Mixed Acid-Base Disturbances: Core Curriculum 2025

Biff F. Palmer and Deborah J. Clegg

Mixed acid-base disorders are frequently encountered in clinical practice and due to their complexity, diagnoses and treatment are challenging. The opposing effects of multiple disturbances can lead to blood pH levels that are near normal or separate acid-base disturbances can have an additive effect leading to more significant changes in blood and intracellular pH. A systematic evaluation of patient history, physical examination, and laboratory results (including acid-base balance, anion gap, electrolytes, and urine parameters) enables the rapid diagnosis of mixed acid-base disorders by analyzing the appropriateness of compensatory mechanisms, assessing changes in serum and urine electrolytes, and estimating urinary acid excretion. Eight cases are provided to illustrate the approach to mixed acid-base disturbances. Examples include mixed metabolic and respiratory acid-base disorders, mixed respiratory acid-base disorders, and mixed metabolic acid-base disorders.

Complete author and article information provided at end of article.

Correspondence to B.F. Palmer (bipalmer@ttuhsc.edu)

Am J Kidney Dis. 86(3):372-382. Published online July 29, 2025.

doi: 10.1053/j.ajkd.2025.04.014

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Mixed acid-base disorders are frequently encountered in clinical practice. In some settings the opposing effects of multiple disturbances can lead to blood pH levels that are near normal. On the other hand, separate acid-base disturbances can have a cumulative effect leading to more significant changes in blood and intracellular pH as compared to a single disturbance, potentially causing a greater negative impact on organ function. Due to their complexity, diagnosing and treating mixed disorders is challenging. Therefore, it is crucial for clinicians to recognize when acid-base parameters indicate a mixed disturbance and to understand both the benefits and complications of treatment.

Approach to the Diagnosis of Mixed Acid-Base Disorders

The installment in *AJKD*'s Core Curriculum in Nephrology will utilize the traditional approach to mixed disorders where acid-base balance is viewed as the outcome of the interaction between the net H^+ balance and the body's buffers, primarily using the H_2CO_3/ HCO_3^- buffer system in the extracellular fluid shown by the reaction below:

$$H^+ + HCO_3^- \Leftrightarrow H_2CO_3 \Leftrightarrow CO_2 + H_2O$$

An alternative method utilized by many surgeons and critical care specialists for analyzing acid-base disorders is the Stewart or strong ion approach where the pH of a solution is determined by 3 independent variables: strong ion difference, pCO_2, and the total concentration of nonvolatile acids. This method is more complex and arguably more prone to error given its reliance on multiple measurements of several variables. The authors' approach utilizing serum pH, HCO_3^-, pCO_2, and anion gap (corrected for albumin concentration) is much simpler to understand and more widely used, and provides the correct clinical diagnosis in the vast majority of circumstances.

Blood pH and $Paco_2$ are generally obtained from blood gas analysis utilizing analytic electrodes. The serum HCO_3^- concentration can either be calculated utilizing the Henderson-Hasselbalch equation (see below) or measured in venous blood where the concentration is approximated by measurement of total CO_2 with either an ion-selective electrode or enzymatic assay. These methods measure total CO_2 by acidifying a sample and determining the amount of CO_2 released. Since HCO_3^- accounts for approximately 95% of total CO_2, the serum HCO_3^- value can be used in place of total CO_2 in the Henderson-Hasselbalch equation, except when $Paco_2$ is significantly elevated.*

$$pH = 6.10 + \log\left(\left[HCO_3^-\right] / \left[0.03 \times Paco_2\right]\right)$$

Venous blood gas values differ from arterial values due to uptake and buffering of metabolically produced CO_2 and organic acids as

*What is the total CO_2 in a patient with a Pco_2 of 80 mm Hg and a serum HCO_3^- of 24 mmol/L? The total CO_2 is the sum of HCO_3^-, dissolved CO_2, and carbamino compounds. Carbamino compounds contribute only a small amount and are not typically measured directly. One can calculate the dissolved CO_2 from the Pco_2 using a solubility coefficient: Dissolved CO_2 = Pco_2 × Solubility coefficient; Dissolved CO_2 = 80 mm Hg × 0.03 mmol/L/mm Hg; therefore, Dissolved CO_2 = 2.4 mmol/L, and the total CO_2 is 24 mmol/L + 2.4 mmol/L = 26.4 mmol/L in this example.

blood emerges from peripheral capillary beds. Compared to arterial blood, peripheral venous blood typically has a slightly lower pH (by 0.03 to 0.04 units), a higher bicarbonate level (by 2 to 3 mEq/L), and a higher partial pressure of carbon dioxide ($Paco_2$) (by 3 to 8 mm Hg).

Definition of Simple and Mixed Acid-Base Disorders

While the Henderson-Hasselbalch equation can be used to calculate the pH, the $Paco_2$ or the HCO_3^- concentration when 2 of the variables are known and one is not known, one of its major advantages is its separation of HCO_3^- concentration and $Paco_2$ as determinants of blood pH. Metabolic disturbances are initiated by changes in serum HCO_3^- concentration, whereas respiratory disturbances are initiated by changes in $Paco_2$. There are 4 primary acid-base disturbances. *Metabolic acidosis* is due to a primary reduction in serum HCO_3^- concentration and *metabolic alkalosis* is initiated by a primary elevation in serum HCO_3^- concentration. *Respiratory acidosis* is due to an elevation in $Paco_2$, whereas *respiratory alkalosis* is due to a reduction in $Paco_2$.

Shortly after the onset of either a primary metabolic or respiratory acid-base disturbance, a compensatory change occurs in the opposite system which mitigates the change in ratio of HCO_3^- and $Paco_2$ in the Henderson-Hasselbalch equation (ie, in metabolic disturbances, $Paco_2$ adjusts, and in respiratory disturbances, HCO_3^- changes). As a result, the serum pH is returned towards but not completely to normal. In certain cases of chronic hypocapnia and hypercapnia, blood pH may remain close to normal suggesting the compensatory response in these disorders is more efficient. Nevertheless, a normal pH in the setting of abnormal values for HCO_3^- and $Paco_2$ should prompt consideration for the presence of a mixed respiratory and metabolic acid-base disturbance. The timing and extent of adaptive responses to each primary acid-base disturbance have been studied and determined in both animals and humans and are given in Box 1. Each primary acid-base disturbance involves not only the initial change in HCO_3^- or $Paco_2$ but also the secondary compensatory response. A simple acid-base disturbance is diagnosed when the compensatory response falls within the predicted range for that disturbance. Mixed metabolic and respiratory acid-base disturbances are present when the compensatory response deviates from the expected range for the primary disturbance. It is important to note that even when the acid-base parameters suggest a simple disturbance, a mixed disturbance may still be present, especially if one of the coexisting disturbances is of small magnitude and not clinically significant.

In addition to assessing the degree of compensation for a given primary disorder, measurement of serum electrolytes to include the serum concentration of Na^+, Cl^-, K^+ and HCO_3^- can assist in the detection of mixed disturbances. The anion gap should be calculated using the serum concentration of Na^+, Cl^-, and HCO_3^- according to the equation below.

$$\text{Anion gap} = Na^+ - \left([Cl^-] + [HCO_3^-]\right)$$

The average value of the anion gap has varied over time based on measurement techniques. Initial value ranged from 11 to 15 when Na^+ and Cl^- were measured by flame photometry and colorimetric assays respectively. With the advent of ion selective electrodes, Cl^- values have increased causing a reduction in the normal anion gap to as low as 6. In an attempt to return values back to historical norms, some laboratories have lowered the calibration set point of Cl^-. Given these variables it is important for the clinician to be familiar with the normal values of the anion gap established by their chosen laboratory. In cases discussed below the authors use a range of 12 to 14 for the normal anion gap. As mentioned previously, one should correct the anion gap for any reduction in serum albumin concentration by adding 2.5 to the calculated anion gap for each g/dL below a normal baseline of 4 g/dL.

The degree to which the anion gap is increased should be compared to the reduction of the serum HCO_3^- from its normal baseline. A simple anion gap metabolic acidosis is present when the magnitude of the 2 changes is roughly equivalent (Δ anion gap/Δ HCO_3^-). Significant deviations from this relationship identifies a mixed disturbance. An additional factor that can disrupt the relationship between the increase in anion gap and fall in serum HCO_3^- concentration is intracellular buffering (Fig 1). The serum K^+ concentration is useful in determining the cause of a normal anion gap metabolic acidosis. Hypokalemia is typically present in type 1 distal and type 2 proximal renal tubular acidosis while hyperkalemia is present in type 4

Box 1. Compensation in Acid-Base Disorders

- Acute respiratory acidosis
  - For every 10 mm Hg rise in $Paco_2$ the HCO_3^- increases by 1 mEq/L
- Chronic respiratory acidosis
  - For every 10 mm Hg rise in $Paco_2$ the HCO_3^- increases by 3.5 mEq/L
- Acute respiratory alkalosis
  - For every 10 mm Hg fall in $Paco_2$ the HCO_3^- decreases by 2 mEq/L
- Chronic respiratory alkalosis
  - For every 10 mm Hg decrease in $Paco_2$ the HCO_3^- decreases by 5 mEq/L
- Metabolic acidosis
  - Winter's formula: $Paco_2 = 1.5\ [HCO_3^-] + 8 \pm 2$
  - 1.2 mm Hg decrease in $Paco_2$ for each 1 mEq/L fall in HCO_3^-
  - $Pco_2 = HCO3^- + 15$
  - Pco_2 = last digits of pH
- Metabolic alkalosis
  - $Paco_2$ increases by 0.7 for each mEq/L in HCO_3^-

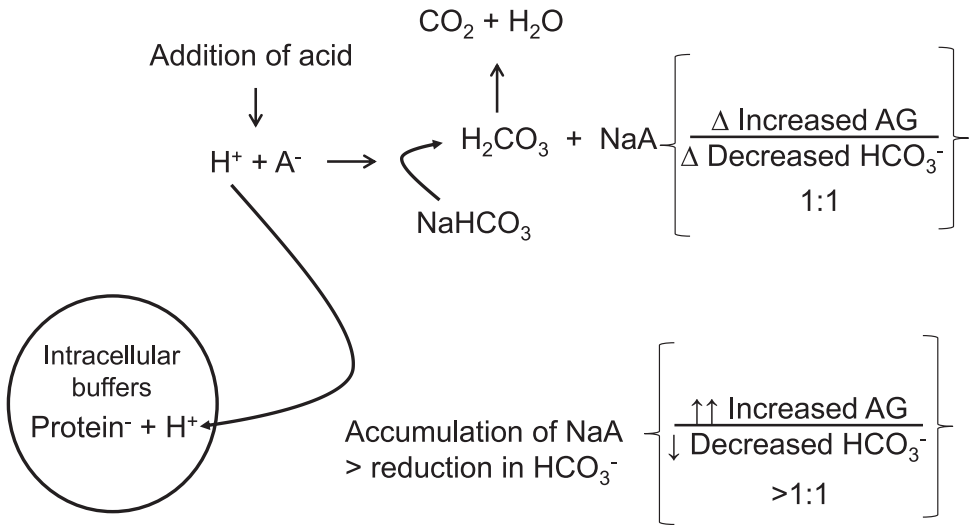

Figure 1. Intracellular buffering of H^+ and effect on the relationship between increased anion gap and reduction in serum HCO_3^- concentration. In the first several hours of increased acid production, buffering primarily occurs within the extracellular space, resulting in an increase in anion gap that is roughly equivalent to the drop in serum HCO_3^- concentration. Over time, the distribution of hydrogen ions becomes markedly different from that of acid anions such as lactate. The anions retained within the body and not eliminated by the kidney remain predominantly confined to the extracellular compartment, contributing to an increased anion gap while up to 50% of H^+ liberated by these acids is buffered intracellularly and within bone. When buffering occurs within cells or bone, there is little to no corresponding decline in serum HCO_3^- concentration. As a result, the increase in the anion gap may exceed the reduction in serum bicarbonate, leading to a widened anion gap that is disproportionate to the fall in HCO_3^-. Abbreviation: AG, anion gap.

renal tubular acidosis. In addition, treatment of mixed acid-base disorders will often impact the serum K^+ concentration due to alterations in total body K^+ content or distribution across the cell membrane.

Examination of the serum Cl^- concentration with respect to the serum Na^+ concentration is also useful in the detection of acid-base disturbances. As the serum Na^+ concentration either increases or decreases due to disorders in tonicity, the serum Cl^- concentration should change in in parallel and to the same extent. If the serum Cl^- concentration moves in a direction opposite or changes disproportionately to the change in serum Na^+ concentration an acid-base disorder is suggested. For example, acute or chronic respiratory acidosis or metabolic alkalosis will cause the Cl^- concentration to decrease with respect to the serum Na^+ concentration. The fall in Cl^- concentration will be accompanied by an increase in the serum HCO_3^- concentration in these conditions. On the other hand, whenever the Cl^- concentration is increased with respect to the serum Na^+ concentration one should suspect the presence of either an acute or chronic respiratory alkalosis or a normal gap metabolic acidosis. The rise in chloride concentration will be accompanied by a fall in the serum bicarbonate concentration in these conditions.

Measurement of urinary electrolytes can also be useful to gain further insight into acid-base disturbances. Calculation of the urinary anion and/or osmolar gap to indirectly assess urinary NH_4^+ excretion gap can provide information as to whether an underlying metabolic acidosis is of kidney or extra renal origin. Of these 2, the urine osmolal gap is preferred since the relationship between the osmolal gap and urine ammonium is not disrupted by a high concentration of unmeasured urine anions such as β-hydroxybutyrate or hippurate. On the other hand, the urinary excretion of non-ammonium solutes not included in the calculation of the osmolal gap such as methanol, ethylene glycol, and mannitol may lead to an increased osmolal gap, even in the absence of elevated renal ammonium excretion. The urinary Cl^- concentration is useful in categorizing patients with metabolic alkalosis as to Cl^- responsive or Cl^- resistant thereby facilitating the diagnosis of the underlying cause.

It is crucial to take a thorough history and conduct a detailed physical examination to identify potential causes of an acid-base disorder. The information gathered during this process alerts the clinician to the possible presence of a mixed disturbance. For instance, patients with poorly controlled diabetes mellitus, or hypotension who are receiving diuretics or undergoing gastric drainage may present with both metabolic acidosis and metabolic alkalosis. Similarly, individuals with salicylate toxicity or sepsis often exhibit metabolic acidosis and respiratory alkalosis. Patients with severe congestive heart failure frequently experience mixed respiratory and metabolic acid-base disturbances.

A systematic evaluation of patient history, physical examination, and laboratory results (including acid-base

balance, anion gap, electrolytes, and urine parameters), enables the rapid diagnosis of mixed acid-base disorders by analyzing the appropriateness of compensatory mechanisms, assessing changes in serum and urine electrolytes, and estimating urinary acid excretion. An approach to interpreting a basic metabolic profile and arterial blood gas is provided in Box 2. In the following sections various cases of acid-base disturbances will be presented illustrating how such a systematic evaluation can be utilized to uncover the presence of mixed disturbances.

Box 2. Steps to Interpreting a Basic Metabolic Profile and Arterial Blood Gas

Step1: First check serum [Na^+], and work up tonicity disorders if abnormal.
Step 2: Check serum [Cl^-].
- If reduced with respect to any change in Na^+, consider presence of:
  - o Metabolic alkalosis
  - o Chronic respiratory acidosis
- If increased with respect to any change in Na^+, consider presence of
  - o Chronic respiratory alkalosis
  - o Normal gap acidosis

Step 3: Calculate anion gap.
Step 4: For ↑ anion gap, determine whether measured [HCO_3^-] is equal to predicted [HCO_3^-].
Step 5: Analyze arterial blood gas.
Step 6: Check K^+.

Additional Readings

- Adrogué H, Gennari F, Galla J, Madias N. Assessing acid-base disorders *Kidney Int*. 2009;76(12):1239-1247. doi:10.1038/ki.2009.359 ★ESSENTIAL READING
- Adrogué HJ, Madias NE. Secondary responses to altered acid-base status: the rules of engagement. *J Am Soc Nephrol*. 2010;21(6):920-923. doi:10.1681/ASN.2009121211
- Brackett N, Cohen J, Schwartz W. Carbon dioxide titration curve of normal man: effect of increasing degrees of acute hypercapnia on acid-base equilibrium. *N Engl J Med*. 1965;272:6-12. doi:10.1056/NEJM196501072720102
- González SB, Menga G, Raimondi GA, Tighiouart H, Adrogué HJ, Madias NE. Secondary response to chronic respiratory acidosis in humans: a prospective study. *Kidney Int Rep*. 2018;3(5):1163-1170. doi:10.1016/j.ekir.2018.06.001
- Krapf R, Beeler I, Hertner D, Hulter HN. Chronic respiratory alkalosis: the effect of sustained hyperventilation on renal regulation of acid-base equilibrium. *N Engl J Med*. 1991;324(20):1394-1401. doi:10.1056/NEJM199105163242003
- Madias NE, Bossert WH, Adrogué HJ. Ventilatory response to chronic metabolic acidosis and alkalosis in the dog. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56(6):1640-1646. doi:10.1152/jappl.1984.56.6.1640
- Palmer BF, Clegg DJ. Metabolic alkalosis treatment standard. *Nephrol Dial Transplant*. 2024;39(12):1985-1992. doi:10.1093/ndt/gfae195
- Palmer BF, Clegg DJ. The use of selected urine chemistries in the diagnosis of kidney disorders. *Clin J Am Soc Nephrol*. 2019;14(2):306-316. doi:10.2215/CJN.10330818 ★ESSENTIAL READING

Mixed Metabolic and Respiratory Acid-Base Disorders

Case 1: *A 28-year-old woman is brought to the emergency department because of a 2-week history of progressive generalized weakness. Her blood pressure is 120/75 mm Hg, and there are generalized reductions in her deep tendon reflexes. The laboratory values show the following (mEq/L): Na^+, 136; K^+, 2.6; Cl^-, 118; HCO_3^-, 8; creatinine, 1.4 mg/dL; and serum urea nitrogen (SUN), 22 mg/dL. An arterial blood gas shows pH of 7.16 and $Paco_2$ of 31 mm Hg. Urine electrolytes show (mEq/L): Na^+, 50; K^+, 35; and Cl^-, 80.*

Question 1: Which one of the following best describes the acid-base disturbance in this patient?

(a) Normal gap metabolic acidosis and respiratory alkalosis
(b) Normal gap metabolic acidosis
(c) Normal gap metabolic acidosis and respiratory acidosis
(d) Chronic respiratory alkalosis

For the answer to this question, see the following text.

The low pH in this patient indicates the net effect of the underlying processes (whether respiratory, metabolic, or both) have resulted in acidemia. Determining which determinant of the arterial pH has moved in the acid direction indicates the primary disturbance. In this case metabolic acidosis is primary since the HCO_3^- concentration has moved in the acid direction. In cases where both the HCO_3^- and $Paco_2$ move in the acid direction then a mixed disturbance of metabolic and respiratory acidosis is present. The acidosis is of the normal anion gap type based on examination of the serum electrolytes. This disturbance was suggested by the disproportionate increase in serum Cl^- concentration with respect to the serum Na^+ concentration since this pattern is only found with either chronic respiratory alkalosis or normal anion gap metabolic acidosis. After metabolic acidosis is identified as the primary process, one then needs to determine if the $Paco_2$ has decreased by the expected amount for compensation. The increase in ventilation in response to metabolic acidosis is rapid and usually complete by 12 to 24 hours and is due to stimulation of peripheral chemoreceptors and those in the medulla oblongata. The Winter's formula is utilized to assess the expected degree of ventilatory response to metabolic acidosis and is given below.

$$Paco_2 = 1.5\ [HCO_3^-] + 8 \pm 2$$

Alternatively, adding 15 to the measured HCO_3^- concentration provides a close approximation to values obtained with the Winter's formula. In this case, the measured $Paco_2$ is higher than expected indicating the simultaneous presence of metabolic acidosis and respiratory acidosis making choice (c) the correct answer. The expected degree of compensation should have resulted in a pCO_2 of approximately 20-23 mm Hg. Even though the measured value of 31 mm Hg is less than the normal value of 40 mm Hg, respiratory acidosis is considered present since this degree of ventilation is an inadequate response to the acidemic pH. A potential cause of the insufficient respiratory response in this case is severe total body K^+ deficiency. Since a normal anion gap acidosis is a cause of K^+ shift into the extracellular compartment, the decreased serum K^+ concentration indicates severe total body depletion placing this patient at risk for respiratory muscle paralysis and/or rhabdomyolysis. K^+ should be given in a non-dextrose containing solution before HCO_3^- therapy because correction of metabolic acidosis will cause an intracellular shift of K^+, leading to a further decrease in the extracellular fluid concentration. The positive urinary anion gap indicating lack of ammoniagenesis, along with hypokalemia, suggests the patient suffers from a type 1 distal renal tubular acidosis, a condition in which weakness can progress insidiously over 24 to 48 hours to complete flaccid quadriplegia.

Respiratory compensation for metabolic acidosis has limitations. In cases where the serum bicarbonate falls below 7-8 mEq/L, maximally increased ventilation can only lower the $Paco_2$ to values typically between 8 and 12 mm Hg. Sustained ventilation in this range can lead to respiratory muscle fatigue ultimately limiting the degree of expected adaptation.

Additional Readings

- Aronson P, Giebisch G. Effects of pH on potassium: new explanations for old observations. *J Am Soc Nephrol* 2011;22(11):1981-1989. doi:10.1681/ASN.2011040414 ★ESSENTIAL READING
- Bushinsky D, Coe F, Katzenberg C, Szidon J, Parks J. Arterial P_{CO2} in chronic metabolic acidosis. *Kidney Int* 1982;22(3):311-314. doi:10.1038/ki.1982.172.
- Kraut J, Madias N. Differential diagnosis of nongap metabolic acidosis: value of a systematic approach. *Clin J Am Soc Nephrol*. 2012;7(4):671-679. doi:10.2215/CJN.09450911 ★ESSENTIAL READING
- Palmer BF, Clegg DJ. Hyperchloremic normal gap metabolic acidosis. *Minerva Endocrinol*. 2019;44(4):363-377. doi:10.23736/S0391-1977.19.03059-1
- Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: core curriculum 2019. *Am J Kidney Dis*. 2019;74(5):682-695. doi:10.1053/j.ajkd.2019.03.427

Case 2: *A 35-year-old woman was found markedly disoriented by her roommate approximately 12 hours ago. Her history is noteworthy for being distraught after breaking up with her partner. She is taking no medications. The physical examination shows a blood pressure of 130/80 mm Hg lying and 110/62 standing, pulse of 102, and respiratory rate of 28. The remainder of the examination is normal. The laboratory values show the following (mEq/L): Na^+, 138; K^+, 3.6; Cl^-, 102; HCO_3^-, 15; creatinine, 1.3 mg/dL; SUN, 22 mg/dL; and serum osmolality, 295 mOsm/kg (osmolar gap <10). An arterial blood gas shows pH of 7.46 and $Paco_2$ of 18 mm Hg.*

Question 2: Which one of the following best describes the acid-base disturbance in this patient?

(a) Chronic respiratory alkalosis
(b) Respiratory alkalosis and anion gap metabolic acidosis
(c) Anion gap metabolic acidosis and normal gap metabolic acidosis
(d) Respiratory alkalosis and metabolic alkalosis

For the answer to this question, see the following text.

The high pH with a $Paco_2$ moving in an alkaline direction identifies the presence of respiratory alkalosis as the primary disturbance. The clinical history suggests this is an acute (<24-48 hours in duration) versus a chronic process which is important in assessing the compensatory change in serum HCO_3^- concentration. The expected immediate compensation with acute respiratory alkalosis is a fall in HCO_3^- concentration of 2 mEq/L for each 10 mm Hg drop in the $Paco_2$. This change is due to movement of HCO_3^- into the red blood cells in exchange for Cl^- via the anion exchange band 3 protein found on the red blood cell membrane. The drop in serum HCO_3^- concentration falls outside of the range expected for compensation and along with the increase in serum anion gap suggests the simultaneous presence of an anion gap metabolic acidosis making choice (b) the correct answer. A likely diagnosis in this case is salicylate poisoning which frequently presents with this mixed disturbance. Salicylate exerts a direct stimulatory effect on the respiratory center to cause increased ventilation and also alters cellular metabolism to increase ketogenesis and lactate production, the latter 2 of which account for the increase in anion gap (Fig 2). Less likely considerations are sepsis and chronic liver disease. Unexplained respiratory alkalosis can be the initial presentation in sepsis due to a stimulatory effect of circulating endotoxin on the respiratory center while increased circulating progesterone drives increased ventilation in advanced liver disease. Both conditions can be associated with lactic acidosis.

The compensatory response to chronic respiratory alkalosis is a fall in HCO_3^- concentration of 5 mEq/L for each 10 mm Hg drop in the $Paco_2$. Sustained hypocapnia of greater than 24 to 48 hours leads to decreased HCO_3^- reabsorption in the proximal tubule through parallel decreases in the rate of the luminal Na^+/H^+ antiporter and the basolateral Na^+-$(HCO_3^-)_3$ cotransporter. Loss of

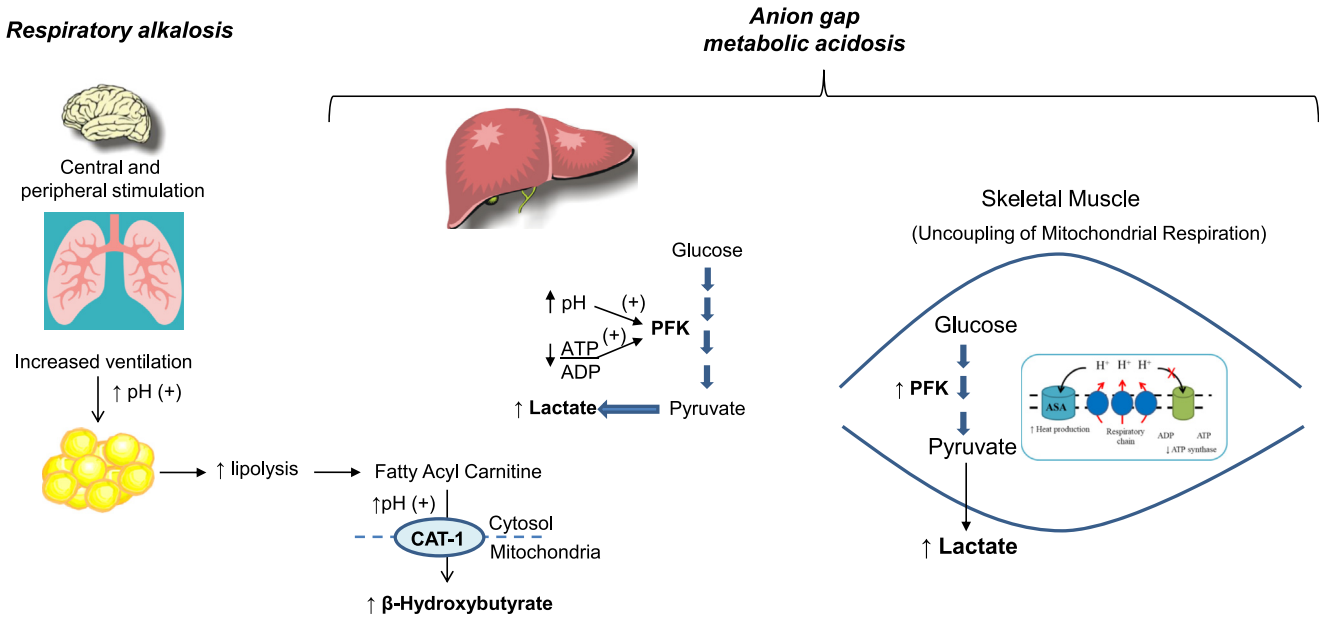

Figure 2. Development of respiratory alkalosis and increased anion gap metabolic acidosis in salicylate poisoning. Salicylates exert a stimulatory effect on the respiratory center accounting for the development of respiratory alkalosis. Alkalemia stimulates hormone-sensitive lipase, resulting in increased lipolysis and delivery of fatty acids to the liver. Increased blood pH also decreases the inhibitory effect of malonyl-coenzyme A on CAT-1, causing delivered fatty acids to preferentially enter the mitochondria and resulting in increased ketogenesis. Salicylates also uncouple oxidative phosphorylation in the mitochondria impairing production of ATP. The reduction in the ATP/ADP ratio and the increased pH both stimulate PFK, the rate-limiting enzyme for glycolysis, resulting in increased lactic acid production. Increased lactic acid and ketoacid production are primarily responsible for the increase in the anion gap. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CAT-1, carnitine palmitoyltransferase; PFK, phosphofructokinase

$NaHCO_3$ in the urine reduces effective arterial blood volume secondarily activating mechanism to retain NaCl. The net effect is a decrease in serum HCO_3^- concentration and an increase in serum Cl^- concentration out of proportion to any change in serum Na^+ concentration.

Additional Readings

- Cogan MG. Chronic hypercapnia stimulates proximal bicarbonate reabsorption in the rat. *J Clin Invest*. 1984;74(6):1942-1947. doi:10.1172/JCI111614
- Gabow P, Anderson R, Potts D, Schrier R. Acid-base disturbances in the salicylate-intoxicated adult. *Arch Intern Med*. 1978;138(10):1481-1484. doi:10.1001/archinte.1978.03630350019008
- Palmer BF, Clegg DJ. Salicylate toxicity. *N Engl J Med* 2020;382(26):2544-2555. doi:10.1056/NEJMra2010852 ★ESSENTIAL READING

Case 3: *A 39-year-old man is evaluated in the emergency department because of severe left flank pain and hematuria after playing softball. The pain is sharp and radiates to the groin. He vomited 8 times before presentation. He has a nonobstructing radio-opaque kidney stone at the ureteropelvic junction on the left side. The physical examination is significant for a blood pressure of 130/90 mm Hg and pulse of 110/minute. Laboratory examination shows the following results (mEq/L): Na^+, 141; K^+, 4.4; Cl^-, 94; HCO_3^-, 34; with a pH of 7.61 and $Paco_2$ of 34 mm Hg. The patient is treated with analgesia and given 2 liters of normal saline and discharged. Two days later his flank pain worsens, but there has been no further vomiting. His blood pressure and pulse are unchanged. The laboratory data now show the following (mEq/L): Na^+, 137; K^+, 4.4; Cl^-, 106; and HCO_3^-, 19; with a pH of 7.48 and $Paco_2$ of 30 mm Hg.*

Question 3: Which one of the following best describes the initial acid-base disturbance in this patient?

(a) Metabolic alkalosis and respiratory alkalosis
(b) Chronic respiratory alkalosis and anion gap metabolic acidosis
(c) Acute respiratory alkalosis and normal gap metabolic acidosis
(d) Chronic respiratory acidosis and metabolic alkalosis

For the answer to this question, see the following text.

The patient has significant and potentially dangerous alkalemia illustrative of how mixed acid base disturbances can have additive effects on arterial pH. Both the serum HCO_3^- and $Paco_2$ are moving in the alkaline direction confirming the presence of both metabolic and respiratory alkalosis making choice (a) the correct answer. The metabolic alkalosis is due to vomiting while pain is presumably responsible for respiratory alkalosis. Unrecognized sepsis from obstructive pyelonephritis can also cause respiratory

alkaloses as circulating endotoxin has a direct effect to stimulate the respiratory center. Alkalemia of this degree is dangerous and can cause clinical tissue hypoxia. Increased pH decreases the ability of hemoglobin to release oxygen in peripheral tissues due to a leftward shift in the oxygen dissociation curve. Tissue hypoxia is further exacerbated by alkalemia induced vasoconstriction and decreased perfusion of the brain, heart, and peripheral circulation. The second set of laboratory data shows resolution of the metabolic alkalosis and the presence of a simple respiratory alkalosis with appropriate compensation.

Additional Readings

- Jhaveri K, Webber A. The case: triple acid-base disorder after drug abuse. *Kidney Int*. 2008;74(10):1363-1364. doi:10.1038/ki.2008.441
- Krapf R, Beeler I, Daniel Hertner M, Hulter H. Chronic respiratory alkalosis-the effect of sustained hyperventilation on renal regulation of acid–base equilibrium. *N Engl J Med* 1991;324(20):1394-1401 doi:10.1056/NEJM199105163242003 ★ESSENTIAL READING
- Laffey J, Kavanagh B. Hypocapnia. *N Engl J Med*. 2002;347(1):43-53. doi:10.1056/NEJMra012457
- Palmer BF. Respiratory alkalosis. *Am J Kidney Dis*. 2012;60:834-838. doi:10.1053/j.ajkd.2012.03.025

Case 4: *A 55-year-old man with a long history of smoking complicated by chronic obstructive pulmonary disease is admitted after increasing shortness of breath over the last 2 to 3 days. One month ago, during a routine follow-up examination, the laboratory tests showed the following results (mEq/L): Na^+, 141; K^+, 4.4; Cl^-, 92; HCO_3^-, 31; with a pH of 7.37, $Paco_2$ of 60 mm Hg, and PO_2 of 64 mm Hg. On physical examination he is noted to have new onset peripheral edema. He is started on a loop diuretic therapy to manage fluid overload with improvement in his shortness of breath. Three days after admission, the following laboratory results are obtained (mEq/L): Na^+, 138; K^+, 3.6; Cl^-, 88; HCO_3^-, 40; creatinine, 1.6 mg/dL; and SUN, 42 mg/dL; with a pH of 7.53 and $Paco_2$ of 60 mm Hg.*

Question 4: Which one of the following best describes the acid-base disturbance in this patient 3 days after admission?

(a) Chronic respiratory alkalosis and anion gap metabolic acidosis
(b) Chronic respiratory acidosis and anion gap metabolic acidosis
(c) Chronic respiratory alkalosis and normal gap acidosis
(d) Chronic respiratory acidosis and metabolic alkalosis

For the answer to this question, see the following text.

The clinical history and laboratory examination one month ago are consistent with a compensated chronic respiratory acidosis. Chronic respiratory acidosis leads to an increase in serum HCO_3^- concentration of 3.5 mEq/L for each 10 mm Hg rise in $Paco_2$ as a compensatory response. Cell acidification leads to augmented HCO_3^- reabsorption in the proximal tubule. As effective arterial blood volume expands, mechanisms to retain NaCl are suppressed resulting in increased urinary excretion of NaCl. The net effect is an increased serum HCO_3^- concentration and a serum Cl^- concentration that is decreased with respect to the serum Na^+ concentration. Acute respiratory acidosis (<24-48 hours) causes similar directional changes in HCO_3^- and Cl^- concertation but to a much lesser extent and is due to a Cl^-/HCO_3^- exchange across the red blood cell membrane. Following initiation of loop diuretic therapy, this patient became alkalemic with the serum HCO_3^- concentration moving in the alkaline direction indicating the primary disturbance is now metabolic alkalosis, likely diuretic induced. If this disorder was the sole disturbance, then the $Paco_2$ should be 51 mm Hg (increase in $HCO_3^- \times 0.7 = 11$). The measure value of 60 mm Hg indicates a mixed disorder due to the presence of respiratory acidosis, making choice (d) correct.

Additional Readings

- Do C, Vasquez P, Soleimani M. Metabolic alkalosis pathogenesis, diagnosis, and treatment: core curriculum 2022. *Am J Kidney Dis* 2022;80(4):536-551. doi:10.1053/j.ajkd.2021.12.016. ★ESSENTIAL READING
- González SB, Menga G, Raimondi GA, Tighiouart H, Adrogué HJ, Madias NE. Secondary response to chronic respiratory acidosis in humans: a prospective study. *Kidney Int Rep* 2018;3(5):1163-1170. doi:10.1016/j.ekir.2018.06.001

Mixed Respiratory Acid-Base Disorders

The importance of the clinical history in interpreting mixed disorders is illustrated by the following scenario. Consider the same set of data from case 4 three days after admission was now found immediately after a patient with a baseline $Paco_2$ of 85 mm Hg was intubated and placed on a ventilator with a high respiratory rate. This scenario is an example of a mixed respiratory acid-base disorder: chronic respiratory acidosis and acute respiratory alkalosis. The predicted compensatory serum HCO_3^- concentration for a $Paco_2$ of 85 mm Hg is 40 mEq/L. The rapid lowering of the $Paco_2$ to 60 mm Hg following intubation results in alkalemia. This sequence of events is referred to as post-hypercapnic metabolic alkalosis and is the result of persistent increased proximal HCO_3^- reabsorption despite lowering of the $Paco_2$. In addition to the increased $Paco_2$, increased reabsorption is due to a combination of factors that reduce effective arterial blood volume to include salt restriction, presence of right sided heart failure, and prior use of diuretics (Fig 3). Restoration of effective arterial blood volume with saline will lower the HCO_3^- concentration to a value predicted for compensation for a $Paco_2$ of 60 mm Hg. Alternatively, acetazolamide is utilized to inhibit proximal HCO_3^- reabsorption in the setting where

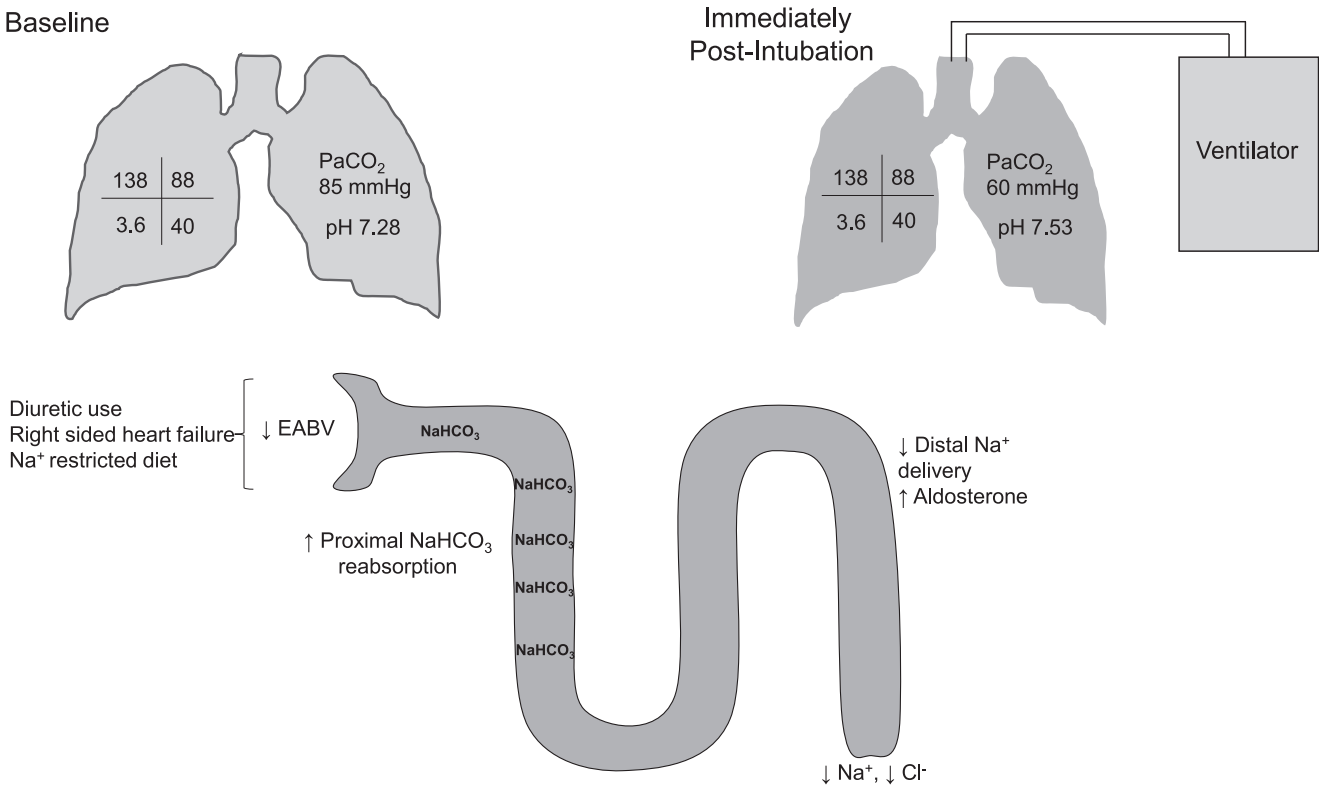

Figure 3. Chronic respiratory acidosis and acute respiratory alkalosis in a patient with chronic obstructive pulmonary disease immediately after intubation (post–hypercapnic metabolic alkalosis). Factors predisposing to the maintenance of metabolic alkalosis are depicted. Abbreviation: EABV, effective arterial blood volume.

an additional salt load would worsen preexisting volume overload.

Case 5: *A 62-year-old man with chronic obstructive pulmonary disease is admitted with fever and increasing shortness of breath; he is discovered to have a right upper load infiltrate. Physical examination is significant for blood pressure, 110/80 mm Hg; pulse, 120; temperature, 38.5° C; and decreased breath sounds and crackles in the right upper lobe. Laboratory results on admission are (mEq/L) Na^+, 135; K^+, 4.6; Cl^-, 90; HCO_3^-, 31; creatinine, 1.2 mg/dL; and SUN, 18 mg/dL; with a pH of 7.32, $Paco_2$ of 60 mm Hg, and Pao_2 of 55 mm Hg. The patient is started on intravenous antibiotic therapy to include vancomycin and gentamicin and is placed on high flow oxygen therapy. Over the next 12 hours the patient is noted to have increased somnolence and the following laboratory data are obtained (mEq/L): Na^+, 135; K^+, 4.6; Cl^-, 88; and HCO_3^-, 33; with a pH of 7.18, $Paco_2$ of 80 mm Hg, and Pao_2 of 70 mm Hg.*

Question 5: Which one of the following best describes the acid-base disturbance in this patient 12 hours after admission?

(a) Chronic respiratory alkalosis and anion gap metabolic acidosis
(b) Chronic respiratory acidosis and acute respiratory acidosis
(c) Chronic respiratory alkalosis and normal gap acidosis
(d) Chronic respiratory acidosis and metabolic alkalosis

For the answer to this question, see the following text.

This case is another example of a mixed respiratory acid-base disorder. The laboratory data on admission is most consistent with chronic respiratory acidosis, consistent with the underlying chronic obstructive pulmonary disease. The admission HCO_3^- concentration of 31 mEq/L is within the predicted range for compensation for a $Paco_2$ 60 mm Hg. Following the administration of antibiotics for treatment of pneumonia and high flow oxygen therapy the patient develops carbon dioxide narcosis with laboratory data showing the superimposition of an acute respiratory acidosis, making choice (b) the correct answer. Red blood cell Cl^- /HCO_3^- exchange in response to the acute 20 mm Hg rise in $Paco_2$ accounts for the small directional changes in serum Cl^- and HCO_3^- concentration in the second set of laboratory data. Gentamicin can cause neuromuscular blockade and is a divalent cation which can compete with calcium entry into skeletal muscle such as the diaphragm resulting in weakness predisposing to respiratory depression in patients with limited respiratory reserve. Administration of high flow rates of supplemental oxygen can lead to reductions in alveolar ventilation and worsening hypercapnia as the hypoxemic drive to ventilation is removed. More

importantly, inhibiting hypoxic pulmonary vasoconstriction with excessive amounts of supplementary oxygen can increase dead space ventilation predisposing to CO_2 retention. Lastly, increased oxygenation in patients with chronic lung disease can cause clinically significant rises in $Paco_2$ due to displacement of CO_2 from hemoglobin, a phenomenon known as the Haldane effect.

Additional Readings

- Hall D, McGibbon D, Evans C, Meadows G. Gentamicin, tubocurarine, lignocaine and neuromuscular blockade. *Br J Anaesth*. 1972;44(12):1329-1332. doi:10.1093/bja/44.12.1329
- Palmer BF, Clegg DJ. Respiratory acidosis and respiratory alkalosis: core curriculum 2023. *Am J Kidney Dis*. 2023;82(3):347-359. doi:10.1053/j.ajkd.2023.02.004 ★ESSENTIAL READING
- Yi Y. Post-hypercapnic alkalosis: a brief review. *Electrolyte Blood Press*. 2023;21(1):18-23. doi:10.5049/EBP.2023.21.1.18

Mixed Metabolic Acid-Base Disorders

Case 6: *A 60-year-old man is referred to the emergency department for evaluation of ataxic gait and slurred speech. He has suffered several similar episodes over the course of 5 months. At baseline, he is fully lucid and ambulatory. Notably, 8 months before presentation he had been admitted for an intestinal volvulus that necessitated the removal of 419 cm of diffusely necrotic jejunum and ileum. Physical examination shows his blood pressure is 140/86 mm Hg, pulse of 86 beats/min, and respiratory rate of 23 breaths/min; his pulse oximetry is 99% on room air. Laboratory results on admission are the following (mEq/L): Na^+, 140; K^+, 4.1; Cl^-, 110; HCO_3^-, 10; creatinine, 1.9 mg/dL; and SUN, 22 mg/dL; with a pH of 7.2 and $Paco_2$ of 25 mm Hg.*

Question 6: Which one of the following best describes the acid-base disturbance in this patient?

(a) Normal gap metabolic acidosis and respiratory alkalosis
(b) Anion gap metabolic acidosis and normal gap metabolic acidosis
(c) Anion gap metabolic acidosis and metabolic alkalosis
(d) Chronic respiratory alkalosis and anion gap metabolic acidosis

For the answer to this question, see the following text.

This patient is acidemic with the serum HCO_3^- concentration going in the acid direction indicating the primary disturbance is a metabolic acidosis. The $Paco_2$ is within the range predicted for compensation. The increased anion gap indicates the presence of an anion gap metabolic acidosis. Whenever the anion gap is increased one should then determine if the serum HCO_3^- concentration has fallen by an amount equal to the increase in anion gap. If the reduction in HCO_3^- is significantly less than the increase in anion gap, a diagnosis of a mixed high anion gap metabolic acidosis and metabolic alkalosis is suggested. In this case, the reduction in HCO_3^- concentration is greater than the increase in anion gap making a diagnosis of both a high anion gap and a normal gap metabolic acidosis, making choice (b) the correct answer. The disproportionate increase in serum Cl^- concentration compared to the serum Na^+ is consistent with the presence of a normal gap metabolic acidosis.

After identification of the underlying acid-base disturbances one then utilizes the clinical history and physical findings to identify the causes of the disorders. The underlying diagnosis in this patient is D-lactic acidosis (Fig 4). In patients with a reduced length of small bowel undigested carbohydrates can reach the colon where the low pH favors growth of bacteria responsible for generation of D-lactate. The standard enzymatic assays used in clinical laboratories are specific for L-lactate, and will not detect elevated levels of D-lactate. Therefore, if D-lactic acidosis is clinically suspected a specific blood test for D-lactate must be explicitly ordered. These patients present with encephalopathy (ataxia, slurred speech) typically following a carbohydrate meal. Accumulation of D-lactate soon after ingestion of the meal when production of D-lactic acid is greatest explains the presence of the high anion gap metabolic. The normal anion gap component of this patients mixed anion non-anion gap acidosis is due to loss of Na^+-D-lactate in the urine which is equivalent to the loss of HCO_3^- from the body since production of D-lactate form D-lactic acid consumes HCO_3^-. Urinary loss of this salt is matched by kidney retention of NaCl in an attempt to maintain volume explaining the development of the normal gap acidosis. The stereospecificity of the lactate cotransporter in proximal tubule is much greater for Na^+-L-lactate compared to Na^+-D-lactate explaining why a normal gap acidosis does not typically develop in cases of L-lactic acidosis. A similar process explains the development of a normal gap metabolic acidosis in the recovery phase of diabetic ketoacidosis and toluene exposure where urinary loss of acid salts (ketoacid and hippuric acid salts respectively) is accompanied by kidney retention of Cl^-.

Additional Readings

- Palmer BF, Clegg DJ. Electrolyte and acid-base disorders in patients with diabetes mellitus. *N Engl J Med*. 2015;373:548-559. doi:10.1056/NEJMra1503102
- Palmer BF, Perazella M, Choi M. American Society of Nephrology quiz and questionnaire 2013: electrolyte and acid-base. *Clin J Am Soc Nephrol*. 2014;9(6):1132-1137. doi:10.2215/CJN.11731113
- Uribarri J, Oh M, Carroll H. D-lactic acidosis: a review of clinical presentation, biochemical features, and pathophysiologic mechanisms. *Medicine (Baltimore)*. 1998;77(2):73-82. doi:10.1097/00005792-199803000-00001 ★ESSENTIAL READING

Case 7: *A 52-year-old unhoused man presents to the emergency department reporting weakness. He typically*

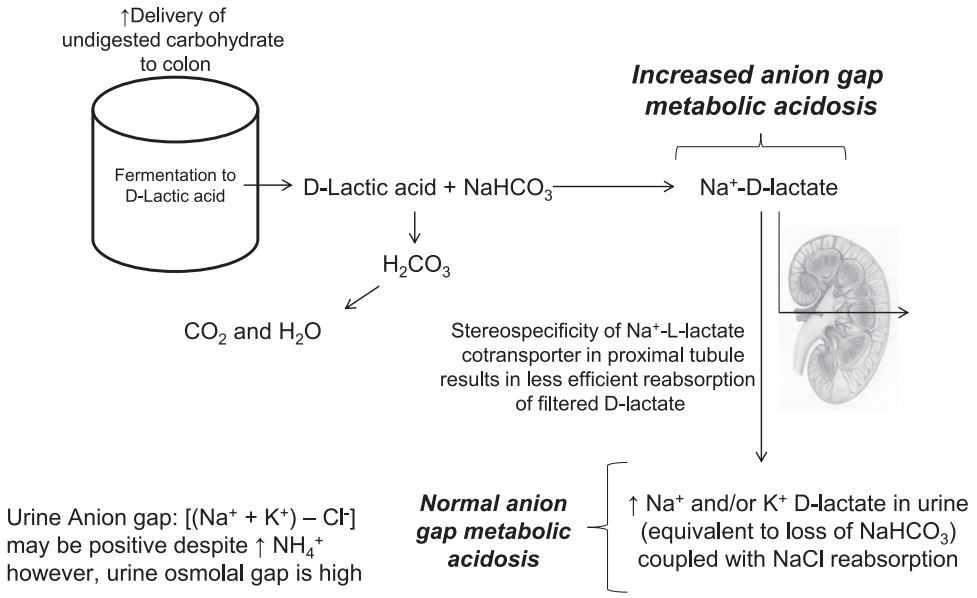

Figure 4. Development of an increased anion gap metabolic acidosis and normal anion gap metabolic acidosis in D-lactic acidosis.

drinks 1 pint of whisky daily. He noted the onset of epigastric pain 4 days ago but continued to drink until 2 days before presentation, when he developed the onset of nausea and persistent vomiting. He reports having had no food intake over the last 24 hours. The physical examination shows a blood pressure of 138/90 mm Hg supine, 110/74 mm Hg standing, and pulse 105 beats/minute. There is tenderness to palpation in the epigastrium but no rebound tenderness. Laboratory results on admission are the following (mEq/L): Na^+, 136; K^+, 3.8; Cl^-, 84; HCO_3^-, 20; creatinine, 1.1 mg/dL; and SUN, 32 mg/dL; with a pH of 7.38 and P_{CO_2} of 34 mm Hg.

Question 7: Which one of the following best describes the acid-base disturbance on admission in this patient?

(a) Normal gap metabolic acidosis and respiratory alkalosis
(b) Anion gap metabolic acidosis and normal gap metabolic acidosis
(c) Anion gap metabolic acidosis and metabolic alkalosis
(d) No acid-base disturbance present

For the answer to this question, see the following text.

A cursory examination of the serum electrolytes given the near normal blood pH might lead one to erroneously conclude there was no significant acid-base disturbance present. The slightly reduced serum Na^+ concentration suggests a disorder in tonicity characterized by a relative increase in total body water content. More importantly, the disproportionate reduction in the serum Cl^- concentration with respect to the Na^+ should alert the clinician to the presence of either a metabolic alkalosis and/or chronic respiratory acidosis. This case highlights the need to always calculate the serum anion gap no matter how unremarkable the electrolyte values may appear at first glance. The anion gap of 32 (an increase of 20 assuming a normal value of 12) indicates the presence of an anion gap metabolic acidosis. If no other acid-base disturbance was present the predicted HCO_3^- concentration would be 4 mEq/L assuming a normal value of 24 mEq/L. Because the reduction in serum HCO_3^- concentration is far less than one would predict based on the increase in anion gap, one concludes this patient also has a metabolic alkalosis making choice (c) the best answer.

After identifying the processes, one then examines the clinical history to determine causes. Alcoholic ketoacidosis is most likely present in this patient. Lack of food intake due to alcohol-induced gastritis and/or pancreatitis leads to mobilization and delivery of long-chain fatty acids to the liver; under conditions of insulin deficiency and glucagon excess, this results in increased production of ketoacids. Metabolic alkalosis fits with the history of protracted vomiting. Manifestations of alcohol withdrawal in such patients frequently result in respiratory alkalosis as the dominant disorder in a mixed disturbance. An example would be the same set of electrolytes but with a P_{CO_2} of 24 mm Hg and pH of 7.53, data that indicates a triple acid base disturbance. In addition to alcohol withdrawal, increased ventilation in these patients can be the result of pain, severe liver disease, or underlying sepsis.

Additional Readings

- Fenves A, Emmett M. Approach to patients with high anion gap metabolic acidosis: core curriculum 2021. *Am J Kidney Dis* 2021;78(4):590-600. doi:10.1053/j.ajkd.2021.02.341
- Kraut J, Madias N. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol.* 2007;2(1):162-174. doi:10.2215/CJN.03020906

➢ Palmer BF, Clegg DJ. Electrolyte disturbances in patients with chronic alcohol-use disorder. *N Engl J Med*. 2017;377:1368-1377. doi:10.1056/NEJMra1704724
➢ Palmer BF, Clegg DJ. Starvation ketosis and the kidney. *Am J Nephrol*. 2021;52:467-478. doi:10.1159/000517305 ★ESSENTIAL READING

Case 8: *A 38-year-old woman presents to the emergency department with a 2-day history of nausea, vomiting, and diarrhea. She has had more than 6 bowel movements daily over the last 48 hours described as large volume, watery in consistency, and without blood. Over the last 24 hours she also has vomited multiple times and cannot eat any food or drink liquids without vomiting. She feels lightheaded when standing. Physical examination shows a blood pressure of 110/80 mm Hg supine, 90/60 mm Hg standing, and pulse of 110 beats/minute. There is tenderness to palpation in the epigastrium and hyperactive bowel sounds. The laboratory results on admission are the following (mEq/L): Na^+, 138; K^+, 2.8; Cl^-, 102; HCO_3^-, 22; creatinine, 1.4 mg/dL; and SUN, 36 mg/dL; with a pH of 7.48 and P_{CO_2} of 30 mm Hg.*

Examination of the laboratory data in the absence of a clinical scenario best fits with an acute respiratory alkalosis. By contrast, given the history of diarrhea and vomiting, these data would also fit with the presence of a triple acid-base disorder. Diarrhea can lead to development of a normal gap metabolic acidosis due primarily to the loss of salts of organic acid anions, which represent potential bicarbonate. At the same time, the kidney retains NaCl in response to volume contraction. The net effect is an increase in serum Cl^- concentration and a fall in serum HCO_3^-. Loss of NaCl and HCl in gastric juice with active vomiting or nasogastric suction leads to volume contraction and generates a metabolic alkalosis causing an increase in serum HCO_3^- concentration and decreased serum Cl^-. If the degree of these 2 acid-base disturbances is similar, the counterbalancing effect on serum electrolytes would result in no significant deviation from normal other than hypokalemia because both diarrhea and vomiting can lead to loss of K^+ from the body.

Article Information

Authors' Full Names and Academic Degrees: Biff F. Palmer, MD, and Deborah J. Clegg, PhD.

Authors' Affiliations: Department of Education (BFP), Department of Internal Medicine (BFP, DJC), and El Paso Office of Research (DJC), Texas Tech University Health Sciences Center, El Paso, Texas.

Address for Correspondence: Biff F. Palmer, MD, Departments of Education and Internal Medicine, Texas Tech University Health Sciences Center, 5001 El Paso, TX 79905. Email: bipalmer@ttuhsc.edu

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received February 5, 2025, in response to an invitation from the journal. Evaluated by 3 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form April 13, 2025. Dr Palmer, who serves on the Core Curriculum Advisory Board, was entirely recused from any involvement in the manuscript consideration process.