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A Synopsis of Acid-Base Analysis

Steps in Acid-Base Analysis

Step 1: Acidemic, alkalemic, or normal?

Step 2: Is the primary disturbance respiratory or metabolic?

Step 3: For a primary respiratory disturbance, is it acute or chronic?

Step 4: For a primary metabolic disturbance, is the respiratory system compensating correctly?

Step 5: For a metabolic acidosis, is there an increased anion gap?

Step 6: For an increased anion gap metabolic acidosis, are there other derangements?

Step 7: For a normal anion gap metabolic acidosis (a.k.a. "hyperchloremic" metabolic acidosis), is the cause gastrointestinal or renal? *[Uses the urinary anion gap]*.

Step 1: Acidemic, alkalemic, or normal?

The pH of the arterial blood gas identifies it as acidemic, alkalemic or normal:

- Normal arterial pH = 7.35 to 7.45

- Acidemic: pH < 7.35

- Alkalemic: pH > 7.45

Step 2: Is the primary disturbance respiratory or metabolic?

Primary **respiratory** disturbances change the arterial PCO2 primarily (normal = 35 - 45 mm Hg), with changes in serum HCO3 occurring in compensation. Thus, a primarily high PCO2 defines a primary respiratory acidosis, while a primarily low PCO2 defines a primary respiratory alkalosis.

Primary **metabolic** disturbances change the serum HCO3 primarily (normal = 22-26 mEq/L) with changes in arterial PCO2 occurring in compensation. Thus, a primarily low HCO3 defines a primary metabolic acidosis, while a primarily high HCO3 defines a primary metabolic alkalosis.

Step 3: For a respiratory disturbance, is it acute or chronic?

To examine this, one must compare the actual pH and PCO2 with the expected pH and PCO2.

Acute respiratory acidosis:
Expected pH = 7.4 - 0.008 (PCO2 - 40)
Expected HCO3 = 24 + 0.1 (PCO2 - 40)
(The increase in PCO2 shifts the equilibrium between CO2 and HCO3 to increase HCO3. This simple physicochemical event occurs almost immediately.)

Chronic respiratory acidosis:
Expected pH = 7.4 - 0.003 (PCO2 - 40)
Expected HCO3 = 24 + 0.4 (PCO2 - 40)
(With chronic respiratory acidosis, the kidneys respond by retaining HCO3. This takes a few days to fully occur.)

Acute respiratory alkalosis:
Expected pH = 7.4 - 0.008 (PCO2 - 40)
Expected HCO3 = 24 + 0.2 (PCO2 - 40)
(The decrease in PCO2 shifts the equilibrium between CO2 and HCO3 to decrease HCO3. This occurs very quickly.)

Chronic respiratory alkalosis:
Expected pH = 7.4 - 0.003 (PCO2 - 40)
Expected HCO3 = 24 + 0.5 (PCO2 - 40)
(With chronic respiratory alkalosis, the kidneys respond by reducing HCO3. This takes a few days to fully occur.)

Step 4: For a metabolic disturbance, is the respiratory system compensating adequately?

STEP 4 A   This step applies only if there is a metabolic acidosis (primarily low HCO3). The physiological response to metabolic acidosis is hyperventilation, with a resulting compensatory drop in PCO2 according to "**Winter's formula**":

Expected PCO2 in metabolic acidosis = 1.5 x HCO3 + 8   (range: +/- 2)

If the actual measured PCO2 is much greater than the expected PCO2 from Winter's formula, then the respiratory system is not fully compensating for the metabolic acidosis, and a respiratory acidosis is concurrently present. This may occur, for instance, when respiratory depressants like morphine or fentanyl are administered to the patient to reduce pain.

STEP 4 B   This step applies only if there is a metabolic alkalosis (primarily elevated HCO3). The response to metabolic alkalosis is hypoventilation, with a resulting increase in PCO2 according to the following formula:

Expected PCO2 in metabolic alkalosis = 0.7 x HCO3 + 20 mmHg (range: +/- 5)

Step 5: For a metabolic acidosis, is there an increased anion gap? If so, are there other metabolic processes present?

This step applies only if there is a metabolic acidosis (primarily low HCO3). This condition is subdivided into those with an increased anion gap and those without an increased gap, where **Anion Gap** = $[Na^+]$ - $[Cl^-]$ - [HCO3]. An anion gap over 12 is increased. The **most common etiologies of a metabolic acidosis with an increased anion gap** are shown below:

- Lactic acidosis (from poor perfusion)
- Renal failure
- Ketoacidosis
    - Diabetic ketoacidosis
    - Ketoacidosis from starvation
- Ingestion of:
    - Salicylate (as in aspirin)
    - Methanol (as in "wood alcohol")
    - Ethylene glycol (as in antifreeze)

Step 6: For an increased anion gap metabolic acidosis, are there other metabolic derangements present?

This step applies only if there is an increased anion gap type metabolic acidosis. In such a case, the bicarbonate is decreased due to the presence of unmeasured anions, and for every molecule of unmeasured anion present, one molecule of bicarbonate is lost (*electroneutrality principle*). To determine if there are other metabolic derangements present we start by determining the "corrected bicarbonate concentration": **Corrected HCO3 = measured HCO3 + (Anion Gap - 12).** If the corrected HCO3 is less than normal (under 22mEq/L) then there is an additional metabolic acidosis present. Corrected HCO3 values over 26 mEq/L reflect a co-existing metabolic alkalosis.

Example: in a patient with diabetic ketoacidosis with a measured HCO3 of 10, and an anion gap of 25 [increased by 13 over normal], the corrected HCO3 would = 10 + (25-12) =23, which is normal. This suggests that there is no secondary metabolic derangement.

Example: If a patient with diabetic ketoacidosis is also vomiting, causing a loss of gastric acid and therefore a metabolic alkalosis, the measured bicarbonate may be 16 and the anion gap 25. The corrected HCO3 would then = 16 + (25-12) =29, which is elevated. This suggests that there are simultaneous metabolic derangements: [1] metabolic acidosis (from the diabetic ketoacidosis) and [2] metabolic alkalosis (from the loss of gastric acid).

Step 7: For a normal anion gap metabolic acidosis (a.k.a. "hyperchloremic" metabolic acidosis), is the cause gastrointestinal or renal?
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Remember that metabolic acidosis can be divided into two groups based on the anion gap (AG): elevated anion gap acidosis and normal anion gap (or hyperchloremic) acidosis. Now, hyperchloremic acidosis, in turn, can be caused by three things [1] loss of bicarbonate via the kidney (e.g. renal tubular acidosis), [2] loss of bicarbonate via the bowel (e.g. diarrhea), or [3] gain of a mineral acid (e.g. from an HCl infusion). While the third circumstance can usually be ruled out immediately, deciding between the first two causes can sometimes be a little difficult. However, if the hyperchloremic acidosis is due to loss of bicarbonate from the bowel then the kidneys will ordinarily respond by increasing ammonium excretion to produce a net loss of H+ from the body, while if the acidosis is due to loss of bicarbonate from the kidney, then as the problem is with the kidney itself, and it is not able to increase ammonium excretion in this setting (renal tubular acidosis). One way of differentiating between the two is from the urinary anion gap (UAG), which is explained as follows.

The **cations** normally present in urine are Na+, K+, NH4+ (ammonium), Ca++ and Mg++.

The **anions** normally present in urine are Cl-, HCO3-, sulphate, phosphate and some organic anions. However, as only Na+, K+ and Cl- are normally measured in urine, the other charged species are said to be **unmeasured anions** (UA) and **unmeasured cations** (UC).

Because of the electroneutrality principle, total urine anion charge must equal total cation charge, or Cl- + UA = Na+ + K+ + UC

Rearranging, this gives us

Urinary Anion Gap = (UA - UC)
= [Na+]+ [K+] - [Cl-]

Finally, here is how the UAG is potentially useful in differentiating between GI and renal causes of hyperchloremic metabolic acidosis:
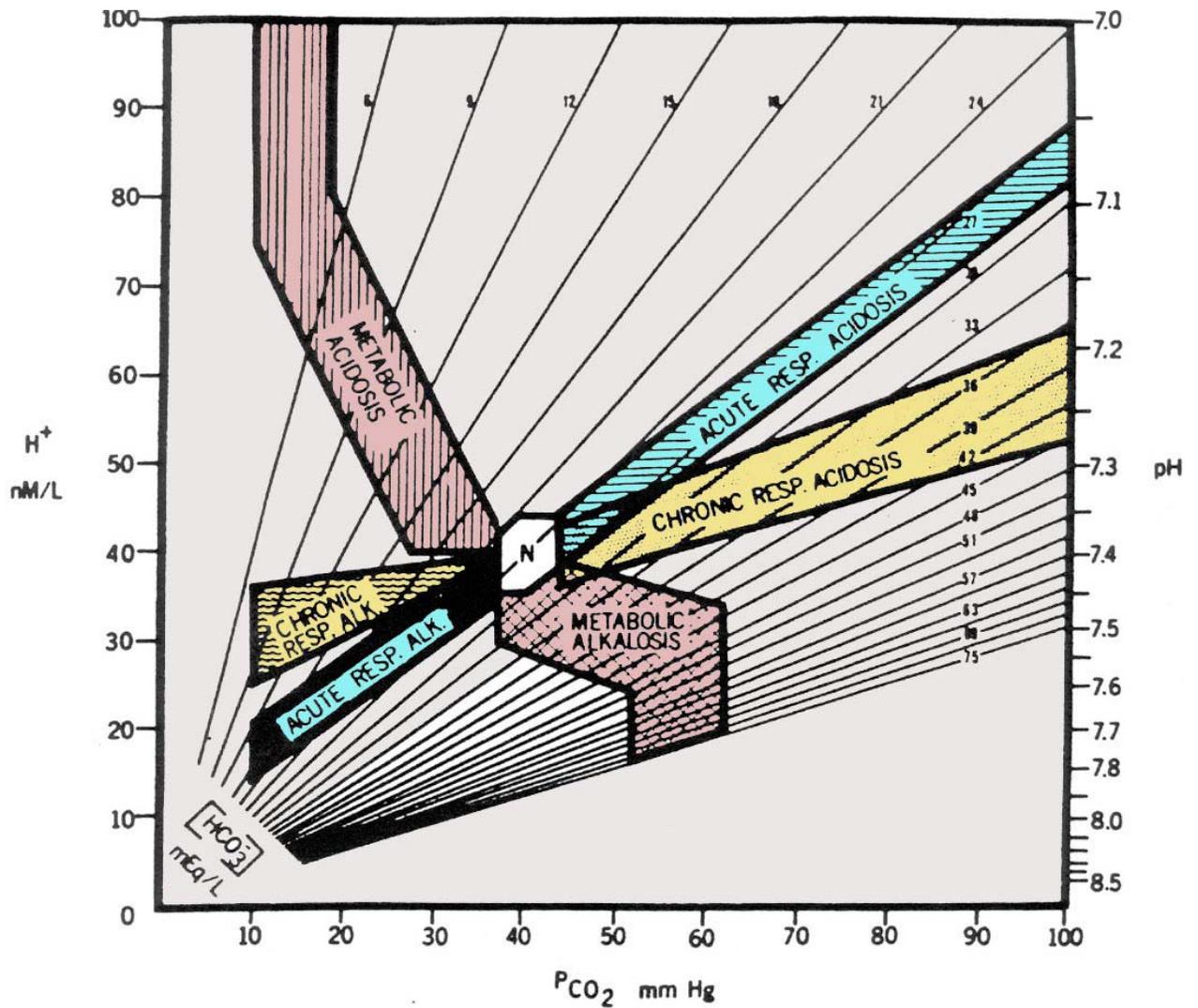
A **positive UAG** suggests that renal distal acidification is impaired (i.e. renal tubular acidosis). (Distinguishing between the various types of renal tubular acidosis (types I, II, and IV – there is no type III) is beyond the scope of this discussion, but can be realized using urine pH and plasma potassium data.)

A **negative UAG** suggests that a GI loss of bicarbonate is responsible for the hyperchloremic metabolic acidosis. Patients with diarrhea severe enough to cause hyperchloremic acidosis have a negative UAG averaging - 27 +/- 10 mEq/l. (As a memory aid, remember 'neGUTive' - negative UAG in bowel causes).

Of course, in many cases the diagnosis may be clinically obvious (e.g. severe diarrhea is hard to miss) and consideration of the urinary anion gap may not always be necessary.

CREDITS: The method presented here is based in part on that developed by Narins et al. [Medicine 59:161-187, 1980; Am J Med 72:496-520, 1982] and refined by Morganroth [J Crit Illness 5:138-150, 1990; 5:460-469, 1990]. The section on urinary anion gap is predominantly from www.qldanaesthesia.com/AcidBaseBook/

FURTHER STUDY: For more information see www.acid-base.com, www.vh.org/adult/provider/internalmedicine/abg/ABGHome.html, and www.qldanaesthesia.com/AcidBaseBook/

Here is a simple **acid-base nomogram** that covers many of the simpler acid-base disorders. To use, simply locate the disorder from the PCO2 and pH (or H+) data. This approach, while potentially useful, does not consider Anion Gap data and other potentially important factors. Still, it nicely illustrates the primary acid-base disorders. Note the lines of constant HCO3 strength that fan out from the origin. For more information see *Can Med Assoc J. 1973; 109: 291-3* and *J Clin Chem Clin Biochem. 1987 25:795-8.*

SUPPLEMENTARY INFORMATION

[1] pH and [H$^+$] *(hydrogen ion concentration)*

$$[H^+] \text{ in nEq/L} = 10^{(9-pH)}$$
$$pH = 9 - \log_{10} [H^+]$$

Example: if [H$^+$] = 100 nEq/L, then pH = 9 – 2 = 7
Note: 1 nEq/L = 10^{-9} Eq/L; 1 mEq/L = 10^{-3} Eq/L

Table : pH and hydrogen ion concentration

pH	[H$^+$] nEq/L
6.0	1000
7.0	100
8.0	10
9.0	1

[2] Normal Values *(arterial blood)*
pH = 7.35 to 7.45
PCO2 = 35 to 45 mmHg
HCO3 = 22 to 26 mEq/L

[3] Henderson-Hasselbalch Equation
The hydrogen ion concentration [H+] in extracellular fluid is determined by the ratio between the partial pressure (tension) of carbon dioxide (PCO2) and the bicarbonate concentration HCO3. This relationship is known as the Henderson-Hasselbalch equation:

$$[H^+] \text{ in nEq/L} = 24 \times PCO2 / HCO3$$

This relationship may also be stated in its classical but awkward form as:

$$pH = 6.1 + \log_{10} (HCO3 / (0.03 \, PCO2))$$

Example: since a normal arterial PCO2 is 40 mm Hg and a normal HCO3 is 24 mEq/L, the normal [H+] in arterial blood is 24 × (40/24) = 40 nEq/L.

[4] Kilopascals and PCO2.

Many Europeans express PCO2 in kilopascals (kPa). A pressure of 1000 pascals (1 kPa) is 10.2 cm H2O or 7.75 mm Hg. Atmospheric pressure (760 mm Hg) is about 1000 cm H2O (1034 to be exact) or 100 kPa (101.9 to be exact).

To convert pressure in mm Hg to kPa, simply divide the value in mm Hg by 7.5.

Example: 760 mm Hg = 760 / 7.5 kPa = 10.13 kPa

For more information on unit conversions of all kinds, visit **http://www.convert-me.com**

[5] Acid-Base Balance

The extracellular pH is determined by the PCO2 /HCO3 ratio; this is the basis for primary and compensatory acid-base changes (**Table 1**). When a "primary" acid-base disturbance changes one component of the PCO2/HCO3 ratio, a compensatory response occurs that shifts the other component in the same direction to keep the PCO2/HCO3 ratio constant. When the primary change is in the HCO3 concentration (i.e, the primary disorder is "metabolic"), the compensatory response is respiratory (i.e., a change in PCO2). When the primary change is in the PCO2 tension (i.e, the primary disorder is "respiratory"), the compensatory response is metabolic (i.e., a change in HCO3). Note that compensatory responses never result in complete pH correction.

TABLE 1. ACID-BASE DISORDERS

Disorder	Primary Change	Compensatory Change
Respiratory acidosis	PCO2 up	HCO3 up
Respiratory alkalosis	PCO2 down	HCO3 down
Metabolic acidosis	HCO3 down	PCO2 down
Metabolic alkalosis	HCO3 up	PCO2 up

[6] Anion Gap = [Na$^+$] - [Cl$^-$] - [HCO3].

Anions and cations in any compartment must be equal (electroneutrality). HCO3 is a measured anion, while unmeasured anions are protein, lactate, phosphate, and ketoanions. In metabolic acidosis, when HCO3 is replaced by Cl-, a measured anion, the anion gap is normal. When HCO3 is replaced by an unmeasured anion (e.g., lactate), the anion gap is increased.

[7] Clinical Gems
Ketoacidosis, either from diabetes or alcohol abuse, is a common cause of elevated anion gap type metabolic acidosis. Since it can lead to vomiting, ketoacidosis can itself also lead to a superimposed metabolic alkalosis (from the loss of gastric acid.)

A variety of ailments causing vomiting may produce metabolic alkalosis. If the resulting volume depletion (dehydration) is severe, lactic acidosis and renal failure may result, producing an elevated anion gap type metabolic acidosis in addition.

The respiratory compensation normally associated with a metabolic acidosis may be impaired when opiate analgesic drugs like morphine, meperidine (Demerol) or fentanyl are used. These drugs are respiratory depressants and will blunt the hyperventilation (Kussmaul breathing) usually found in patients with metabolic acidosis.

Some mixed disorder hints. Respiratory acidosis + metabolic acidosis = COPD + lactic acidosis. Respiratory alkalosis + metabolic acidosis = aspirin overdose. Metabolic acidosis + metabolic alkalosis = diarrhea + vomiting.

The Merck Manual of Geriatrics

Disorders of Acid-Base Metabolism

The normal pH of extracellular fluid (range, 7.35 to 7.45) is unaffected by age. However, age-related changes do occur in certain respiratory and renal regulatory processes involved in maintaining normal pH, and the ability to respond to a challenge may be limited. For example, the ability to hyperventilate in response to acute metabolic acidosis may be blunted, leading to a further decline in pH. The aging kidney is slower to respond to an acid load, and the blood pH may take longer to recover. Many disorders common in the elderly (eg, heart failure, anemia, sepsis, diabetes mellitus, renal and pulmonary disease) can overwhelm the regulatory systems and contribute to acid-base disturbances. Also, many commonly used drugs (eg, salicylates, diuretics, laxatives) may precipitate acid-base disturbances. The combination of impaired homeostatic mechanisms and the high prevalence of drug use and disease in the elderly make acid-base disturbances common.

Metabolic Acidosis

A condition characterized by a primary decease in extracellular fluid bicarbonate; serum pH and carbon dioxide content are decreased.

The serum anion gap, which may help identify the cause of metabolic acidosis (see Table 59-1 [next column]), is determined as follows: Serum sodium - (serum chloride + total CO_2) = ± 2. The urine anion gap is calculated as follows: (urine sodium + urine potassium) - urine chloride <= 0.

A non-anion gap metabolic acidosis (NAGMA) is due to a failure of bicarbonate homeostasis and is characterized by a compensatory retention of the other main body anions, which results in hyperchloremia. NAGMA results from renal tubular acidosis or from a loss of bicarbonate or organic acid anions in patients with diarrhea.

TABLE 59–1. METABOLIC ACIDOSIS IN THE ELDERLY

Non-anion gap
Urine anion gap < 0 → GI losses of bicarbonate
Urine anion gap ≥ 0
  Urine pH < 5.5 → type 2 (proximal) RTA or carbonic anhydrase inhibitors
  Urine pH always > 5.5 + low or normal potassium → type 1 (distal) RTA due to amphotericin or myeloma
  Urine pH always > 5.5 + hyperkalemia → type 4 RTA due to urinary tract obstruction, diabetes mellitus, or drugs that interfere with the prostaglandin-renin-aldosterone axis

Anion gap elevation
Ketoacidosis
Uremia
Salicylate ingestion
Methanol intoxication
Alcohol ingestion
Lactic acidosis

GI = gastrointestinal; RTA = renal tubular acidosis.

If there is a serum NAGMA and the urine anion gap is <= 0, gastrointestinal loss of bicarbonate (diarrhea) is the cause of the metabolic acidosis. A NAGMA with a urine anion gap >= 0 suggests type 1 (distal) or type 4 renal tubular acidosis. A urine pH > 5.5 with metabolic acidosis suggests distal tubular inability to acidify the urine and occurs with type 1 or type 4 renal tubular acidosis. In the elderly, type 1 renal tubular acidosis may be caused by amphotericin therapy or by tubular dysfunction due to the myeloma protein in multiple myeloma. Type 2 (proximal) renal tubular acidosis is uncommon in the elderly as a primary defect of tubular function but can result from the bicarbonate diuresis caused by carbonic anhydrase inhibitors used to treat glaucoma. In this disorder, there is NAGMA, but after the bicarbonate diuresis, urine pH is < 5.5 during acidosis due to normal distal hydrogen ion urine acidification capability.

Type 4 renal tubular acidosis is caused by urinary tract obstruction, diabetes mellitus, or drugs that interfere with aldosterone (eg, distal angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers). Acidosis with an increased anion gap (such as occurs with lactic acidosis, diabetic ketoacidosis, salicylate toxicity, toxic alcohol ingestion, and renal failure) is more common. Type 4 renal tubular acidosis is characterized by tubular dysfunction that is worse than that in type 1. The added tubular dysfunction is suggested by concomitant hyperkalemia.

Diagnosis is usually established by the history, physical examination findings (eg, hyperpnea), and laboratory findings (eg, blood gas determinations; urine pH; and blood urea nitrogen [BUN], creatinine, blood glucose, and ketone levels).

Initial treatment aims to correct the underlying disease process. When severe acidosis (pH < 7.2) is accompanied by anorexia, nausea, lethargy, hyperventilation, and decline in cardiac output, treatment should be started with IV sodium bicarbonate. Acute complete correction of arterial pH is not a goal of therapy, and caution must be used to avoid volume and sodium overload. Commonly, 2 to 3 ampules (44 mEq/L each) of sodium bicarbonate are dissolved in 5% dextrose in water and administered at a rate of 50 to 100 mL/h.

Metabolic Alkalosis

A condition characterized by a primary increase in extracellular fluid bicarbonate; pH and carbon dioxide content are increased.

Metabolic alkalosis results from net acid loss or alkali gain in the extracellular fluid. Acid loss can result from vomiting, prolonged gastric suctioning, and diuretic use. The concomitant chloride deficiency requires that the high bicarbonate be reabsorbed with sodium and will not correct until adequate chloride ion is available (ie, treated with sodium chloride, potassium chloride, or hydrochloride). The chloride-resistant forms of metabolic alkalosis common in the elderly include an excessive mineralocorticoid effect of chronic prednisone administration, renin-angiotensin-aldosterone stimulation due to renal atherosclerosis, Cushing's disease, primary aldosteronism, and ectopic corticotropin (ACTH) production due to malignancy. In these cases, the mineralocorticoid excess dictates excessive renal generation of bicarbonate because of stimulated sodium/hydrogen exchange. Treatment is directed toward mineralocorticoid antagonism.

Lethargy and stupor may occur from adverse effects on the cerebral circulation. Arrhythmias, especially due to digitalis toxicity, are common. Therapy depends on whether the metabolic alkalosis is sensitive or resistant to chloride. The chloride-sensitive forms respond to administration of chloride, such as in normal saline. Gastric acid and chloride losses can be reduced by giving a histamine-2 blocker or a proton pump inhibitor. Bicarbonate diuresis can also be accomplished using carbonic anhydrase inhibition; acetazolamide 250 mg IV can be given bid or qid in severe cases or when patients are unable to take drugs orally. Chloride-resistant forms require treatment of the underlying disorder or mineralocorticoid antagonism with spironolactone. A dose of 50 to 100 mg/day po in divided doses may help patients with chronic alkalosis.

Respiratory Acidosis

A primary increase in arterial carbon dioxide partial pressure; pH is decreased and total carbon dioxide content is increased if renal function is intact.

Respiratory acidosis is caused by carbon dioxide retention from alveolar hypoventilation, which may result from

disorders that depress the central respiratory center, restrict chest wall mobility, reduce pulmonary alveolar surface area, or narrow the upper airway. The elderly are at risk because of their reduced vital capacity and ventilatory responses to hypoxia and hypercapnia. Common causes are drugs that can produce respiratory depression, neuromuscular disorders, and pulmonary disorders. Respiratory acidosis is often accompanied by hypoxia. Progressive respiratory failure often results in a metabolic encephalopathy with headache, drowsiness, and ultimately stupor and coma. Asterixis and myoclonus may develop.

Treatment aims to improve the underlying pulmonary disorder and may include intubation and assisted mechanical ventilation. Hypoxia must be corrected with the lowest possible oxygen concentration to avoid further depression of respiratory drive. Many patients also have concomitant metabolic alkalosis.

Respiratory Alkalosis

A primary decrease in arterial carbon dioxide partial pressure; pH is increased and total carbon dioxide content is decreased.

The hyperventilation usually present leads to an excessive loss of carbon dioxide. Common causes include mechanical overventilation, hypoxemia, sepsis, pulmonary embolism, heart failure, hepatic failure, primary central nervous system disorders, and salicylate toxicity. Anxiety can cause a mild, acute respiratory alkalosis with a characteristic hyperventilation syndrome. Physiologic consequences of respiratory alkalosis include cerebral vasoconstriction, with resulting cerebral hypoxia and decreased ionized serum calcium concentrations leading to tetany and hypophosphatemia. Treatment consists of correcting the underlying disorder or, in the case of hyperventilation syndrome, supervised breathing into a paper bag.