Simple and mixed acid-base disorders

AUTHORS: Michael Emmett, MD, Biff F Palmer, MD
SECTION EDITOR: Richard H Sterns, MD
DEPUTY EDITOR: John P Forman, MD, MSc

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PHYSIOLOGY AND ASSESSMENT OF ACID-BASE STATUS

Each day, adults generate large amounts of acids that must be expired, excreted, metabolized to noncharged neutral molecules, and/or buffered to avoid fatal acidemia. These acids are of three major classes:

- Approximately 15,000 mmol (considerably more with exercise) of carbon dioxide (CO_2) is produced each day, which combines with water to form carbonic acid (H_2CO_3).
- Metabolic reactions generate several thousand mmol per day of organic acids, such as lactic acid and citric acid. These acids are metabolized to neutral products (such as glucose) and to CO_2 and water. Normally, the generation and utilization rates of these organic acids are equal so that their steady state concentration in the extracellular fluid is relatively low and stable.
- Approximately 50 to 100 mEq of nonvolatile, inorganic acid is produced each day (mostly sulfuric acid derived from the metabolism of sulfur-containing amino acids in the diet).

Acid-base balance is maintained by normal pulmonary excretion of carbon dioxide, metabolic utilization of organic acids, and renal excretion of nonvolatile acids.

Renal excretion of acid is achieved by combining hydrogen ions with either urinary buffers to form titratable acid, such as phosphate ($HPO_4^{2-} + H^+ \rightarrow H_2PO_4^-$), urate, and creatinine, or with

ammonia to form ammonium ($NH3 + H^+ \rightarrow NH4^+$) [1]. When increased quantities of acid must be excreted by the kidney, the major adaptive response is an increase in ammonia production (derived from the metabolism of glutamine) with a resultant increase in ammonium excretion into the urine.

Acid-base status is usually assessed by measuring the components of the bicarbonate-carbon dioxide buffer system in blood:

$$\text{Dissolved } CO2 + H2O \leftrightarrow H2CO3 \leftrightarrow HCO3^- + H^+$$

When blood gas analysis is carried out, the partial pressure of CO2 (PCO2) and the pH are each measured using analytical electrodes. The serum bicarbonate (HCO3-) concentration is then calculated with the Henderson-Hasselbalch equation. Generally, the PCO2 is reported in mmHg, and HCO3- in mEq/L:

$$pH = 6.10 + \log([HCO3^-] \div [0.03 \times PCO2])$$

where the pH is equal to (-log [H+]); 6.10 is the negative log of Ka (-log Ka), which is the dissociation constant for this reaction; 0.03 is the solubility coefficient for CO2 in blood; and the PCO2 is the partial pressure of carbon dioxide in blood [2].

When measured in venous blood, HCO3- is usually approximated by measurement of "total CO2" with either an ion-selective electrode or an enzymatic assay [3]. The directly measured venous "total CO2" is generally approximately 3 mEq/L greater than the simultaneously calculated arterial HCO3-.

NORMAL VALUES ACCORDING TO SITE OF SAMPLING

The range of normal values for acid-base parameters is different for arterial and venous samples and also varies among laboratories. These issues are discussed in detail elsewhere but will be briefly summarized here. (See "Arterial blood gases" and "Venous blood gases and other alternatives to arterial blood gases".)

Arterial blood gas sample — For an arterial blood gas sample, the normal range for pH is 7.35 to 7.45; for bicarbonate (HCO3) concentration, 21 to 27 mEq/L; and for PCO2, 35 to 45 mmHg (4.7 to 6.0 kPa).

Peripheral venous blood gas sample — Normal values for peripheral venous blood gases differ from those of arterial blood due to the uptake and buffering of metabolically produced

CO2 in the capillary circulation and the addition of organic acids produced by the tissue bed drained by the vein. If a tourniquet is used to facilitate phlebotomy, it should be released approximately one minute before the sample is drawn to avoid changes induced by ischemia [4]. (See "Venous blood gases and other alternatives to arterial blood gases".)

The range for peripheral venous pH is approximately 0.03 to 0.04 pH units lower than in arterial blood, the HCO3 concentration is approximately 2 to 3 mEq/L higher, and the PCO2 is approximately 3 to 8 mmHg (0.4 to 1.1 kPa) higher [3,5-7]. If venous measurements are used for serial monitoring, periodic correlation with arterial measurements should be performed. (See "Arterial blood gases".)

Central venous sample — Central venous samples may be analyzed in patients with central venous catheters. The central venous pH is usually 0.03 to 0.05 pH units lower than in arterial blood and the PCO2 is 4 to 5 mmHg (0.5 to 0.7 kPa) higher, with little or no increase in serum HCO3 [8,9]. (See "Venous blood gases and other alternatives to arterial blood gases".)

DEFINITIONS OF ACID-BASE DISORDERS

The following definitions of acid-base disorders are based upon principles of the Henderson-Hasselbalch equation:

- Acidemia – An arterial pH below the normal range (less than 7.35).
- Alkalemia – An arterial pH above the normal range (greater than 7.45).
- Acidosis – A process that tends to lower the extracellular fluid pH (hydrogen ion concentration increases). This can be caused by a fall in the serum bicarbonate (HCO3) concentration and/or an elevation in PCO2.
- Alkalosis – A process that tends to raise the extracellular fluid pH (hydrogen ion concentration decreases). This can be caused by an elevation in the serum HCO3 concentration and/or a fall in PCO2.
- Metabolic acidosis – A disorder that reduces the serum HCO3 concentration and pH. (See "Approach to the adult with metabolic acidosis".)
- Metabolic alkalosis – A disorder that elevates the serum HCO3 concentration and pH. (See "Pathogenesis of metabolic alkalosis" and "Causes of metabolic alkalosis".)
- Respiratory acidosis – A disorder that elevates the arterial PCO2 and reduces the pH.

- Respiratory alkalosis – A disorder that reduces the arterial PCO2 and elevates the pH.

- Simple acid-base disorder – The presence of one of the above disorders with the appropriate respiratory or renal compensation for that disorder. (See 'Compensatory respiratory and renal responses' below.)

- Mixed acid-base disorder – The simultaneous presence of more than one acid-base disorder. Mixed acid-base disorders can be suspected from the patient's history, from a lesser- or greater-than-expected compensatory respiratory or renal response, and from analysis of the serum electrolytes and anion gap. As an example, a patient with severe vomiting would be expected to develop a metabolic alkalosis due to the loss of acidic gastric fluid. If, however, the patient also developed hypovolemic shock from the fluid loss, the ensuing lactic acidosis would lower the elevated serum HCO3 possibly to below normal values, resulting in acidemia. (See 'Mixed acid-base disorders' below.)

COMPENSATORY RESPIRATORY AND RENAL RESPONSES

General principles — The Henderson-Hasselbalch equation described above shows that the pH is determined by the ratio of the serum bicarbonate (HCO3) concentration and the PCO2, not by the value of either one alone. Each of the simple acid-base disorders is associated with a compensatory respiratory or renal response that limits the change in ratio and therefore in pH (figure 1) [10].

- When a metabolic acid-base disorder reduces the serum HCO3 (metabolic acidosis) or increases the HCO3 (metabolic alkalosis), there should be an appropriate degree of respiratory compensation moving the PCO2 in the **same direction** as the serum HCO3 (falling in metabolic acidosis and rising in metabolic alkalosis). The respiratory compensation mitigates the change in the ratio of the serum HCO3 to PCO2 and therefore in the pH. Respiratory compensation in metabolic acidosis or alkalosis is a rapid response. With metabolic acidosis, for example, the response begins within 30 minutes [11] and is complete within 12 to 24 hours [10,12].

- When a respiratory acid-base disorder causes the PCO2 to increase (respiratory acidosis) or decrease (respiratory alkalosis), compensation occurs in two phases. There is an immediate, small change in serum HCO3 (in the same direction as the PCO2 change), which is due to whole body buffering mechanisms. If the respiratory disorder persists for more than minutes to hours, the kidneys respond by producing larger changes in serum HCO3 (again, in the **same direction** as the PCO2). These HCO3 changes mitigate the

change in pH. Renal compensations are mediated by increased hydrogen ion secretion (which raises the serum HCO3 concentration) in respiratory acidosis and decreased hydrogen ion secretion and urinary HCO3 loss (which reduces the serum HCO3 concentration) in respiratory alkalosis. The renal compensation takes three to five days for completion. As a result, the expected findings are very different in acute (whole body buffering without significant renal compensation) and chronic (full renal compensation) respiratory acid-base disorders [10]. (See 'Respiratory acid-base disorders' below.)

The compensatory renal and respiratory responses are thought to be mediated, at least in part, by parallel pH changes within sensory and regulatory cells including renal tubule cells and cells in the respiratory center [10,13]. The magnitude of the compensatory response is proportional to the severity of the primary acid-base disturbance.

It follows from the above discussion that a high HCO3 concentration may be due to metabolic alkalosis or compensation for chronic respiratory acidosis. Conversely, a low HCO3 may be due to metabolic acidosis or compensation for chronic respiratory alkalosis. Analogous issues apply to a high or low PCO2. At least two of the three variables in the Henderson-Hasselbalch equation (pH, HCO3, PCO2) must be measured to assess an acid-base disorder (and if two are measured, the third can be calculated).

The expected degree of compensation for each acid-base disorder has been determined empirically by observations in humans with either spontaneous or experimentally induced simple acid-base disorders (figure 1). The degree of compensation is usually defined by the decrease or increase in arterial PCO2 from its normal range (in metabolic acid-base disorders) or the decrease or increase in serum HCO3 from its normal range (in respiratory acid-base disorders). This approach presumes that the patient had normal values prior to the onset of the acid-base disorder. Thus, in the absence of known baseline values, there is the potential for error if the patient's acid-base status was not normal at the onset of the disorder.

Metabolic acid-base disorders

Response to metabolic acidosis — Respiratory compensation for metabolic acidosis causes the arterial PCO2 to fall approximately 1.2 mmHg (0.16 kPa) for every 1 mEq/L reduction in the serum HCO3 concentration [10,14]. The respiratory response to metabolic acidosis begins within 30 minutes [11] and is complete within 12 to 24 hours [10,12]. There is no lag in respiratory compensation when metabolic acidosis develops slowly (eg, 4 mEq/L fall in serum HCO3 over 15 hours) [12]. An inability to generate the expected respiratory response is usually indicative of significant underlying respiratory or neurologic disease, but can also occur at the

onset of acute metabolic acidosis before there has been adequate time for respiratory compensation to fully develop [15].

Several other predictive relationships have been proposed to determine the appropriate respiratory compensation to metabolic acidosis. These include:

- Arterial $PCO_2 = 1.5 \times \text{serum } HCO_3 + 8 \pm 2$ (Winters' equation) [16]
- Arterial $PCO_2 = \text{Serum } HCO_3 + 15$
- Arterial PCO_2 should be similar to the decimal digits of the arterial pH (eg, 25 mmHg when the arterial pH is 7.25, a setting in which the serum HCO_3 concentration would be approximately 11 mEq/L) [17]

These formulas and rules generally give similar results. Because there are no data on comparative accuracy (see 'Case 2' below), the reader may use the relationship rule they find easiest to remember and implement.

There is a limit to the maximum respiratory compensation that can be attained. With severe metabolic acidosis (eg, serum HCO_3 concentration less than 6 mEq/L), the PCO_2 can fall no lower than 8 to 12 mmHg (1.1 to 1.6 kPa). In addition, the duration that such compensation can be maintained is limited due to respiratory muscle fatigue. Thus, when the HCO_3 is 5 mEq/L or lower, the PCO_2 should be 8 to 12 mmHg.

In addition to assessing the respiratory compensation, another component in the evaluation of patients with acid-base disorders is calculation of the serum anion gap to determine whether it is normal or elevated. Metabolic acidosis may be of the high anion gap type, normal anion gap type (hyperchloremic), or combined normal and elevated anion gap acidosis. As an example, with severe diarrhea, loss of bicarbonate and potential bicarbonate in the stool typically generates a normal anion gap metabolic acidosis, but the resulting hypovolemia can also lead to lactic acidosis and kidney dysfunction generating a high anion gap acidosis. When a high anion gap metabolic acidosis exists, comparing the change in anion gap (or the delta anion gap) with the change in bicarbonate (or the delta bicarbonate) may be helpful. These issues are discussed in detail elsewhere. (See "Approach to the adult with metabolic acidosis", section on 'Physiologic interpretation of the serum anion gap' and "The delta anion gap/delta HCO_3 ratio in patients with a high anion gap metabolic acidosis".)

Response to metabolic alkalosis — The respiratory compensation to metabolic alkalosis should raise the PCO_2 by approximately 0.7 mmHg (0.09 kPa) for every 1 mEq/L elevation in the

serum HCO3 concentration [10,18,19]. A very-easy-to-use relationship to determine if the PCO2 is appropriately increased in response to metabolic alkalosis is [20]:

$$PCO2 = HCO3 + 10$$

Although the PCO2 should not increase above 55 mmHg (7.3 kPa) with severe metabolic alkalosis, higher PCO2 levels may develop. It is believed that these very high PCO2 levels are probably caused by respiratory muscle weakness associated with marked hypokalemia and potassium depletion, which almost invariably develop in these patients [18,20].

Respiratory acid-base disorders — The compensatory response to respiratory acid-base disorders occurs in two stages:

- The initial acute response is generated by a variety of pH buffering molecules present in all of the fluid compartments of the body (ie, total body buffering). When the PCO2 (and H2CO3) acutely increases, protons are taken up by hemoglobin and other buffers, generating HCO3-. When the PCO2 (and H2CO3) acutely decreases, protons are released by hemoglobin and other buffers, reducing the HCO3- concentration. These reactions cause the serum HCO3 to increase (in respiratory acidosis) or decrease (in respiratory alkalosis) within 5 to 10 minutes. This acute compensation response is relatively modest.

- A larger compensatory response is generated by the kidneys. This response begins soon after the onset of the primary respiratory disorder but requires **three to five days** to become complete. After completion, the decrease, or increase, in HCO3- is designated chronic compensation for a respiratory acid-base disorder.

- Consequently, different compensatory responses are expected with acute and chronic respiratory disorders:

  - Chronic respiratory acidosis increases kidney acid excretion in the form of titratable acid and ammonium. This generates additional HCO3. Renal tubule HCO3 reabsorption is also increased, and this maintains the higher HCO3 concentration (figure 2) [21,22].

  - Chronic respiratory alkalosis reduces renal HCO3- reabsorption and renal acid excretion. This generates positive acid balance that reduces the serum HCO3 concentration.

  - These kidney responses are carefully regulated and maintained. As an example, administering exogenous HCO3 in the setting of a chronic respiratory acidosis and

relatively normal kidney function results in the urinary excretion of the administered alkali without any further elevation in the serum HCO3 concentration [23].

Response to respiratory acidosis — The compensatory response to acute respiratory acidosis increases the serum HCO3 concentration by approximately 1 mEq/L for every 10 mmHg (1.3 kPa) elevation in the PCO2 (figure 3) [10,24]. If the elevated PCO2 persists, the serum HCO3 will continue to gradually increase and, after three to five days, the disorder is considered chronic. Studies mostly performed in hospitalized patients found that the serum HCO3 increases by 3.5 to 4 mEq/L for every 10 mmHg elevation in PCO2 in patients with chronic respiratory acidosis [10,21,22,25]. One study in stable outpatients with chronic respiratory acidosis found a slightly greater compensatory rise in serum HCO3 of approximately 5 mEq/L per 10 mmHg (1.3 kPa) elevation in PCO2; however, this was a small sample of only 18 patients [26].

The compensatory response to mild to moderate chronic respiratory acidosis (PCO2 less than 70 mmHg [9.3 kPa]) results in an arterial pH that is usually modestly reduced [10,21,22,25] or in the low-normal range (figure 2) [26]. Thus, moderate to severe acidemia in a patient with mild to moderate chronic respiratory acidosis is usually indicative of concurrent metabolic acidosis or superimposed acute respiratory acidosis. Conversely, an arterial pH of 7.40 or higher suggests a concurrent metabolic alkalosis or a superimposed acute respiratory alkalosis.

Response to respiratory alkalosis — The compensatory response to acute respiratory alkalosis reduces the serum HCO3 concentration by 2 mEq/L for every 10 mmHg (1.3 kPa) decline in the PCO2 (figure 3) [10,24]. If the reduced PCO2 persists for more than three to five days, then the disorder is considered chronic and the serum HCO3 concentration should fall by approximately 4 to 5 mEq/L for every 10 mmHg (1.3 kPa) reduction in the PCO2 (figure 4) [10,27].

DIAGNOSIS

There are four primary acid-base disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. Because the renal compensation to respiratory disorders takes three to five days to complete, each primary respiratory disorder can be further subdivided into acute and chronic respiratory acidosis and respiratory alkalosis.

Initial evaluation — Accurate diagnosis of an acid-base disorder requires measurement of serum electrolytes to determine the serum HCO3 concentration, the serum potassium (hypokalemia or hyperkalemia can accompany, and contribute to, many metabolic acid-base

disorders), and the serum sodium and chloride concentrations to detect possible hyponatremia or hypernatremia and calculation of the serum anion gap. In addition, with a high anion gap metabolic acidosis, the magnitude of increase of the anion gap from its baseline should be compared with the reduction in bicarbonate from its normal baseline. The magnitude of these two changes, or deltas, can be evaluated as a "delta anion gap/delta HCO3." (See "Approach to the adult with metabolic acidosis", section on 'Physiologic interpretation of the serum anion gap' and "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

Although a definitive diagnosis of acid-base disorders requires measurement of the arterial pH and PCO2 as well as the serum chemistries to identify the underlying disorder and to determine whether a mixed acid-base disorder exists, measurement of arterial pH is not always required. When the history, physical examination, and serum electrolytes all clearly point toward a particular diagnosis, a presumptive diagnosis can be made. As an example, arterial blood gas analysis might not be required in a previously healthy patient with a recent history of severe diarrhea who has a low serum bicarbonate, hypokalemia, and a normal anion gap. This patient can be assumed to have a nonanion gap (or hyperchloremic) metabolic acidosis because there is no reason to suspect chronic respiratory alkalosis (a disorder that can generate identical electrolytes as a compensatory response).

Although measurement of peripheral venous pH and PCO2 is a less invasive and more convenient approach than arterial measurements, venous results have some important limitations. Thus arterial measurements are preferred for establishing a definite diagnosis. Venous measurements are often used for serial monitoring, but periodic correlation with arterial measurements should be performed. These issues are discussed in detail elsewhere. (See 'Normal values according to site of sampling' above.)

We suggest the following four-step approach:

- Step 1: Establish the primary diagnosis:
    - Metabolic acidosis is characterized by a low serum HCO3 and a low arterial pH; the serum anion gap may be increased or normal.
    - Metabolic alkalosis is characterized by an elevated serum HCO3 and an elevated arterial pH.
    - Respiratory acidosis is characterized by an elevated arterial PCO2 and a low arterial pH.
    - Respiratory alkalosis is characterized by low arterial PCO2 and an elevated arterial pH.

- With the exception of chronic respiratory alkalosis and mild to moderate respiratory acidosis (see 'Mixed acid-base disorders' below), compensatory responses do not usually return the arterial pH to normal.

  Thus, a normal arterial pH in the presence of substantial changes in both serum HCO3 and arterial PCO2 is usually indicative of a **mixed** acid-base disorder (which could include an iatrogenic acute respiratory alkalosis if discomfort from the arterial puncture causes the patient to hyperventilate).

- Step 2: Assess the degree of compensation as defined above for the individual disorders. If the compensatory response is inadequate or excessive for the patient's clinical circumstances, then a **mixed** acid-base disorder exists. (See 'Compensatory respiratory and renal responses' above.)

  Determination of the expected compensatory response requires historical information. This is particularly true for the respiratory acid-base disorders, in which compensation evolves from acute (minutes to a few days) to chronic (three to five days or more). The normal compensatory response to acute respiratory acidosis is an increase in the serum HCO3 concentration by approximately 1 mEq/L for every 10 mmHg (1.3 kPa) elevation in the PCO2. When the respiratory acidosis persists for more than three to five days, the HCO3 increases by approximately 3.5 to 5 mEq/L for every 10 mmHg (1.3 kPa) elevation in the PCO2. (See 'Response to respiratory acidosis' above.)

- Step 3: Determine whether or not the anion gap is elevated. This is especially important for patients with metabolic disorders. If metabolic acidosis exists and the anion gap is increased, compare the increase in anion gap to the decrease in the HCO3 concentration. This delta anion gap/delta HCO3 ratio should be approximately 1 when a simple anion gap metabolic acidosis exists. Interpretation of the anion gap and the delta anion gap/delta HCO3 ratio are discussed elsewhere. (See "Approach to the adult with metabolic acidosis", section on 'Physiologic interpretation of the serum anion gap' and "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

- Step 4: The fourth and final step is to establish the clinical diagnosis. Once the acid-base disorder, or disorders, is identified, the underlying cause or causes of each disorder should be determined and addressed.

Case 1 — A patient with an unknown past history presents with respiratory distress. Arterial blood shows a pH of 7.32, PCO2 of 70 mmHg (9.3 kPa), and HCO3 of 35 mEq/L. The patient is acidemic and has a high PCO2. This is consistent with respiratory acidosis. The PCO2 is approximately 30 mmHg above its normal range. If this is chronic then the HCO3 should

increase by approximately 12 mEq/L (and it was increased by 11 mEq/L from a normal value of 24 mEq/L). Thus, these values are compatible with a diagnosis of a simple (fully compensated) chronic respiratory acidosis.

However, the results are also compatible with a mixed acid-base disorder. This patient could have developed metabolic alkalosis due to gastroenteritis and vomiting. This may have increased his HCO3 from 24 to 32 mEq/L. Perhaps the patient then developed acute respiratory acidosis (from ingestion of a drug that depressed the respiratory center) causing an acute increase in PCO2 from 40 (5.3 kPa) to 70 mmHg (9.3 kPa). This acute respiratory acidosis would further increase the HCO3 by approximately 3 to 36 mEq/L. These two acid-base diagnostic possibilities (chronic respiratory acidosis versus acute respiratory acidosis and metabolic alkalosis) have identical laboratory findings. The only way to differentiate them is an accurate history.

Case 2 — A patient presents with diarrhea. Arterial blood shows a pH of 7.24, PCO2 of 24 mmHg (3.2 kPa), and HCO3 or 10 mEq/L. The low pH indicates acidemia, and the low serum HCO3 concentration indicates metabolic acidosis. The serum HCO3 concentration of 10 mEq/L is approximately 14 mEq/L below normal. This should stimulate respiratory compensation, and the Winters' equation suggests that the PCO2 should be approximately 23 mmHg (3.1 kPa). The HCO3 + 15 rule suggests that the PCO2 should be approximately 25 mmHg (3.3 kPa). Thus, the patient's PCO2 of 24 mmHg (3.2 kPa) is in the appropriate range for compensation for this degree of metabolic acidosis. In addition, the PCO2 is the same as the decimal digits of the arterial pH. (See 'Response to metabolic acidosis' above.)

If the PCO2 had been significantly higher than 24 mmHg (3.2 kPa) these results would be consistent with a mixed metabolic acidosis and respiratory acidosis. This might occur, for example, if the patient were obtunded and had respiratory center depression. If, on the other hand, the PCO2 had been significantly lower than 24 mmHg (3.2 kPa), then mixed metabolic acidosis and respiratory alkalosis exists. Mixed metabolic acidosis and respiratory alkalosis often develops with salicylate intoxication or septic shock [28].

Mixed acid-base disorders — Some patients have two, three, or more relatively independent acid-base disorders. These mixed disorders include combinations of metabolic disorders (eg, vomiting-induced metabolic alkalosis plus hypovolemia-induced lactic acidosis), mixed metabolic and respiratory disorders (eg, metabolic acidosis and respiratory alkalosis in salicylate intoxication), and more complex combinations.

Evaluation of acid-base disorders initially requires identification of the major disorder and then determination of whether the degree of compensation is appropriate. If the compensation is

not appropriate, this is indicative of a second acid-base disorder (ie, a mixed acid-base disorder is present). The following examples are illustrative:

- If metabolic acidosis is the primary disorder, an arterial PCO2 substantially higher than the expected compensatory response defines the mixed disorder of metabolic acidosis and respiratory acidosis, while an arterial PCO2 substantially lower than expected defines the mixed disorder of metabolic acidosis and respiratory alkalosis (which could be produced by acute hyperventilation due to the discomfort of obtaining the blood sample).

- If respiratory acidosis is the major disorder, then the serum HCO3 should be appropriately increased. If the serum HCO3 is not as high as expected, then metabolic acidosis also exists and the arterial pH may be substantially reduced. By contrast, if the serum HCO3 is higher than expected, then metabolic alkalosis complicates the respiratory acidosis and the arterial pH may be inappropriately "normal."

In patients with a high anion gap metabolic acidosis, a diagnosis of a mixed metabolic acidosis and a metabolic alkalosis is generally suggested by calculation and comparison of the delta anion gap and the delta HCO3. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

Case 3 — Determining the appropriate compensatory response may be more difficult with respiratory acid-base disorders because compensatory responses differ in acute and chronic disturbances. Consider a patient with the following arterial blood values: pH 7.27, PCO2 70 mmHg (9.3 kPa), and HCO3 31 mEq/L. The low pH and hypercapnia indicate that the patient has respiratory acidosis. If this patient has acute hypercapnia, then the 30 mmHg (4 kPa) rise in PCO2 should increase the serum HCO3 concentration by approximately 3 mEq/L (to approximately 27 mEq/L). If this patient has chronic hypercapnia, the serum HCO3 should increase by approximately 11 mEq/L (to approximately 35 mEq/L). The observed value of 31 mEq/L is between these expected levels and could have multiple explanations, including:

- Chronic respiratory acidosis with a superimposed metabolic acidosis that has reduced the serum HCO3 from 35 to 31 mEq/L. This might occur in a patient with chronic obstructive pulmonary disease who developed diarrhea due to viral gastroenteritis or lactic acidosis from sepsis.

- Acute respiratory acidosis with a superimposed metabolic alkalosis that has increased the HCO3 from 27 to 31 mEq/L. This could occur in a patient with respiratory depression due to a sedating drug who also developed vomiting or was taking diuretics.

- Acute respiratory acidosis superimposed on mild chronic respiratory acidosis. Suppose, for example, that a patient has chronic respiratory acidosis with a PCO2 of 55 mmHg (7.3 kPa) and an appropriate serum HCO3 of 30 mEq/L. The patient then develops pneumonia, which acutely causes a further increase in the PCO2 to 70 mmHg (9.3 kPa). The serum HCO3 would rise further to approximately 31 mEq/L.

- Acute respiratory acidosis that is evolving into a chronic disorder (between one and three days).

Thus, the correct diagnosis in a primary respiratory acid-base disorder can be established only when correlated with the patient's history and physical examination. This is true even when the arterial blood values appear to represent a simple disorder. If the serum HCO3 concentration had been 35 mEq/L in this example, the findings would have been compatible with an uncomplicated chronic respiratory acidosis. However, similar findings could have been induced by acute respiratory acidosis plus metabolic alkalosis. The history usually helps to distinguish among the possibilities. (See 'Respiratory acid-base disorders' above.)

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: Assessment of oxygenation and gas exchange".)

SUMMARY

- Acid-base status is usually assessed by measuring the components of the bicarbonate-carbon dioxide buffer system in blood. When blood gas analysis is carried out, the partial pressure of CO2 (PCO2) and the pH are each measured using electrodes, and the bicarbonate (HCO3) concentration is calculated with the Henderson-Hasselbalch equation. When the HCO3 is measured in venous blood, it is usually measured directly as "total CO2" with an ion-selective electrode. The directly measured venous "total CO2" is generally approximately 2 mEq/L greater than the simultaneously calculated arterial HCO3. (See 'Physiology and assessment of acid-base status' above.)

- The range of normal values for acid-base parameters is different for arterial and venous samples and also varies among laboratories (see 'Normal values according to site of sampling' above):

- For an arterial sample, the normal range for pH is 7.35 to 7.45; for bicarbonate (HCO3) concentration, 21 to 27 mEq/L; and for PCO2, 35 to 45 mmHg (4.7 to 6.0 kPa).
- For a peripheral venous sample, the range for pH is approximately 0.03 to 0.04 pH units lower than in arterial blood; for HCO3 concentration, approximately 2 to 3 mEq/L higher; and for PCO2, approximately 3 to 8 mmHg (0.4 to 1.1 kPa) higher.
- For a central venous sample, the range for pH is usually 0.03 to 0.05 pH units lower than in arterial blood, and the PCO2 is 4 to 5 mmHg (0.5 to 0.7 kPa) higher, with little or no increase in serum HCO3.

- Each simple acid-base disorder is normally associated with a compensatory response that reduces the change in the HCO3/PCO2 ratio and therefore in pH (figure 1). (See 'Metabolic acid-base disorders' above and 'Respiratory acid-base disorders' above.)
- A simple acid-base disorder includes the initial disturbance of acid-base status and the appropriate degree of compensation for that disturbance. (See 'Definitions of acid-base disorders' above.)
- The simultaneous presence of more than one acid-base disturbance is called a mixed acid-base disorder. Mixed acid-base disorders can be suspected from the patient's history, from a lesser- or greater-than-expected compensatory response, and from analysis of the delta anion gap and delta HCO3. (See 'Definitions of acid-base disorders' above.)
- We suggest the following four-step approach for the evaluation of patients with acid-base disorders (see 'Initial evaluation' above):
  - Establish the primary diagnosis. Metabolic acidosis is characterized by a low serum HCO3 and a low arterial pH; the serum anion gap may be increased or normal. Metabolic alkalosis is characterized by an elevated serum HCO3 and an elevated arterial pH. Respiratory acidosis is characterized by an elevated arterial PCO2 and a low arterial pH. Respiratory alkalosis is characterized by low arterial PCO2 and an elevated arterial pH. (See 'Initial evaluation' above.)
  - Assess the degree of compensation as defined above for the individual disorders. If compensation is inadequate or excessive, this is indicative of a mixed acid-base disorder. (See 'Initial evaluation' above and 'Compensatory respiratory and renal responses' above.)
  - Determine whether or not the anion gap is elevated. If it is, then analyze the ratio of the increase in anion gap to the decrease in the HCO3 concentration. This is the delta

anion gap/delta HCO3 ratio. When an anion gap acidosis exists, these changes should be quantitatively similar to one another; that is, the delta anion gap should be of similar magnitude as the delta HCO3. (See 'Initial evaluation' above.)

- Establish the clinical diagnosis. Once the acid-base disorder, or disorders, is identified, the underlying cause or causes of each disorder should be determined and addressed.

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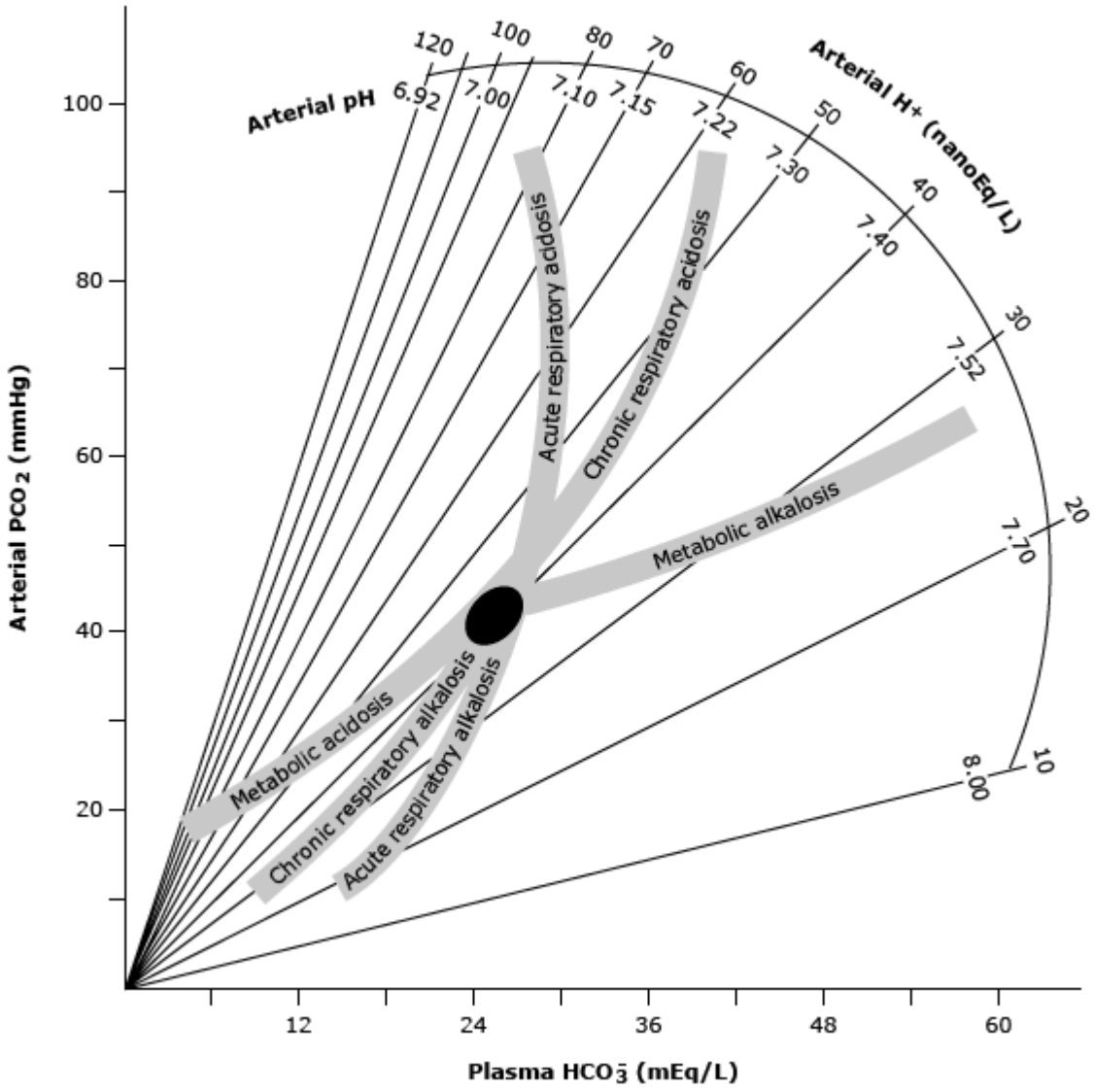
Topic 2352 Version 28.0

GRAPHICS

Expected compensation ranges for simple acid-base disorders



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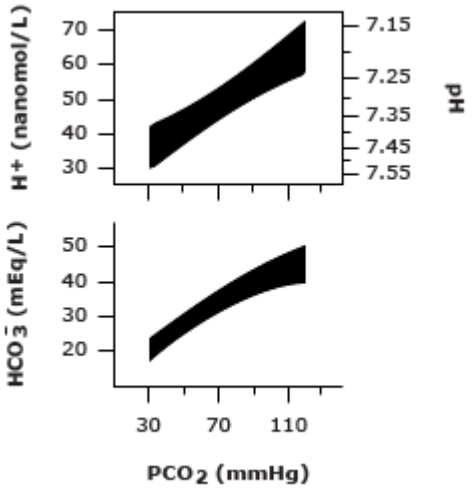
Graphic 79833 Version 9.0

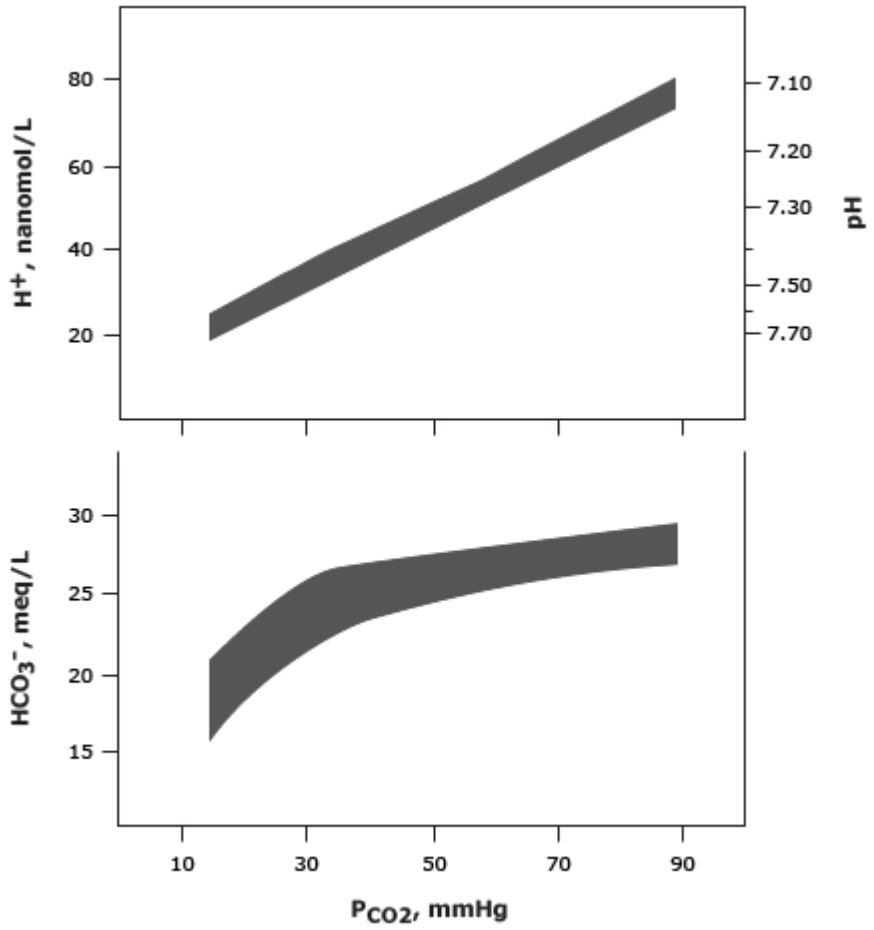
Compensation to chronic respiratory acidosis



95% significance bands for plasma pH and H^+ and HCO_3^- concentrations in chronic hypercapnia. Because of the compensatory rise in the plasma HCO_3^- concentration, there is much less change in H^+ concentration and pH than in acute hypercapnia.

Graphic 63315 Version 4.0

Compensations to acute respiratory acidosis and alkalosis

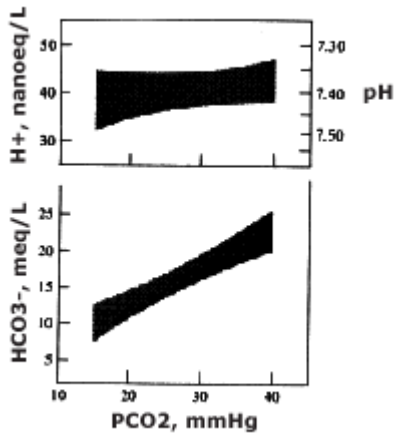


Combined significance bands for plasma pH and concentrations of H+ and HCO3- in acute respiratory acidosis and alkalosis in humans. In uncomplicated acute respiratory acid-base disorders, values for the H+ and HCO3- concentrations will, with an estimated 95 percent probability, fall within the band. Values lying outside the band indicate the presence of a complicating metabolic acid-base disturbance.

Arbus GS, Herbert LA, Levesque PR, et al. N Engl J Med 1969; 280:117. By permission from the New England Journal of Medicine.

Graphic 58687 Version 5.0

Compensatory response to chronic respiratory alkalosis



Combined significance bands for plasma pH and concentrations of H+ and HCO3- in chronic respiratory alkalosis in humans. In uncomplicated chronic respiratory alkalosis, values for the H+ and HCO3- concentrations will, with an estimated 95 percent probability, fall within the band. Values lying outside the band indicate the presence of a complicating metabolic acid-base disturbance. Note that the compensatory reduction in the plasma HCO3- concentration is so effective that there is little fall in pH.

Graphic 75327 Version 2.0