

Objectives

1. Understand the basic mechanisms of metabolic acidosis
2. Understand the normal kidney response to an acid load and how this becomes impaired in kidney failure
3. Appreciate the use of the anion gap in the differential diagnosis of metabolic acidosis
4. Recognize the major causes of metabolic acidosis
5. Understand the basic principles of therapy in the different types of metabolic acidosis

Readings

Rose and Rennke, pages 152-167.

Rennke and Denker, pages 157-174.

I. Definition

A. Metabolic acidosis is the acid-base disturbance characterized by:

1. A primary reduction in plasma bicarbonate concentration
2. A low extra-cellular pH (or elevated hydrogen ion concentration)
3. Compensatory hyperventilation, resulting in a 1.0 to 1.2 mmHg fall in the $p\text{CO}_2$ for every 1 mEq/L drop in HCO_3^-

B. Respiratory Compensation

1. The time course of distribution, buffering, respiratory compensation, and kidney excretion of an acid load is shown in Figure 1.
2. Alveolar ventilation during metabolic acidosis is governed by the degree of cerebral interstitial fluid acidity.

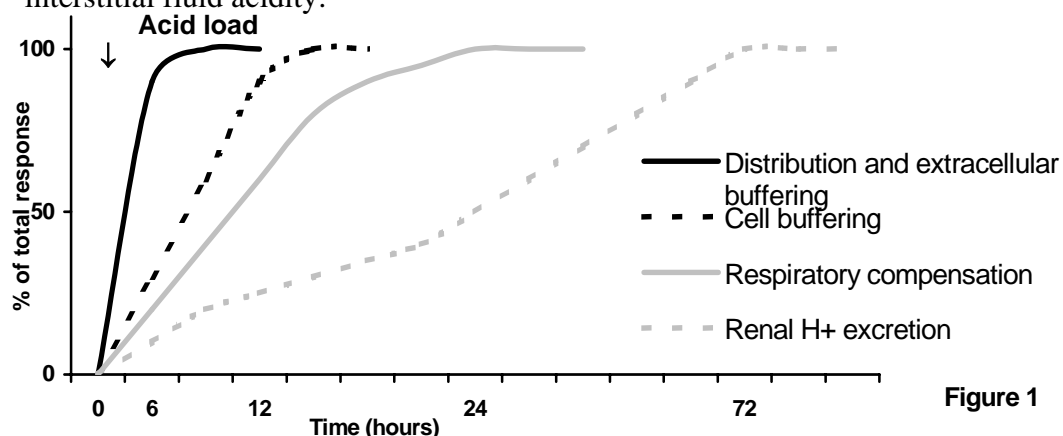


Figure 1

II. Basic Mechanisms

A. Increased acid production = hydrogen ion (H^+) load (Figure 2)

1. Addition of an organic acid such as:
 - a. lactic acid = lactic acidosis
 - b. acetoacetic acid and β -hydroxybutyric acid = ketoacidosis
2. Addition of a mineral acid such as:
 - a. Hydrochloric acid

3. If the rate of hydrogen input exceeds the rate at which the kidney excretes net acid, then hydrogen ion balance becomes positive and serum bicarbonate falls. Simultaneously, the concentration of the acid anion increases reciprocally.

4. If the acid is organic, the anion that accompanies the hydrogen ion replaces the bicarbonate and the chloride concentration remains unaffected. In such instances, the metabolic acidosis is characterized by an increase in the concentration of unmeasured anions in the plasma.
5. If the acid is HCl, the anion that accompanies the hydrogen ion replaces the bicarbonate and the chloride concentration increases. In such instances, unmeasured anions do not increase in the plasma.

B. Decreased acid excretion = decrease in kidney's ability to excrete hydrogen ion

1. The metabolism of dietary foodstuffs (sulfur-containing amino acids) results in the generation of 50 to 100 mEq of acid per day (about 1 mEq/kg/day of hydrogen ion).

Increased Acid Production

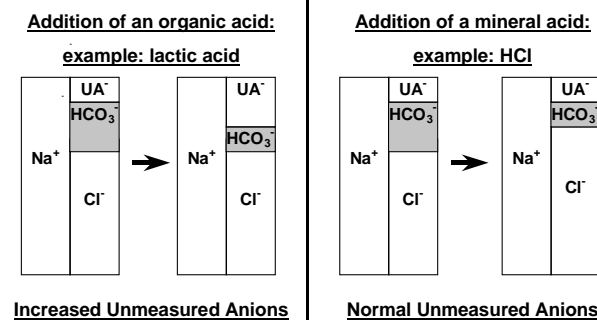


Figure 2

2. This acid load is excreted in the urine as ammonium (NH_4^+) and titratable acids (HPO_4^- ; H_2PO_4). Thus

$$\text{net acid excretion} = \text{NH}_4^+ + \text{titratable acids}.$$

3. If the acid load increases, the kidney response is to increase acid excretion, primarily as ammonium. (Figure 3)
4. Disorders characterized by decreased acid excretion include kidney failure (common) and distal renal tubular acidosis (rare).
5. Kidney failure = *too few functioning nephrons* (Figure 3)
 - a. Loss of functioning nephrons in progressive kidney disease requires an adaptation in tubular function to maintain acid-base balance
 - b. Initially, net acid excretion is maintained by increased ammonium excretion per functioning nephron
 - c. During chronic kidney disease (CKD) Stage III (GFR 30-60 ml/min/1.73 m²), total ammonium excretion begins to fall below the level necessary to maintain acid-base balance. Serum bicarbonate concentration begins to fall and the concentration of anions increases progressively (Figure 3).
 - d. As patients approach CKD Stage V (GFR < 15 ml/min/1.73 m²), the plasma bicarbonate concentration usually stabilizes at 12-20 mEq/L. Further reduction in plasma bicarbonate is prevented by buffering of the excess acid primarily by bone. This buffering causes calcium release from the bone and contributes to metabolic bone disease.
 - e. There is a reduction in the serum bicarbonate in CKD long before there is a severe reduction in GFR. This occurs long before symptoms and/or signs of uremia are evident (Figure 4).

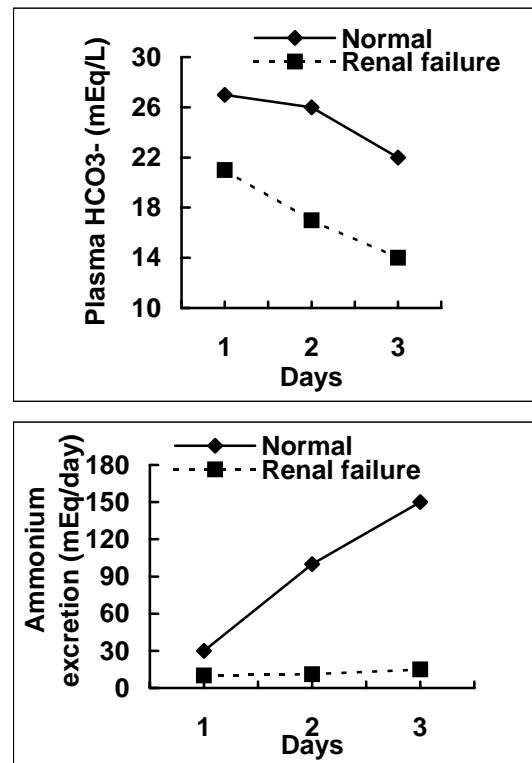


Figure 3. Effect of an acid load. Normal subject vs. patient with chronic kidney disease

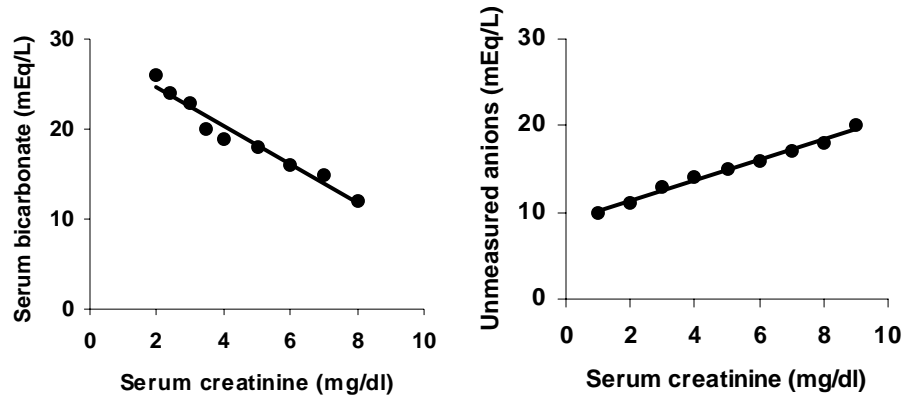


Figure 4. Relationship between serum creatinine, bicarbonate and unmeasured anions

6. Distal (Type 1) Renal Tubular Acidosis (RTA)

- Decreased net acid excretion results from an inability to lower urine pH below 5.5-6.0, rather than from diminished ammonium production
- The higher urine pH (*fewer free* hydrogen ions present) reduces the efficiency of hydrogen buffering by titratable acids and of ammonia trapping in the tubular lumen as ammonium
- The most common mechanism for decreased hydrogen secretion in the collecting tubule is due to impairment of the apical H^+ -ATPase pump.

C. Loss of bicarbonate (HCO_3^-)

1. Diarrhea

- Loss of bicarbonate in diarrheal fluids
- Decreased extracellular fluid (ECF) volume due to concomitant sodium loss in diarrheal fluid
- Plasma bicarbonate concentration falls and plasma chloride concentration rises as ECF volume is reduced.

2. Proximal (Type 2) RTA
 - a. Impaired proximal bicarbonate reabsorption
 - b. The bicarbonate reabsorptive capacity is reduced. Consequently, bicarbonate loss occurs until the lower reabsorptive capacity is reached. At this point, all of the filtered bicarbonate is reabsorbed and the daily acid load can be excreted (Figure 5).

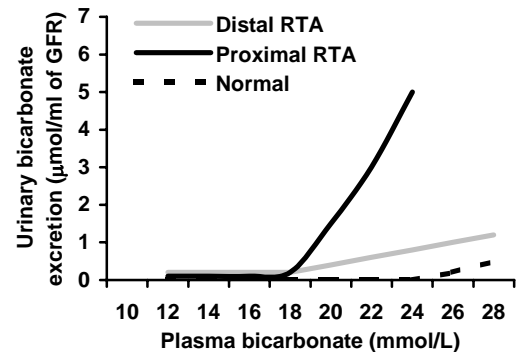


Figure 5

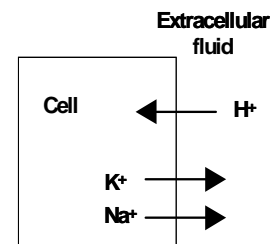
III. Clinical Manifestations

A. Respiratory system: increased alveolar ventilation (to increase CO₂ excretion)

B. Cardiovascular system:

1. Depressed myocardial contractility (at pH < 7.20)
2. Ventricular arrhythmia
3. Decreased vascular resistance (impaired response to catecholamines)

C. Gastrointestinal system: nausea, vomiting, abdominal pain, and diarrhea (especially in diabetic ketoacidosis and uremic acidosis)



Hyperkalemia
(mineral acid load)

Figure 6

D. Electrolyte/metabolic disturbances:

1. Potassium: In the presence of a mineral acid load, hydrogen ion moves into the cell where it is buffered. To maintain electro-neutrality, potassium leaves the cell, resulting in an increase in the plasma potassium concentration (Figure 6).
2. Calcium
 - a. Hydrogen ions displace calcium from albumin and increase ionized calcium without changing total calcium concentration.
 - b. Chronic metabolic acidosis: urine losses of calcium largely due to bone buffering.

IV. Anion Gap

- A. Calculation of the anion gap (AG) is an integral part of the evaluation of metabolic acidosis.
- B. The calculation of the AG allows the differentiation of two causes of metabolic acidosis: high and normal AG metabolic acidosis
- C. Electro-neutrality demands that the concentrations of cations and anions are equal in the serum.

Cations	Anions
Na^+ , K^+ , Ca^{++} , Mg^{++}	Cl^- , HCO_3^- , HPO_4^{--} , SO_4^- , Albumin, organic acids (OA)

If K^+ , Ca^{++} , Mg^{++} are unmeasured cations (UC), and HPO_4^{--} , SO_4^- , albumin and OA are unmeasured anions (UA), the equation can be reorganized as follows:

$$\begin{aligned}\text{Na}^+ + \text{UC} &= \text{Cl}^- + \text{HCO}_3^- + \text{UA} \\ \text{UA} - \text{UC} &= [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-]) \\ \text{Anion gap} &= [\text{UA}] - [\text{UC}] = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])\end{aligned}$$

- D. The AG is equal to the difference between serum concentrations of the major extracellular cation (sodium) and the two major extracellular anions (chloride and bicarbonate). Under normal circumstances, this gap is between 8 and 12 mEq/L.
- E. Although usually not clinically significant, albumin contributes the largest amount to the anions that comprise the anion gap. Hemo-concentration, which causes the serum albumin concentration to rise, increases the anion gap. Conversely, low serum albumin level causes a low anion gap.
- F. The approximate correction factor is a reduction in the AG of 2.5 mEq/L for every 1 gm/dL reduction in the plasma albumin concentration

V. The Role of the Anion Gap in Metabolic Acidosis

- A. Organic metabolic acidosis: when hydrogen ions accumulate with an unmeasured anion such as lactate, β -hydroxybutyrate, acetoacetate, or salicylate, the extracellular bicarbonate is replaced by an unmeasured anion, leading to an elevation of the AG.
- B. Mineral metabolic acidosis such as HCl administration leads to rapid buffering of excess acid by extracellular bicarbonate. There is mEq-for-mEq replacement of extracellular bicarbonate by chloride, with a resulting unchanged AG
- C. Gastrointestinal or kidney loss of sodium bicarbonate (as with diarrhea or proximal RTA) indirectly produces a similar result. Volume depletion induced by sodium loss activates counter-regulatory mechanisms, which lead to Na^+ and Cl^- tubular reabsorption, with a resulting unchanged AG
- D. Anion gap in chronic kidney disease (CKD)
 1. Metabolism of dietary proteins leads to the generation of sulfuric acid. The hydrogen ion is normally secreted by the tubule and the sulfate anion is filtered
 2. CKD Stage III results in disrupted hydrogen ion excretion from impaired ammonia-genesis and defective tubular hydrogen secretion, but preserved sulfate filtration and diminished tubular reabsorption. This produces a normal AG metabolic acidosis.
 3. CKD Stages IV and V see further reduction in nephron mass and GFR leading to retention of hydrogen ion and sulfate anion, resulting in a high AG metabolic acidosis

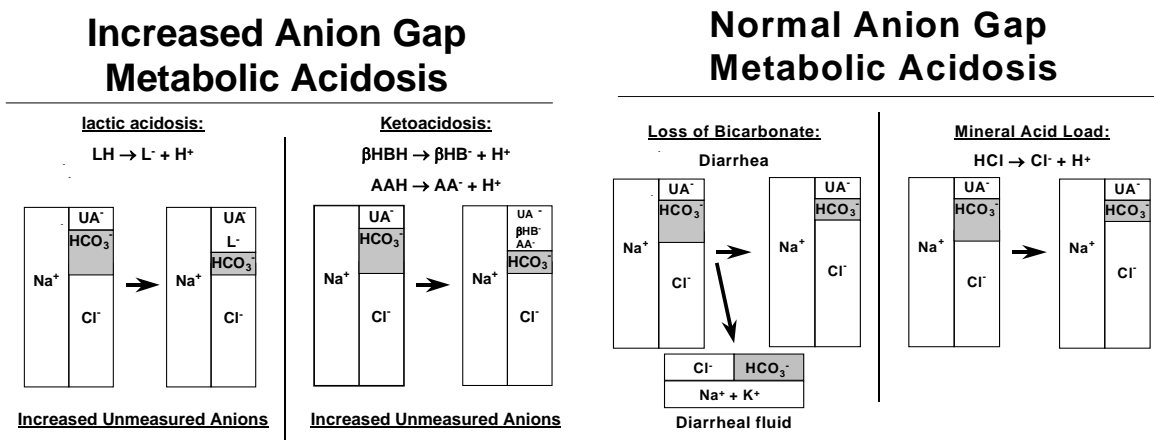


Figure 7. Patterns of extracellular electrolyte composition under normal conditions and during metabolic acidosis. Under all circumstances, sodium ions account for the bulk of cation equivalents, whereas chloride and bicarbonate ions account for most of the anion equivalents.

VI. Major Causes of Metabolic Acidosis: Clinical Syndromes

<i>Bicarbonate loss</i>	<i>Increased acid load</i>	<i>Impaired acid excretion</i>
Gastrointestinal losses <ul style="list-style-type: none"> - Diarrhea - Pancreatic drainage - Biliary drainage Kidney losses <ul style="list-style-type: none"> - Carbonic anhydrase inhibition - Proximal (Type 2) RTA Dilutional acidosis	Organic acid <ul style="list-style-type: none"> - Lactic acidosis - Diabetic ketoacidosis - Ethylene glycol intoxication - Methanol intoxication - Salicylate intoxication Mineral acid <ul style="list-style-type: none"> - HCL administration - NH₄Cl administration - Cationic amino acid administration 	<ul style="list-style-type: none"> - Kidney failure - Distal (Type 1) RTA - Adrenal insufficiency

Table 1

A. Bicarbonate Loss

1. The intestinal fluids below the stomach, including pancreatic and biliary secretions, are relatively alkaline
2. As a result, diarrhea or loss of pancreatic or biliary secretion can lead to metabolic acidosis
3. Example – *Cholera*
 - a. The cholera toxin stimulates intestinal fluid and electrolyte secretion, particularly bicarbonate (stool bicarbonate often > 40 mEq/L).
 - b. Stool volume can exceed 15 liters/day, leading to ECF volume contraction
 - c. Plasma bicarbonate concentration often falls below 10 mEq/L and death can occur from ECF volume depletion, azotemia, and acidosis.
 - d. Loss of K⁺ may be marked (stool K⁺ 30-60 mEq/L)
 - e. Oral fluid replacement therapy (which includes glucose) has dramatically reduced death rate.

B. Increased acid load

1. Lactic Acid
 - a. Lactic acid is derived from the metabolism of pyruvic acid in a reaction catalyzed by the enzyme lactate dehydrogenase (LDH) and involving the conversion of NADH to NAD⁺

- b. Normal subjects produce 15-20 mmol/kg of lactic acid per day, which is converted to glucose in the liver or back to pyruvate and then to CO₂ and water
- c. Three mechanisms can underlie the accumulation of lactate (see Table):
 - i. Enhanced pyruvate production
 - ii. Reduced pyruvate conversion to carbon dioxide and water or to glucose
 - iii. An altered redox state within the cell in which pyruvate is preferentially converted into lactate = suboptimal tissue oxygen delivery

Etiology of Lactic Acidosis¹	
Increased lactate production	
A. Increased pyruvate production	
1. Enzymatic defects in glycogenolysis or gluconeogenesis (as with type 1 glycogen storage disease)	
2. Respiratory alkalosis, including salicylate intoxication	
3. Pheochromocytoma	
B. Impaired pyruvate utilization	
1. Decreased activity of pyruvate dehydrogenase or pyruvate carboxylase	
a. Congenital	
b. Possibly a role in diabetes mellitus, Reye's syndrome	
C. Altered redox state favoring pyruvate conversion to lactate	
1. Enhanced metabolic rate	
a. Grand mal seizure	
b. Severe exercise	
c. Hypothermic shivering	
d. Severe asthma	
2. Decreased oxygen delivery	
a. Shock	
b. Cardiac arrest	
c. Acute pulmonary edema	
d. Carbon monoxide poisoning	
e. Severe hypoxemia (P _{O₂} <25 to 30 mmHg)	
f. Pheochromocytoma	
3. Reduced oxygen utilization	
a. Cyanide intoxication (↓ oxidative metabolism), which may result from cyanide poisoning or, during a fire, from smoke inhalation of vapors derived from the thermal decomposition of nitrogen-containing materials such as wool, silk, and polyurethane	
b. Drug-induced mitochondrial dysfunction due to zidovudine or stavudine	
D. D-Lactic acidosis	
Primary decrease in lactate utilization	
A. Hypoperfusion and marked acidemia	
B. Alcoholism	
C. Liver disease	
Mechanism uncertain	
A. Malignancy	
B. Diabetes mellitus, including metformin in the absence of tissue hypoxia	
C. Acquired immune deficiency syndrome	
D. Hypoglycemia	
E. Idiopathic	
Although this table has been divided into either increased production or decreased utilization of lactate, there is considerable overlap among listed causes.	

- d. Excess lactate can accumulate in plasma due to increase in lactate production and/or decrease in lactate utilization by the liver. In shock, for example, there may be both increased production due to tissue hypoperfusion and decreased utilization due in part to reduction in perfusion to the liver. Most cases of lactic acidosis are due to shock, such as cardiac arrest or sepsis.
 - e. Treatment of the underlying disorder is the primary therapy in lactic acidosis. For example, in shock, restoration of normal tissue perfusion will reduce lactate production and allow metabolism of excess lactate to HCO_3^- .
 - f. Of note, during shock, CO_2 removal is diminished due to a reduction in pulmonary blood flow. This results in marked mixed venous acidemia.
 - g. Bicarbonate therapy for lactic acidosis is controversial due to the following concerns:
 - i. Transient elevation in plasma bicarbonate
 - ii. Possible worsening of intracellular acidosis
 - h. Bicarbonate therapy should be reserved for arterial pH of < 7.15 .
2. Diabetic ketoacidosis
- a. The combination of insulin deficiency and glucagon excess lead to increased hepatic synthesis of ketoacids, mainly β -hydroxybutyric acid and acetoacetic acid
 - b. Two factors are required for increased ketoacid production:
 - i. Increased delivery of free fatty acids to the liver and lipolysis is driven by insulin deficiency
 - ii. Alteration of hepatic metabolism such that free fatty acids are converted to ketoacids (acetoacetic acid and β -hydroxybutyric acid) rather than triglycerides. This is driven by glucagon excess which increases the activity of the rate-limiting enzyme carnitine palmitoyl transferase.
 - c. Lack of insulin also increases fatty acetyl-CoA entry into hepatic mitochondria, where it is converted to ketones (acetone).
 - d. The morbidity of DKA is primarily due to the hyperosmolality, ECF volume depletion (osmotic diuresis), electrolyte imbalance, and impaired kidney function due to decreased GFR.

e. Treatment:

- i. Insulin: which stops further ketoacid synthesis and allows the excess ketoacids to be metabolized, resulting in the generation of bicarbonate and spontaneous correction of the acidemia
- ii. ECF volume replacement (NaCl and water)
- iii. Potassium repletion (once plasma K^+ is less than 4 mEq/L) as insulin therapy will promote intracellular shift of potassium
- iv. Bicarbonate therapy is to be avoided unless arterial pH < 7.2 or plasma HCO_3^- < 10 mEq/L

VIII. References

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