REVIEWS

Metabolic acidosis: pathophysiology, diagnosis and management

Jeffrey A. Kraut and Nicolaos E. Madias

Abstract | Metabolic acidosis is characterized by a primary reduction in serum bicarbonate (HCO_3^-) concentration, a secondary decrease in the arterial partial pressure of carbon dioxide ($PaCO_2$) of ~1 mmHg for every 1 mmol/l fall in serum HCO_3^- concentration, and a reduction in blood pH. Acute forms (lasting minutes to several days) and chronic forms (lasting weeks to years) of the disorder can occur, for which the underlying cause/s and resulting adverse effects may differ. Acute forms of metabolic acidosis most frequently result from the overproduction of organic acids such as ketoacids or lactic acid; by contrast, chronic metabolic acidosis often reflects bicarbonate wasting and/or impaired renal acidification. The calculation of the serum anion gap, calculated as $[Na^+] - ([HCO_3^-] + [Cl^-])$, aids diagnosis by classifying the disorders into categories of normal (hyperchloremic) anion gap or elevated anion gap. These categories can overlap, however. Adverse effects of acute metabolic acidosis primarily include decreased cardiac output, arterial dilatation with hypotension, altered oxygen delivery, decreased ATP production, predisposition to arrhythmias, and impairment of the immune response. The main adverse effects of chronic metabolic acidosis are increased muscle degradation and abnormal bone metabolism. Using base to treat acute metabolic acidosis is controversial because of a lack of definitive benefit and because of potential complications. By contrast, the administration of base for the treatment of chronic metabolic acidosis is associated with improved cellular function and few complications.

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Learning objectives

Upon completion of this activity, participants should be able to:
1 Describe the pathophysiology of metabolic acidosis.
2 Diagnose the cause of metabolic acidosis effectively.
3 Distinguish the causes of metabolic acidosis associated with an elevated anion gap.
4 Treat metabolic acidosis effectively.

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Competing interests

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Introduction

Metabolic acidosis is characterized by a primary reduction in the serum concentration of bicarbonate (HCO_3^-), a secondary decrease in the arterial partial pressure of carbon dioxide ($PaCO_2$), and a reduction in blood pH. Metabolic acidosis frequently occurs as a part of mixed acid–base disorders, especially among the critically ill. Metabolic acidosis can be acute (lasting minutes to several days) or chronic (lasting weeks to years) in duration. Acute metabolic acidosis is relatively common among seriously ill patients, with one study showing that the disorder affected approximately 64% of patients in a large intensive care unit in the US.[1] Chronic metabolic acidosis is less common; only 1.9% of more than 15,000 individuals surveyed in the NHANES III study[2] had a serum HCO_3^- concentration below 22 mmol/l, although this value rose to 19% in patients with an estimated glomerular filtration rate (eGFR) within the range 15–29 ml/min/1.73 m². Therefore, the frequency of chronic metabolic acidosis might increase with the anticipated rise in chronic kidney disease (CKD) in our aging population. Metabolic acidosis—acute or chronic—can have considerable adverse effects on cellular function and can contribute to increased morbidity and mortality.[1,3–5]

In this Review, we summarize current views on the pathogenesis, diagnosis, adverse effects, and management of metabolic acidosis. Owing to space constraints, we address the causes of this acid–base disorder only briefly.

Pathophysiology of metabolic acidosis

Metabolic acidosis occurs when either an increase in the production of nonvolatile acids or a loss of bicarbonate from the body overwhelms the mechanisms of acid–base homeostasis or when renal acidification mechanisms are compromised.

Acid production

Under normal dietary and metabolic conditions, average net acid production is 1 mmol/kg per day in adults[6] and 1–3 mmol/kg per day in infants and children.[7] Abnormalities in intermediary metabolism, such as those that occur in lactic acid synthesis or ketogenesis, and ingestion of substances that are metabolized to organic acids, such as methanol or ethylene glycol, can increase acid production severalfold.

Renal regulation of acid–base balance

To maintain a normal acid–base balance, each day the renal tubules must quantitatively reabsorb the filtered HCO_3^- (~4,500 mmol) and synthesize sufficient HCO_3^- to neutralize the endogenous acid load. The details of the renal regulation of acid–base balance have been reviewed in depth elsewhere[8,9] and will be addressed only briefly here.

The majority (80–85%) of filtered HCO_3^- is reabsorbed in the proximal convoluted tubule (PCT) via the NHE3 isoform (90%) of the Na^+/H^+ exchanger and a proton-translocating ATPase (H^+-ATPase; 10%).[9] Carbonic anhydrase II (CA II) in the PCT facilitates the splitting of cytosolic H_2CO_3 into H^+ and HCO_3^-, thus providing the protons for secretion into the lumen. The HCO_3^- formed exits the cell via the basolateral electrogenic Na^+/HCO_3^- co-transporter, SLC4A4 (also known as kNBCe1). Luminally situated CA IV enhances dissociation of luminal H_2CO_3 into CO_2 and H_2O, which prevents a buildup of a proton gradient that would slow the process. Major determinants of HCO_3^- reabsorption include luminal HCO_3^- concentration, luminal pH, luminal flow rate, peritubular partial pressure of CO_2 (pCO_2), and luminal and peritubular concentrations of angiotensin II.[9,10] Defective or absent activity of CA II or CA IV,[11] or mutations in the SLC4A4 gene,[12] lead to impaired HCO_3^- reabsorption and can therefore cause proximal renal tubular acidosis (RTA).

HCO_3^- that escapes the PCT is reabsorbed in the thick ascending limb of the loop of Henle via the NHE3 Na^+/H^+ exchanger and an electrogenic H^+-ATPase, and is also reabsorbed in the collecting duct via an electrogenic H^+-ATPase and possibly an electroneutral H^+/K^+-ATPase.[13,14] With normal renal acidification mechanisms, little HCO_3^- is excreted in the urine and fasting urine pH is usually below 6.0.

New HCO_3^- is generated by processes involving both the PCT and collecting duct.[8,15] The bulk of the HCO_3^- is generated in the PCT as a result of NH_3 production and its excretion in the urine as NH_4^+. Glutamine is metabolized by glutaminase to generate NH_3 and HCO_3^-. The HCO_3^- formed exits the cell via the Na^+/HCO_3^- SLC4A4 co-transporter.[9] NH_3 can

Key points

- Categorizing metabolic acidosis into acute and chronic varieties can be valuable for anticipating adverse effects and for determining the risks and benefits of therapy

- A systematic approach to diagnosis of metabolic acidosis is valuable; use of the serum anion gap is an important initial tool although its limitations should be understood

- The adverse effects of acute metabolic acidosis primarily involve the cardiovascular system, whereas the adverse effects of chronic metabolic acidosis primarily involve the musculoskeletal system

- The treatment of acute metabolic acidosis with the administration of base has not proven beneficial in improving cardiovascular function; alternative therapies are needed

- The treatment of chronic metabolic acidosis with the administration of base is beneficial but the goal of therapy remains unclear

enter the lumen passively and is also secreted as NH_4^+ via the NHE3 Na^+/H^+ exchanger,[16] possibly under the influence of angiotensin II.[16] NH_4^+ leaving the PCT is reabsorbed in the medullary thick ascending limb of the loop of Henle via the $Na^+/K^+/2Cl^-$ co-transporter, a process that increases the medullary concentration of NH_4^+ and NH_3, thereby resulting in a concentration gradient that favors entry of NH_3 into the lumen of the collecting duct.[17] Contrary to older beliefs that NH_3 enters the lumen at this site solely by passive diffusion, recent studies suggest that a highly regulated, active process exists. Although NH_3 can enter the lumen via nonionic diffusion, it seems that it is predominantly transported on one of the Rhesus-like proteins, RhCG, localized to the luminal membrane of the collecting duct.[18] Secreted NH_3 is then trapped as NH_4^+ as a result of urine acidification. Metabolic acidosis augments NH_3 production, in part via the decreased pH and the increased production of glucocorticoids.[15]

New HCO_3^- is also returned to the blood as a result of titratable acid formation throughout the nephron. Protons secreted into the lumen largely combine with HPO_4^{2-} to form $H_2PO_4^-$. The quantity of HCO_3^- returned to the blood by this mechanism is fixed by the urine pH level achieved (lowest pH achievable is 4.5–5.0) and the quantity of phosphate excreted in the urine. The latter is dependent on the filtered load of phosphate and the fractional reabsorption of phosphate by the renal tubules. This process is not, therefore, a very adaptable one for altering HCO_3^- generation.

Protons entering the luminal fluid of the collecting duct to combine with NH_3 and titratable acid are secreted via the H^+-ATPase[19] and possibly an H^+/K^+-ATPase,[14] both localized to the luminal membrane of α-intercalated cells. The HCO_3^- formed returns to the blood via the basolateral Cl^-/HCO_3^- anion exchanger (AE1). Pendrin, a Cl^-/HCO_3^- exchanger that is localized to the apical surface of β-intercalated cells, secretes HCO_3^- into the lumen, thereby reducing net proton transport.[20] The activity of pendrin is reduced in metabolic acidosis.[21]

The rate at which the H^+-ATPase transports H^+ depends on the number of proton pumps inserted into

the apical membrane and the electrochemical potential across the collecting duct. The electrochemical potential across the collecting duct is dependent on the rate of the Cl^--independent Na^+ transport, which is in turn affected by the quantity of Na^+ reaching the collecting duct and the level of aldosterone (which enhances Na^+ reabsorption).[22] The excretion of acid by the collecting duct is tightly regulated by additional systemic and local factors, including angiotensin II, calcium-sensing receptors (CaSRs), extracellular Ca^{2+}, pH, and pCO_2.[8]

Dysfunction of the H^+-ATPase, the AE1, and possibly the H^+/K^+-ATPase, and decreased aldosterone levels or resistance to its action can reduce net acid excretion and lead to distal renal tubular acidosis.[8,19] However, a reduction in net acid excretion is more commonly caused by decreased NH_3 production (associated with CKD), rather than by a defect in the H^+-ATPase, AE1, or aldosterone.[3,23]

Diagnosis of metabolic acidosis

A systematic approach is effective in the diagnosis of all acid–base disorders, including metabolic acidosis.[24] As the secondary ventilatory response to metabolic acidosis is an integral part of the disorder, documenting the presence and magnitude of the ventilatory response is an appropriate next step after the diagnosis of metabolic acidosis has been established.

Secondary ventilatory response

Acidemia engendered by metabolic acidosis promptly triggers hyperventilation that decreases $PaCO_2$.[25,26] Acutely, this hypocapnia is beneficial, blunting the decrease in blood pH.[27] However, results of studies in dogs have led to the theory that the secondary decrement in $PaCO_2$ can further reduce serum HCO_3^- concentration through an indiscriminant renal response to hypocapnia.[27] This renal response is clearly maladaptive as it reduces the protection of systemic acidity afforded acutely by secondary hypocapnia; under certain circumstances, this response might result in a more acidic pH than would occur in the complete absence of hyperventilation. Indeed, the hypobicarbonatemia of chronic metabolic acidosis seems to be a composite of the metabolic process itself (acid load) and the associated chronic hypocapnia.[27]

Once a steady state ensues, a predictable relationship between change in (Δ) $PaCO_2$ and Δ HCO_3^- concentration exists in uncomplicated metabolic acidosis.[26–28] In humans with mild metabolic acidosis lasting 8 h or less, the slope of this relationship is 0.85.[26] When the metabolic acidosis is prolonged for approximately 24 h or longer, the expected $PaCO_2$ for any value of stable serum HCO_3^- concentration can be derived using the following formula, familiarly referred to as Winter's formula:[25,29]

$$PaCO_2 = 1.5[HCO_3^-] + 8 \pm 2$$

Other studies have indicated that the appropriate Δ $PaCO_2$ can be calculated by multiplying the Δ HCO_3^- concentration by 1.2.[30]

In summary, given that reported Δ $PaCO_2/\Delta$ HCO_3^- values have a small range (0.85–1.2),[25,26,28–30] a slope of 1 seems reasonable for clinical use. A Δ $PaCO_2$ greater than anticipated indicates the presence of a coexisting respiratory alkalosis. Conversely, if Δ $PaCO_2$ is less than expected, a coexisting respiratory acidosis is present.

Once it has been determined whether metabolic acidosis is present alone or with a coexisting respiratory disturbance, the cause of the metabolic acidosis should be explored. First, a good patient history should be obtained and a complete physical examination performed to detect clues to a particular disorder. Next, the serum anion gap should be calculated and, when appropriate, the ratio of the Δ anion gap to the Δ HCO_3^- concentration should be determined.[24,31–33]

Serum anion gap

The serum anion gap, defined as $[Na^+] - ([Cl^-] + [HCO_3^-])$, is a valuable diagnostic tool as the various disorders that produce metabolic acidosis can affect the serum anion gap differently. No change in the anion gap is observed in some disorders (normal anion gap or hyperchloremic acidosis), whereas in other disorders the serum anion gap is increased (high anion gap metabolic acidosis).[32,33] Mixed normal and high anion gap patterns are also common. The normal range for the serum anion gap is relatively wide (6–10 mmol/l), a finding that reflects the biologic variability of its constituents. In addition, mean values from different clinical laboratories vary: mean serum anion gap was 11 ± 2.5 mmol/l in one laboratory[34] and 6 ± 3 mmol/l in another.[35] Lower mean values result from the higher serum Cl^- concentration obtained when using an ion-specific electrode.[35] Knowledge of the mean and range of normal values for the serum anion gap for a particular laboratory and the baseline value of an individual's anion gap are therefore necessary for optimal interpretation of a change in value.

Several factors can alter the serum anion gap. This parameter is reduced by ~2.3 mmol/l for every 10 g/l decrease in serum albumin concentration.[36] The accumulation of cationic paraproteins, bromide, or iodide in the serum can lower the anion gap or even render it negative.[32] By contrast, the accumulation of anionic paraproteins or the development of hyperphosphatemia can raise the serum anion gap.[32,37] Indeed, most cases of a very high serum anion gap (that is, values >45 mmol/l) are associated with severe hyperphosphatemia.[37] However, the most common cause of an elevated serum anion gap is the accumulation of organic or inorganic anions in metabolic acidosis.

The impact of acid accumulation on the anion gap has been conceptualized as follows. If the acid accumulating in blood is hydrochloric acid, then no change in anion gap would be expected (normal anion gap or hyperchloremic metabolic acidosis) because the retained Cl^- is stoichiometrically equivalent to the HCO_3^- titrated by the retained protons. The serum anion gap in this type of acidosis can actually fall slightly owing to acidic titration of circulating proteins.[38] On the other hand, if the accumulating acid contains an anion other than Cl^- (as

is the case with beta-hydroxybutyrate, for example), then the fall in serum HCO_3^- concentration is associated with an elevation in the anion gap (high anion gap metabolic acidosis).[33] When the Δ HCO_3^- concentration exceeds the Δ anion gap, one can infer that a coexisting hyperchloremic acidosis is present. However, if the Δ HCO_3^- concentration is lower than the Δ anion gap, a coexisting metabolic alkalosis (or other hyperbicarbonatemic disorder) is thought to be present.[31,32]

As discussed in detail elsewhere,[31,32,39] the evolution of the relationship between the Δ anion gap and the Δ HCO_3^- concentration with organic acidosis is more complex than is suggested by this analysis. Factors involved in determining this relationship include the spaces of distribution of the involved anion/s and protons, the rates of urinary anion excretion and renal generation of HCO_3^-, and the quantity of infused Cl^--containing fluids.[40] As a consequence, the Δ anion gap/Δ HCO_3^- concentration is typically 1:1 in patients with ketoacidosis, is often greater than 1:1 (and can be as high as 1.6–1.8:1) in patients with lactic acidosis, and is usually less than 1:1 in patients with toluene intoxication and in some cases of diabetic ketoacidosis.[32,40]

The characterization of the anion gap pattern has implications for not only diagnosis, but also for treatment. Increments in the serum anion gap related to the accumulation of organic anions represent potential sources of base. Once the metabolic disturbance is corrected, accumulated anions will be converted to equivalent quantities of base and must be taken into account during treatment (see below).

Additional diagnostic studies

Box 1 shows studies that should be performed in the evaluation of both high anion and normal anion gap metabolic acidosis. The measurement of serum and urine ketones, serum lactate, serum creatinine, serum salicylates, serum osmolality and osmolal gap, and in some cases, serum levels of toxic alcohols and urinary concentrations of organic acids, will detect more than 90% of the causes of a high anion gap metabolic acidosis. In some instances, the nature of the accumulating acid will defy even sophisticated studies, such as high performance liquid chromatography.[41]

The measurement of serum and urinary ketones will usually identify ketoacidosis, but the test for ketones recognizes only acetoacetate. Thus, in alcoholic ketoacidosis or in cases where lactic acidosis coexists (that is, in disorders that favor beta-hydroxybutyrate formation), a trace positive or even a negative reading can be obtained. A serum lactate concentration >5 mmol/l will identify patients with classic type A lactic acidosis. However, the routine test for lactate detects only the L-isomer; a specialized test is required to detect the D-isomer present in D-lactic acidosis.[42]

The metabolites of certain toxic alcohols produce metabolic acidosis. As these alcohols have a low molecular weight (ranging from 32 kDa to 106 kDa), their accumulation substantially elevates serum osmolality and causes a disparity between the estimated and measured serum

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Box 1 | Tests useful in the DD of metabolic acidosis

High anion gap metabolic acidosis
- Serum and urine ketones
- Serum creatinine
- Serum L-lactate
- Serum D-lactate
- Serum osmolality
- Serum toxic alcohols*
- Urine microscopy for crystals*
- Wood's lamp examination of urine*
- Urine organic acids

Normal anion gap metabolic acidosis
- Serum potassium
- Serum creatinine
- Urine electrolytes‡
- Urine osmolality§
- Urine pH
- Fractional excretion of HCO_3^-
- Urine urea nitrogen§
- Urine glucose§

*Useful in cases of suspected toxic alcohol ingestion.
‡Needed for the calculation of urine anion and osmolar gaps.
§Needed for the calculation of urine osmolal gap. Abbreviations: DD, differential diagnosis; HCO_3^-, bicarbonate.

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osmolality, termed the osmolal gap. Serum osmolality can be estimated using the following formula:

$$\text{Serum osmolality (mOsm/l)} = 2 \times [Na^+] \text{ (mmol/l)} + [\text{blood urea nitrogen}] \text{ (mg/dl)}/2.8 + [\text{glucose}] \text{ (mg/dl)}/18$$

Normally, the difference between the estimated serum osmolality and that measured by freezing point depression is ≤10 mOsm/l (≤10 mmol/kg). A small increment in the osmolal gap can be seen in ketoacidosis, lactic acidosis, and chronic renal failure.[43] However, a serum osmolal gap >20 mOsm/l (>20 mmol/kg) invariably indicates the accumulation of one of the toxic alcohols or ethanol.[44] Notably, the absence of an increment in the serum osmolality does not exclude toxic alcohol ingestion. If sufficient time has elapsed for most of the parent alcohol to be metabolized into organic acids, serum osmolality can only be minimally perturbed.[44,45] The measurement of ethanol, methanol, ethylene glycol, diethylene glycol, and in some instances propylene glycol, is indicated in the presence of an increased serum osmolal gap or when toxic alcohol intoxication is suspected on the basis of clinical findings. Microscopic examination of the urine for calcium oxalate crystals or use of the Wood's lamp examination to detect fluorescence of the urine can be helpful in cases where ethylene glycol toxicity is suspected, although these methods do have limitations, including a potential for false-negative and false-positive results.[46]

In patients who have been receiving acetaminophen and have an unexplained high anion gap metabolic

Box 2 | Causes of metabolic acidosis

High anion gap metabolic acidosis
- Acute kidney injury
- Chronic kidney disease
- Diabetic ketoacidosis*
- Alcoholic ketoacidosis
- Lactic acidosis (L-lactic acidosis and D-lactic acidosis*)
- Salicylate intoxication
- Toxic alcohol intoxication (methanol, ethylene glycol, diethylene glycol or propylene glycol)
- Pyroglutamic acidosis
- Fasting ketoacidosis
- Toluene intoxication*

Normal (hyperchloremic) anion gap metabolic acidosis associated with normal or high serum K^+
- Administration of HCl or precursors
- Administration of cationic amino acids
- Chronic kidney disease
- Adrenal insufficiency (primary or secondary)
- Hyporeninemic hypoaldosteronism
- Hyperkalemic distal RTA
- Pseudoaldosteronism type I
- Pseudoaldosteronism type II (Gordon's syndrome)
- Drugs (spironolactone, prostaglandin inhibitors, triamterene, amiloride, trimethoprim, pentamidine, ciclosporin)

Normal (hyperchloremic) anion gap metabolic acidosis associated with low serum K^+
- Diarrhea
- Intestinal, pancreatic, or biliary fistulae
- Proximal RTA
- Distal RTA
- Ureterosigmoidostomy
- Ureteroileostomy
- Diabetic ketoacidosis*
- Toluene intoxication*
- D-Lactic acidosis*

*Can have a high anion gap, a normal anion gap, or a mixed pattern. Abbreviations: HCl, hydrochloric acid; RTA, renal tubular acidosis.

acidosis, the detection of 5-oxoproline on a urinary screen for organic acids indicates a diagnosis of pyroglutamic acidosis.[47]

The measurement of serum potassium and serum creatinine levels, and determination of the urine anion and/or osmolal gaps and urine pH, are the most helpful studies for the differential diagnosis of hyperchloremic acidosis. The measurement of serum potassium level is helpful because some disorders impair potassium excretion thereby causing hyperkalemia, whereas others cause urinary or gastrointestinal potassium wasting, which results in hypokalemia.

Indices of renal acidification can determine whether or not the kidney contributes to generation of the acidosis. The measurement of urine pH in the presence of hypobicarbonatemia is often used to assess renal acidification, with a urine pH below 5.3–5.5 indicating normal acidification and a value above 5.5 reflecting impaired acidification. However, urine pH value can in some instances be misleading. For example, urine pH is often above 6.0 in diarrhea-associated metabolic acidosis, even though NH_4^+ excretion is abundant (a reflection of the robust production of NH_3).[48,49] Conversely, urine pH is always below 5.5 in hyporeninemic hypoaldosteronism, even though NH_4^+ excretion is low (reflecting low production of NH_3).[50]

Ammonia constitutes the most important urinary buffer; therefore, the measurement of urinary ammonium excretion is another method of assessing renal acidification. As the level of urinary ammonium is not easily measured, the urine anion and osmolal gaps were developed to indirectly estimate its concentration. The urine anion gap $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$, is determined using values from a spot urine specimen.[51] Bicarbonate can be omitted when urine pH is below 6.5. With normal acidification, urinary NH_4^+ and the accompanying Cl^- levels will increase during metabolic acidosis. As a result, urinary Cl^- level will exceed the sum of $Na^+ + K^+$, leading to a urine anion gap ≥ -30 mmol/l.[48,52] Less-negative values or a positive value suggests reduced NH_4^+ excretion. However, if NH_4^+ is excreted with anions other than Cl^- (as occurs in ketoacidosis), the urine anion gap can be positive even though urinary NH_4^+ excretion is increased.[52,53] In such cases, the urine osmolal gap can be calculated using the following equation:[24,52]

Urine osmolal gap = measured urine osmolality – 2 $([Na^+] + [K^+]) + [$urea nitrogen$]/2.8 + [$glucose$]/18$.

Dividing the obtained value by two gives an estimate of total NH_4^+ excretion. A low urinary ammonium excretion in the presence of a urine pH above 5.5 is consistent with various types of distal RTA, including aldosterone resistance.[54] A low urinary ammonium excretion in the presence of a urine pH below 5.5 can be observed in metabolic acidosis of CKD and that of hypoaldosteronemic states.[3]

If proximal RTA is suspected, the diagnosis can be confirmed by measuring the fractional excretion of HCO_3^- when serum HCO_3^- concentration is raised to 24 mmol/l. A value >20% is diagnostic of proximal RTA.

Causes of metabolic acidosis
The causes of metabolic acidosis, both high anion gap and normal anion gap varieties, are shown in Box 2. Although such categorization is useful, some disorders, such as ketoacidosis, can manifest either a normal or a high anion gap pattern, and can therefore be properly placed in either category.

High anion gap metabolic acidosis
Both acute kidney injury and CKD can cause metabolic acidosis, the latter disorder being the most common cause of chronic metabolic acidosis.[3] Diabetic ketoacidosis and

lactic acidosis are the most common causes of acute metabolic acidosis: together they account for approximately 85% of cases when the metabolic acidosis is severe (blood pH <7.1).[41] Alcoholic ketoacidosis is a less frequent cause of acute metabolic acidosis and is most commonly observed after binge drinking. D-Lactic acidosis is a rare disorder usually found in individuals with short-bowel syndrome.[42] The presence of neurological signs and symptoms, such as ataxia and slurred speech, can be suggestive of D-lactic acidosis. Salicylate intoxication most commonly occurs in individuals attempting suicide or in older patients taking medications for treatment of rheumatic disorders.[55] In the absence of a history of ingestion of salicylates, the presence of respiratory alkalosis is an important clue for a diagnosis of salicylate intoxication. Toxic alcohols, including methanol, ethylene glycol, diethylene glycol, and propylene glycol, are uncommon causes of metabolic acidosis.[44,45] Metabolic acidosis caused by methanol, ethylene glycol and diethylene glycol intoxication has a high risk of mortality, if not recognized early. Propylene glycol, a commonly used diluent in several medications including benzodiazepines, can cause lactic acidosis in patients receiving high doses of these medications intravenously.[56] A rare cause of metabolic acidosis is the accumulation of pyroglutamic acid resulting from the excessive ingestion of acetaminophen.[57] Finally, fasting, particularly if prolonged, can lead to mild ketoacidosis.

Normal anion gap metabolic acidosis

Metabolic acidosis with a hyperchloremic pattern can be further separated into disorders associated with a high or normal serum K^+ level and those associated with a low serum K^+ level (Box 2). Hyperkalemic hyperchloremic acidosis can be caused by the administration of substances that are metabolized to hydrochloric acid (for example, total parenteral nutrition solutions containing cationic amino acids).[58] However, it is more frequently caused by disorders characterized by impaired renal tubular acid and potassium excretion.[22,54] These disorders include CKD, aldosterone-deficient states such as adrenal insufficiency and hyporeninemic hypoaldosteronism,[54] tubular resistance to aldosterone,[22,54] pseudohypoaldosteronism type 1 (due to mutations in the epithelial Na^+ channel or the mineralocorticoid receptor),[59] and pseudohypoaldosteronism type 2 (Gordon's syndrome associated with increased distal Na^+ and Cl^- transport or impaired ROMK activity).[60]

Several drugs can also produce hyperkalemic hyperchloremic acidosis by different mechanisms. For example, spironolactone blocks the actions of aldosterone, amiloride, trimethoprim and pentamidine reduce Na^+ reabsorption in the collecting duct, and prostaglandin inhibitors produce hyporeninemic hypoaldosteronism.[22,54]

Hyperchloremic metabolic acidosis with a low serum K^+ level is most commonly caused by diarrhea. Although it can occur with disease of either the small or large bowel, the acid–base and electrolyte disturbances are often most severe with small-bowel diarrhea.[61] With severe volume depletion that occurs with diarrhea, the serum anion gap can increase as a result of the accompanying hyperphosphatemia, increased serum albumin concentration, and lactate accumulation.[62] Although much less common, pancreatic or small-bowel fistulae can also produce a hyperchloremic metabolic acidosis.

Proximal RTA results from inherited or acquired disorders of proximal bicarbonate transport. Although this disorder can present as an isolated defect in HCO_3^- reabsorption, more commonly there are also defects in other proximal tubular transporters which lead to phosphaturia, aminoaciduria, and glycosuria (Fanconi's syndrome).[63] Known inherited causes of isolated impaired bicarbonate reabsorption include defective SLC4A4 function and CA II deficiency.[63,64] Inherited disorders manifesting as Fanconi's syndrome include Wilson's disease, cystinosis, and fructose intolerance. Acquired diseases that produce the syndrome include multiple myeloma and renal transplant rejection. Administration of CA inhibitors causes urinary bicarbonate wasting and mild metabolic acidosis.

Distal RTA can result from inherited defects in the AE1 or the H^+-ATPase.[8,19,64] Patients with inherited defects in the H^+-ATPase can also have impaired hearing, which indicates the importance of the pump in the inner ear. Acquired causes of distal RTA include systemic lupus erythematosus, Sjögren's syndrome, primary biliary cirrhosis and other hypergammaglobulinemic disorders, renal transplant rejection, exposure to certain toxins, and other disorders characterized by damage to the collecting ducts.[65] An infant with distal RTA who was postulated to have a defect in the H^+/K^+-ATPase pump has been reported, although evidence of the defective pump was lacking.[66]

Hyperchloremic acidosis is observed after ureterosigmoidostomy or ureteroileostomy. Acidosis is more common with the former procedure because it involves a larger surface area of intestine and transit time is slower. The presence of hyperchloremic acidosis after ureteroileostomy suggests obstruction of the conduit.[67]

Patients with organic acidoses can also develop a hyperchloremic pattern when the urinary anion excretion exceeds the rate of bicarbonate generation.[40] As an example, toluene intoxication (caused by the accumulation of hippuric acid) is prototypically a hyperchloremic acidosis, because renal hippurate excretion is very high.[40,68] About 20–30% of patients with diabetic ketoacidosis also have hyperchloremia at presentation or develop it after the administration of sodium chloride.[69] In addition, some patients with D-lactic acidosis can manifest hyperchloremia.

Adverse effects of metabolic acidosis

The adverse effects of metabolic acidosis are divided into those primarily associated with acute metabolic acidosis and those primarily associated with chronic metabolic acidosis (Figure 1).

Acute metabolic acidosis

Although acute metabolic acidosis can affect a number of organ systems, animal studies suggest that it affects
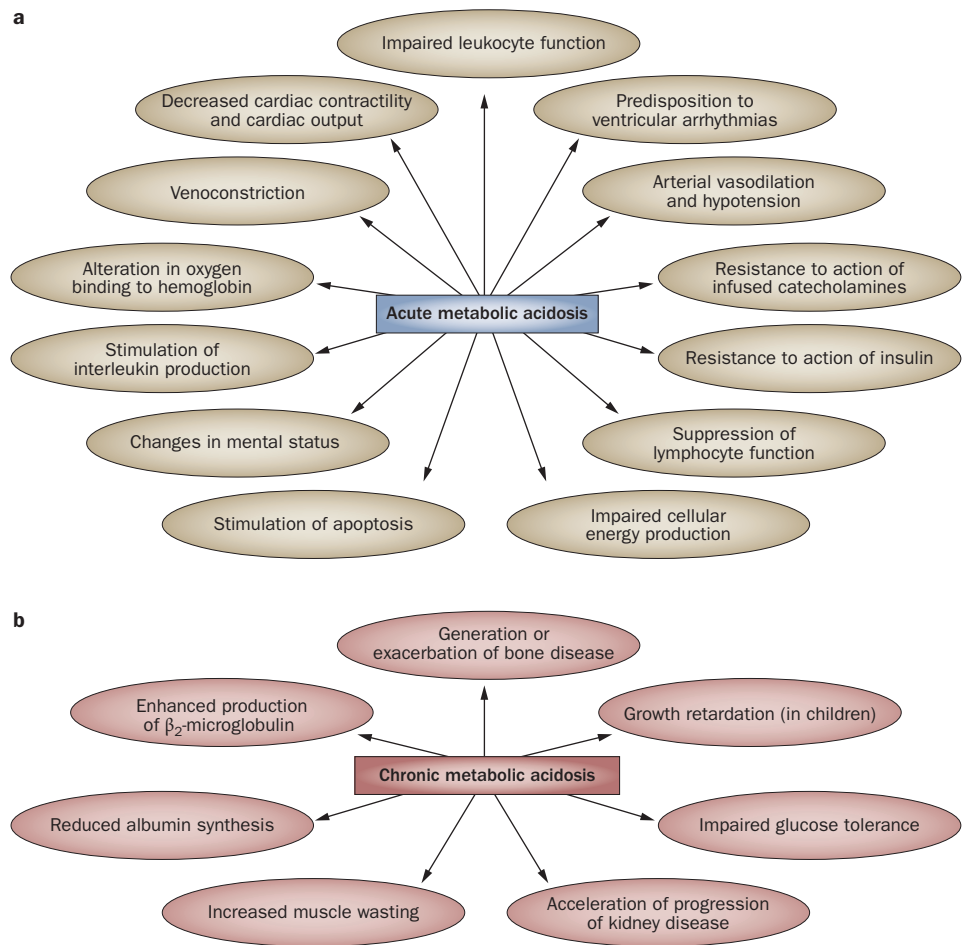
a

b

Figure 1 | Adverse effects of **a** | acute metabolic acidosis and **b** | chronic metabolic acidosis.

the cardiovascular system most critically. Cardiac contractility and cardiac output are reduced[70–72] and arterial vasodilatation develops, which contributes to the development of hypotension.[73] The cardiovascular dysfunction that occurs varies depending on pH. When blood pH decreases from 7.4 to 7.2, cardiac output can increase due to increased catecholamine levels.[70,72] When blood pH falls below 7.1–7.2, however, a fall in cardiac output is inevitable.[70] There is also resistance to the inotropic and vasoconstrictive effects of infused catecholamines with severe acidemia.[70,74] A predisposition to ventricular arrhythmias is often found in animal models of metabolic acidosis.[75] Similar abnormalities in cardiovascular function might be expected in humans, as patients with severe metabolic acidosis are often hypotensive. However, the limited controlled studies in humans with severe lactic acidosis and ketoacidosis performed so far have been unable to demonstrate impaired cardiovascular function that is directly attributable to the metabolic acidosis.[76–78] Further studies are warranted to resolve this disparity.

Mental confusion and lethargy are often observed in patients with acute metabolic acidosis, despite minor changes in cerebrospinal and brain pH.[79] A pH-dependent reduction in the affinity of hemoglobin for oxygen (Bohr effect) is seen immediately.[80] Within 8 h, a

decrease in 2,3-diphosphoglycerate production occurs, which increases the affinity of hemoglobin for oxygen. Given that the time-dependent changes in pH and in 2,3-diphosphoglycerate have disparate effects on the affinity of hemoglobin for oxygen, the final effect on the affinity of hemoglobin for oxygen will depend on the duration of the acidosis.

In acute metabolic acidosis, macrophage production of interleukins is stimulated and lymphocyte function is suppressed, leading to increased inflammation and an impaired immune response.[81] The chemotactic properties and bactericidal capacity of leukocytes are dampened,[82] potentially making patients with acute metabolic acidosis more susceptible to infection. In addition, the cellular response to insulin is impaired, partly as a result of a pH-dependent decrease in the binding of insulin to its receptor.[83]

Cellular energy production can be compromised in metabolic acidosis[84] as the activity of 6-phosphofructokinase, a critical enzyme in glycolysis, is pH dependent. Apoptosis is stimulated by metabolic acidosis predisposing to cellular death.[85]

Chronic metabolic acidosis

Chronic metabolic acidosis does not seem to have a significant effect on cardiovascular function, although

mortality is increased in patients with CKD when serum HCO_3^- concentration is <22 mmol/l.[86] Chronic metabolic acidosis exerts its most prominent effects on the musculoskeletal system. Metabolic acidosis can produce or exacerbate pre-existing bone disease,[87,88] accelerate muscle degradation leading to muscle loss,[89] and retard growth in children.[90] Glucose tolerance can be impaired because of interference with the actions of insulin,[91] albumin synthesis can be reduced,[2] progression of CKD can be accelerated,[92] and production of β_2-microglobulin can be augmented, which predisposes patients to amyloidosis.[93] Although once disputed, the concept that metabolic acidosis represents an important factor in accelerating the progression of CKD is gaining support.[92]

Underlying the clinical abnormalities reported with chronic metabolic acidosis are the direct effects of metabolic acidosis on bone and muscle, and possibly kidney, as well as indirect effects on these tissues emanating from alterations in the secretion and/or action of several hormones, including corticosteroids,[89] thyroid hormone,[94] and parathyroid hormone.[95] A generalized stimulation of inflammation also seems to contribute to the adverse effects of chronic metabolic acidosis.[4] These abnormalities are more frequent and severe with greater degrees of metabolic acidosis, but even mild metabolic acidosis might contribute to the development of bone disease and muscle degradation,[96,97] a finding that has important implications for treatment.

Management of metabolic acidosis

Metabolic acidosis is caused by either the loss of HCO_3^- or the net addition of strong acids. The elimination or control of the underlying cause, if feasible, is obviously a high priority in the treatment of all forms of metabolic acidosis. Decisions about the type of therapy also depend on the duration and severity of the disorder.

Acute metabolic acidosis

As changes in extracellular and intracellular pH underlie the adverse effects of acute metabolic acidosis, the administration of base—primarily in the form of sodium bicarbonate—has been the mainstay of therapy. However, uncontrolled studies of lactic acidosis and randomized controlled studies of ketoacidosis, the most frequent causes of acute metabolic acidosis,[41] have not revealed that such treatment results in a reduction in morbidity or mortality.[5,98,99] Furthermore, controlled studies of sodium bicarbonate administration were not shown to improve cardiovascular dysfunction in patients with lactic acidosis.[76,77] Sodium bicarbonate administration has also been postulated to be a contributory factor in the development of cerebral edema in children with ketoacidosis.[100] Consequently, there is disagreement among clinicians about the value of bicarbonate administration in these acid–base disorders and criteria for the administration of bicarbonate vary widely.[101] For example, nephrologists tend to recommend bicarbonate administration in the treatment of lactic acidosis and ketoacidosis more frequently than critical care physicians.[101]

The failure of sodium bicarbonate administration to improve cardiovascular function, morbidity and mortality could result, in part, from particular adverse effects ascribed to this therapy. These adverse effects include the exacerbation of intracellular acidosis caused by generation of the permeable gas CO_2 in the process of buffering, hypertonicity of the extracellular fluid when bicarbonate is given as a hypertonic solution, volume overload, overshoot metabolic alkalosis, potentiation of organic acid synthesis, and acceleration of cellular Na^+–H^+ exchange causing deleterious increments in cellular Na^+ and Ca^{2+}.[5,102]

To obviate some of these complications, alternative forms of base have been developed and tested. Tris-hydroxymethyl aminomethane (THAM), an agent introduced in the late 1950s, can raise extracellular pH without reducing intracellular pH and might even increase it.[103] Studies in humans have shown that THAM is as effective as bicarbonate in raising extracellular pH.[104] Furthermore, some animal studies have demonstrated that THAM can have beneficial effects on cardiovascular function.[105] THAM is used much less frequently than bicarbonate, however, because rare cases of liver toxicity have been reported in newborn babies, hyperkalemia and pulmonary dysfunction has been reported, and the agent requires sufficient renal function to ensure its urinary excretion and thus, its effectiveness.[103] However, given the limitations of bicarbonate therapy, it might be worthwhile to conduct randomized controlled studies to further determine the safety and effectiveness of THAM. Other buffers, including Carbicarb® (Church & Dwight Co. Inc., Princeton, NJ, USA), a combination of $NaHCO_3$ and Na_2CO_3,[106] and pyruvate,[107] have been developed and shown promise in animal models but have not been introduced into clinical practice. The use of dialytic therapy for delivering bicarbonate to correct acidosis without inducing extracellular volume expansion or hyperosmolality has been suggested as a promising treatment, but controlled studies of this therapy have not been performed.[108]

Studies of acute lactic acidosis (caused by ischemia or sepsis) have revealed additional targets for treatment that might warrant further study. Selective inhibition of the Na^+/H^+ exchanger NHE1 in animals with lactic acidosis improves cardiovascular function and reduces mortality by preventing deleterious increments in intracellular sodium and calcium.[102,109,110] Similarly, reducing the activity of the calcium-permeable, sodium-permeable, acid-sensing ion channel, ASIC1A, in the brain attenuates the cellular damage caused by ischemia.[111,112] Studies to uncover other targets for treatment are ongoing.

Our current recommendations for the treatment of acute metabolic acidosis are summarized in Box 3. The administration of base to patients with ketoacidosis can be considered if blood pH is below 7.1, there is associated hemodynamic instability, and insulin and fluid administration does not result in a rapid improvement of acid–base parameters. Children with ketoacidosis treated with base should be carefully monitored for any suggestive evidence of the development of cerebral edema. Similar

Box 3 | Recommendations for the treatment of acute metabolic acidosis

- In patients with ketoacidosis, consider administration of base if acidemia is severe (pH <7.1), there is evidence of cardiovascular compromise, and insulin and fluids fail to rapidly improve acidemia; aim to maintain blood pH at ~7.2 and monitor patient carefully
- In patients with lactic acidosis, consider administration of base if blood pH is <7.1 in patients with evidence of cardiovascular compromise; aim to maintain blood pH at ~7.2, while carefully monitoring patient
- In patients with ketoacidosis or lactic acidosis, administer the minimum quantity of base necessary to achieve the goal; estimate the quantity of base required to raise serum HCO_3^- concentration to desired level using the following equation:

Bicarbonate requirement = desired $[HCO_3^-]$ − measured $[HCO_3^-]$ × HCO_3^- space, where HCO_3^- space = $[0.4 + (2.6/[HCO_3^-])]$ × body weight

- If sodium bicarbonate is given, administer it slowly as an isotonic solution, with the initial dose limited to ≤1–2 mEq/kg body weight
- Consider augmenting alveolar ventilation temporarily, particularly in individuals with CO_2 retention, while monitoring for possible barotrauma
- Monitor acid–base status extremely carefully, including a determination of central or mixed venous acid–base data, particularly in patients with severe circulatory failure
- In patients with renal impairment or evidence of volume overload, consider utilization of hemofiltration or dialysis
- In patients with CO_2 retention and adequate renal function, consider administration of THAM
- In patients with hyperchloremic acidosis, administer base if blood pH is <7.1; aim to maintain blood pH ~7.2, while carefully monitoring patient

Abbreviations: CO_2, carbon dioxide; HCO_3^-, bicarbonate; THAM, tris-hydroxymethyl aminomethane.

acid–base criteria apply for the administration of base in lactic acidosis. If sodium bicarbonate is administered, it should be given as an isosmotic preparation (to prevent hyperosmolality) and as a slow infusion rather than an intravenous bolus (to reduce generation of CO_2), in quantities designed to raise blood pH to levels not greater than 7.2 (serum HCO_3^- concentration ~10 mmol/l) with close monitoring.[113] The quantity of bicarbonate required to raise serum HCO_3^- concentration depends on the apparent space of distribution of bicarbonate, endogenous acid production, and the ability of the kidney to generate HCO_3^-. The space of distribution of administered bicarbonate can vary from 50% body weight when serum HCO_3^- concentration is >10 mmol/l to as high as 100% body weight or more when serum HCO_3^- concentration is ≤5 mmol/l.[114] A more precise estimate of HCO_3^- space can be obtained by solving the equation $[0.4 + (2.6/[HCO_3^-])]$ × body weight.[115] Bicarbonate requirements can be calculated using the following equation:

$$\text{Bicarbonate requirement} = \text{desired } [HCO_3^-] - \text{measured } [HCO_3^-] \times HCO_3^- \text{ space}$$

THAM might be a reasonable option in some patients with acute metabolic acidosis, particularly those with CO_2 retention.[116] In intubated patients, a mild increase in ventilation to raise pH by reducing $PaCO_2$ might be an effective treatment, but its benefits should be weighed against the risk of barotrauma.

Therapies other than base might be indicated in individuals with high anion gap acidoses. For example, the administration of fomepizole, a selective inhibitor of alcohol dehydrogenase, will reduce generation of organic acids from the metabolism of methanol, ethylene glycol, or diethylene glycol.[44,45] In addition, hemodialysis will remove the parent alcohol while providing base.[44] The administration of insulin together with provision of fluids and electrolytes are often sufficient for the treatment of ketoacidosis. Forced alkaline diuresis or dialysis is indicated in patients with salicylate intoxication. In patients with ischemic lactic acidosis, measures to improve tissue perfusion are essential, and in patients with sepsis-related lactic acidosis, the treatment of infection is crucial.

As noted previously, metabolic acidoses with a predominantly hyperchloremic pattern are characterized by the absence of circulating bicarbonate precursors. Therefore, the correction of the metabolic acidosis in such cases depends solely upon the base administered by the physician and the bicarbonate generated by the kidney. Also, tissue accumulation of CO_2 after bicarbonate administration should be less than occurs in ischemic lactic acidosis, assuming tissue perfusion is intact.[117] Consequently, both nephrologists and critical care physicians are much more likely to recommend the administration of base for the treatment of acute hyperchloremic metabolic acidosis than for the treatment of organic acidosis.[101] Although patients with hyperchloremic metabolic acidosis might experience some of the complications of base therapy discussed above, we currently recommend the administration of base in such patients, with the goal of raising blood pH to 7.2.

Chronic metabolic acidosis

Several, but not all, studies of patients with chronic metabolic acidosis with and without renal impairment have demonstrated that the administration of base improves or decreases the progression of bone disease,[87,95,118] normalizes growth,[90] reduces muscle degradation,[95] improves albumin synthesis,[119] and retards the progression of CKD.[120] At present, most experts recommend that serum concentration of HCO_3^- be raised to at least 22–23 mmol/l,[3] although complete normalization might be more beneficial.[96,97]

Base can be given as oral bicarbonate to individuals with normal renal function or those with CKD not on dialysis. Since patients given this medication often experience abdominal discomfort from the generated CO_2, the administration of sodium citrate (Shohl's solution) is often preferred. Although citrate potentially augments aluminum absorption, this problem is much less common now that aluminum-containing binders are rarely used. Potassium citrate is the preferred agent in patients with concomitant hypokalemia. The magnitude of sodium retention might be less when sodium is administered with bicarbonate rather than with chloride, but only when dietary sodium chloride intake is markedly reduced.[121] Base therapy therefore has the potential to exacerbate pre-existing hypertension and produce

volume overload, meaning that careful attention should be paid to maintaining neutral sodium balance.

Mineralocorticoid therapy is indicated for the treatment of chronic metabolic acidosis in individuals with hyporeninemic states,[50] but this therapy should be used with caution in patients with pre-existing hypertension. In such patients, the acidosis and hyperkalemia can be controlled instead with diuretics or sodium polystyrene sulfonate (Kayexalate®, Sanofi-Aventis, Bridgewater, NJ, USA).[122]

In patients on hemodialysis, the use of dialysate with a high HCO_3^- concentration (~40 mmol/l) is usually sufficient to correct metabolic acidosis.[123] For individuals on peritoneal dialysis, a dialysate with high base concentration will usually be effective.[3,124] Theoretically, the normalization of serum HCO_3^- concentration might promote metastatic calcification by decreasing the solubility of calcium phosphate. However, studies performed in hemodialysis patients in whom pH rose into the alkalemic range at the end of the dialysis session showed that the normalization of serum HCO_3^- did not enhance factors that promote metastatic calcification.[123]

Conclusions

Metabolic acidosis is a common acid–base disorder that can occur acutely or chronically. Diagnosis of this disorder relies on a systematic approach that utilizes the serum anion gap as an integral component. Acute metabolic acidosis is associated with increased morbidity and mortality owing to diverse effects on cellular function.

Treatments for acute metabolic acidosis should aim to eliminate the cause. Theoretically, improving acid–base parameters with administration of sodium bicarbonate should be helpful, but this strategy is often not beneficial, partly as a result of potential complications. Alternative modes of base delivery, such as THAM or dialysis, should be studied further in the treatment of acute metabolic acidosis. Investigation of the pathophysiologic events that accompany acute metabolic acidosis has provided potential additional treatment targets, including the Na^+/H^+ exchanger NHE1 and the acid-sensing ion channel ASIC1A. Such agents should be examined further, and the identification of other targets might be valuable. Chronic metabolic acidosis, even when mild, has considerable adverse effects, which seem to be ameliorated with the administration of base in the majority of cases.

Review criteria

Information for this Review was obtained by searching MEDLINE for articles published between 1969 and 2009, using the terms "metabolic acidosis", "acute metabolic acidosis", "chronic metabolic acidosis", "respiratory response", "bicarbonate", "THAM", "toxic alcohol", "ketoacidosis", "lactic acidosis", "serum anion gap", "osmolality", "osmolal gap", "urinary anion gap", and "urinary osmolal gap". In addition, references from each article identified were carefully reviewed for additional suitable references. Studies involving humans or animals were examined, and the search was restricted to papers published in the English language.

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