohl's solution modified (solution)	Solution: Each 5 mL contains 5 mEq sodium and delivers the equivalent of 5 mEq bicarbonate.
Sodium citrate-potassium citrate-citric acid	Polycitra, Cytra-3 (solution, syrup)	Solution (syrup): Each 5 mL contains 5 mEq potassium and 5 mEq sodium and delivers equivalent of 10 mEq bicarbonate.
Potassium bicarbonate-potassium citrate	Klor-Con/EF, Effer-K, K-Effervescent (effervescent tablet)	Effervescent tablet (diluted in water): Each tablet contains 10, 20, or 25 mEq potassium and delivers approximately 10, 20 or 25 mEq bicarbonate or equivalent.
Sodium bicarbonate	Tablet	Tablet: Each 650 mg tablet contains 7.7 mEq of sodium and 7.7 mEq of bicarbonate (325 mg tablet contains 3.8 mEq of bicarbonate).
	Baking soda (powder)	Powder: One-half teaspoonful (2.4 grams) contains approximately 29 mEq of sodium and 29 mEq bicarbonate (roughly equivalent to three 650 mg sodium bicarbonate tablets).[1]

For approach to product selection, dosing recommendations, and target urine pH for alkalinization therapy, refer to separate UpToDate clinical reviews of uric acid nephrolithiasis and cystine stones.

* Orally administered citrate is a bicarbonate equivalent.

Reference:

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Graphic 118006 Version 7.0