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Primer on Clinical Acid-Base Problem Solving

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Acid-base problem solving has been an integral part of medical practice in recent generations. Diseases discovered in the last 30-plus years, for example, Bartter syndrome and Gitelman syndrome, D-lactic acidosis, and bulimia nervosa, can be diagnosed according to characteristic acid-base findings. Accuracy in acid-base problem solving is a direct result of a reproducible, systematic approach to arterial pH, partial pressure of carbon dioxide, bicarbonate concentration, and electrolytes. The “Rules of Five” is one tool that enables clinicians to determine the cause of simple and complex disorders, even triple acid-base disturbances, with consistency. In addition, other electrolyte abnormalities that accompany acid-base disorders, such as hypokalemia, can be incorporated into algorithms that complement the Rules and contribute to efficient problem solving in a wide variety of diseases. Recently urine electrolytes have also assisted clinicians in further characterizing select disturbances. Acid-base patterns, in many ways, can serve as a “common diagnostic pathway” shared by all subspecialties in medicine. From infectious disease (eg, lactic acidemia with highly active antiviral therapy) through endocrinology (eg, Conn’s syndrome, high urine chloride alkalemia) to the interface between primary care and psychiatry (eg, bulimia nervosa with multiple potential acid-base disturbances), acid-base problem solving is the key to unlocking otherwise unrelated diagnoses. Inasmuch as the Rules are clinical tools,

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they are applied throughout this monograph to diverse pathologic conditions typical in contemporary practice.

A strange thing happened to the art of acid-base problem solving in the last decade. For some, the addition of a simple tool, the pulse oximeter, or so-called fifth vital sign, seemed to relegate blood gas values to unfamiliar territory. It seemed that monitoring of oxygen saturation substituted for information obtained from arterial blood gas values! In fact, since the advent of oximetry, to many senior physicians (including the second author, G.W.R.), it appears that blood gas values have been used less frequently. This primer has been undertaken to prove that “reports of the demise of acid-base problem solving have been greatly exaggerated”! As important as the noninvasive monitoring of oxygen saturation is, if the partial arterial oxygen tension (PaO_2) is removed from the context of acid-base physiology, the disease puzzle will not fit together successfully. Fluctuation in pH and contingent compensation by the kidneys and lungs are the remaining pieces. Pulse oximetry, as important as it has been, has not obviated the contribution of acid-base problem solving. As a group, PaO_2 or oxygen saturation, partial arterial carbon dioxide tension (PaCO_2), bicarbonate concentration, and the many “gaps” (anion, delta or 1:1, osmotic and urinary) complement one another. The skills required to interpret blood gas values must remain in the repertoire of practitioners everywhere, beginning with primary care and continuing throughout subspecialty medicine.

The senior author (G.W.R.) had the benefit of experiencing the effect of acid-base physiology on diseases that were part of his generation-in-training. Phenformin-induced lactic acidemia, elevated urine chloride-metabolic alkalemia in Bartter syndrome and Gitelman syndrome, and metabolic acidemia in ethylene glycol poisoning were all entities to which the acid-base component contributed relevant information. The junior author (W.L.W.) has been trained in a similar arena, nephrology, but with the new additions of acid-base to his generation, such as lactic acidemia during highly active antiviral therapy (HAART), D-lactic acid in short gut syndromes, and the multiple perturbations consequent to bulimia nervosa and the abuse of methylenedioxymethamphetamine (MDMA; Ecstasy). Each medical generation seems to identify certain diseases and popular toxins from their acid-base fingerprints.

As acid-base curricula are implemented, skill acquisition should be viewed as a systematic undertaking. There appear to be four interrelated ways to solve acid-base problems. The skills may be acquired by gestalt, learned through acid-base “maps,” or inculcated by human teacher or computer software. Gestalt, that is, irreducible experiential knowledge that cannot be defined by simple summary, can be remarkably accurate for the “master,” but is not for the novice. Gestalt must be developed through experience. The teacher’s experience cannot be transferred to students on ready-made templates. The second approach, that is, the map of acid-base curves, also has shortcomings. An acid-base map cannot diagnose triple disorders, cannot be used for written examinations, and may be lost when one needs it most. Two educational methods, teacher and software, have become the keys to unlocking acid-base complexity.¹ The teacher, by systematic repetition and with supplemental software, nurtures the necessary skills. Taken together, teacher and computer software are complementary. Even though the four methods of interpreting blood gas values may be hard to separate in the hustle of a busy service, students and clinicians should always retest themselves with the systematic programs that follow. If an acid-base map is used, it should only reinforce conclusions already reached by the practitioner.

The systematic approach to acid-base problem solving, called the “Rules of Five,” is used in this monograph.²⁻⁴ The Rules will be supplemented with tools that broaden the scope of study, in essence, applying information already deduced from arterial blood gas values to electrolyte disorders (eg, hypokalemia), to diseases in disciplines other than nephrology (eg, acquired immune deficiency syndrome), and in the evaluation of secondary hypertension (eg, due to aldosteronoma).⁵ Interpretation of spot urine electrolytes in the context of acid-base problem solving is also stressed. The overall objective is to teach a reproducible problem-solving technique to readers, with progression from simple to complex clinical situations. The template applied from the combination of the Rules, urine electrolytes, and potassium algorithm is developed through case studies.

USING THE “RULES OF FIVE” FOR CLINICAL ACID-BASE PROBLEM SOLVING

Systematic problem solving in acid-base involves applying the Rules of Five (Box 1).

Box 1.

Key definitions and formulas for clinical acid-base problem solving^{2,3}

Normal values utilized for acid-base problem solving:

pH: 7.40 – 7.44
PCO₂: 40 - 44 mm Hg
Cations: Sodium: 140-144 mEq/l
Potassium: 3.8-4.4 mEq/l
Anions: Bicarbonate: 25 meq/l (24-28 meq/l range may vary)
Chloride: 100 mEq/l (99-104 range may vary)
Anion gap: 3 – 10 with ion-specific electrodes
Albumin: 4 gm/dl

Rule 1. Determine pH status (alkalemia or acidemia; > 7.44 or < 7.40)

Rule 2. Determine whether the primary process is respiratory, metabolic, or both.

Alkalemia

Respiratory Alkalemia: If PCO₂ substantially (+/-2) less than 40 mm Hg

Metabolic Alkalemia: If bicarbonate greater than 25 mEq/l

Acidemia

Respiratory Acidemia: If PCO₂ greater than 44 mEq/l

Metabolic Acidemia: If bicarbonate less than 25 mEq/l

Rule 3. Calculate the serum anion gap

Anion gap = Sodium - (Bicarbonate + Chloride)

- Anion gap that is increased (greater than 10 mEq/l) can indicate metabolic acidosis
- Anion gap increased beyond 20 mEq/l always indicates a metabolic acidosis
- For every 1Gm/dl albumin is less than normal (4gm/dl) add 2.5 to the calculated anion gap

Rule 4. Check the degree of compensation

Metabolic Acidemia

1-Decrease in pCO₂ = 1.3 decrease in bicarbonate

Metabolic Alkalemia

1-Increase in pCO₂ = 0.6 increase in bicarbonate

Respiratory Acidemia

Acute: For every pCO₂ increase of 10m Hg, bicarbonate increases by 1 mEq/l

Chronic: For every pCO₂ increase of 10mm Hg, bicarbonate increases by 4 mEq/l

Respiratory Alkalemia

Acute: For every pCO₂ decrease of 10mm Hg, bicarbonate decreases by 2 mEq/l

Chronic: For every pCO₂ decrease of 10mm Hg, bicarbonate decreases by 5 mEq/l

Rule 5. Determine whether there is a 1:1 relationship between anions in blood (also called the delta gap)

Increased anion gap metabolic acidemia: Every 1 point increase in anion gap should be accompanied by a 1 mEq/l decrease in bicarbonate. If the bicarbonate is higher than predicted by the 1:1, a metabolic alkalosis is also present. If the bicarbonate is lower than predicted by the 1:1 relationship, a normal anion gap metabolic acidosis is also present.

However, to use the Rules efficiently, specific information must be available to the clinician. Acquiring maximum information from the Rules requires access to data including arterial blood gas values (with PaO₂, PaCO₂, and pH), serum electrolytes (sodium [Na⁺], chloride [Cl⁻], bicarbonate [HCO₃⁻], for calculation of the anion gap; potassium [K⁺], for combined problem solving), and albumin level (Box 2).

BOX 2. THE INCREDIBLE SHRINKING ANION GAP!⁶⁻⁸

There is really no such thing as an anion gap. As early as 1939, Gamble correctly observed that the principle of electroneutrality demanded that the positive and negative charges in serum must be balanced. The so-called gap represents a variety of “unmeasured” anions, such as albumin, phosphate, and sulfate. In the 1970s the range of normal for this gap was accepted as 12 ± 4 (8-16 mEq/L).

Since then, two important changes have occurred. First, the range for normal has changed, and this adjustment has decreased the accepted range to 6.6 ± 4 (2.6-10.6 mEq/L). Why has this change occurred? The first range for normal was postulated at a time when electrolytes were exclusively measured with flame photometry. Contemporary laboratories now measure electrolytes with ion-specific electrodes. The difference between the two techniques, at least with regard to the range for the anion gap, is that the electrodes have a “chloride bias” when they are compared with measurements of chloride with flame photometry. In other words, the electrode technique consistently measures chloride, in the same sample, as higher than flame photometry would. Therefore, if chloride concentration rises, even if it is a result of a different way of measuring electrolytes, the difference of $Na^+ - (Cl^- + HCO_3^-)$ will decrease, and the so-called gap will be in a lower range of normal.

Second, albumin has been added to the calculation of anion gap, at least when it is decreased. Because albumin is an anion, for practical purposes, and unlike the other supposedly unmeasured anions can be measured and fluctuate significantly in a number of diseases (eg, nephrotic syndrome), it has been added to the determination of anion gap. For every 1-g decline in plasma albumin concentration, 2.5 should be added to the gap that has been calculated from the formula $Na^+ - (Cl^- + HCO_3^-)$. For example, if the albumin is 2 gm/dL in a patient with Na^+ of 140 mEq/L, Cl^- 100 mEq/L, and HCO_3^- 20 mEq/L ($140 - 120 = 20$), the albumin adjustment increases the gap to 25 or $20 + (2.5 \times 2)$, because the albumin decreased by 2 g/dl.

Because the Rules are structured, no matter what the pH and other markers are, even if they are all normal, always calculate the anion gap! The gap can help in two ways. If it is low, it can identify another disease process. Multiple myeloma, excess cations (eg, hypermagnesemia), lithium, or bromide intoxication can be inferred from a lowered anion gap. Also, a patient with normal pH but a mixed acid-base disorder (anion gap acidosis and metabolic alkalosis) may have a normal pH but an elevated anion gap.

After these data are “mined,” interpretation is enriched by inclusion of spot urine electrolytes (Box 3).

BOX 3. ADDING A DIMENSION TO URINE ELECTROLYTES⁹: THERE ARE NO SPARKS IN URINE!

Urine “lytes” have become integral to acid-base problem solving. Their interpretation can discern the cause of normal anion gap acidemia, differentiating between the diarrheal loss of bicarbonate versus a distal renal tubular acidosis. They are also critical in metabolic alkalemia; urine chloride is the key to classification of this disorder as high or low urine chloride alkalosis. Furthermore, in the context of the metabolic alkalemiias, urine chloride can differentiate early (<48 hours) from late (>48 hours) vomiting or nasogastric suction. The key to the application of urine lytes in these particular disorders is not the level of ions per se (eg, saying that a low sodium concentration suggests volume contraction), but the exact balance between cations and anions. The rule of electroneutrality holds for urine, just as it does for serum. There are no “sparks” in either, because sparks would be the expected result of unbalanced charges! That is why any charge gap in the urine is helpful to acid-base problem solving.

The best way to conceptualize the diagnostic utility of urine lytes, particularly the interpretation of total measured and unmeasured cations and anions, is to practice with normal anion gap acidemia and metabolic alkalemia. For example, after the Rules of Five are applied and normal anion gap metabolic acidemia is diagnosed, the question is, where is the bicarbonate loss occurring? Only two sources are possible: the gut (diarrhea) or the kidney (renal tubular acidosis).

Two sets of urine electrolytes are presented. Both patients have the same serum chemistry values: Na^+ 138 mEq/L, K^+ 3.0 mEq/L, HCO_3^- 18 mEq/L, and chloride 112 mEq/L (note that the anion gap is normal at 8). Blood gas values are pH 7.32, PCO_2 31 mm Hg, and O_2 96 mm Hg. Spot urine lytes are sent to the laboratory.

Patient #1	Patient #2
Na^+ 10 meq/L	Na^+ 15 meq/L
K^+ 25 meq/L	K^+ 32 meq/L
Cl^- 54 meq/L	Cl^- 50 meq/L

Urine electrolyte determinations do not include bicarbonate. With urine gaps, the difference between $(\text{Na}^+ + \text{K}^+) - \text{Cl}^-$ can be called a delta gap, as the difference between positive (cations) and negative charges (anions). Inasmuch as the rule of electroneutrality cannot be broken, the difference must be occupied by an unmeasured ion. In metabolic acidemia, one can begin by asking, what should a normal kidney do for a patient with systemic acidemia? It should excrete acid. So the fingerprints of acid excretion should be identified. How does the kidney excrete acid? $\text{H}^+ \text{Cl}^-$ will not work, because the collecting system and bladder would not survive a pH of 1.0! Titratable acidity gets rid of acid in a way that is safe for biologic systems. The molecule is titratable ammonia, or more accurately NH_4^+ . Getting back to our patients with identical systemic acid-base disturbances but dissimilar urine lytes, patient 1 has the following: $(\text{Na}^+ + \text{K}^+) - \text{Cl}^-$

= (10 + 25) – 54 = 19 fewer cations or less positive charges. Those elusive 19 cations are in the spot urine sample as unmeasured cations, more specifically as NH_4^+ . This patient with acidemia has an intact renal response in the form of NH_4^+ . This is the patient with diarrhea, not distal renal tubular acidemia. Patient 2, however, has a mere 3 unmeasured cations and is not generating adequate titratable acidity in response to systemic acidemia. That is distal renal tubular acidosis. Acidemia should stimulate the kidney to generate at least 10 to 20 mEq/L of NH_4^+ .

The pendulum swings both ways. The disparity between cations and anions may be composed of anions. In the two following patients, both undergoing nasogastric suction, the same systemic acid-base disturbance exists: pH 7.54, PCO_2 45 mm Hg, and bicarbonate 38 mEq/dL. The pH for Rule 1, and the bicarbonate and PCO_2 values are consistent with metabolic alkalemia after the Rules of Five are applied. There are only two kinds of metabolic alkalemia, namely, low and high urine chloride varieties (sometimes called saline-responsive and saline-unresponsive, respectively). Urine lytes are sent, and two questions are asked: Is this a volume-responsive metabolic alkalemia? If it is, is it “early” (<48 hours) or later (>48 hours) in the course?

Patient #1	Patient #2
Na^+ 35 meq/L	Na^+ 6 meq/L
K^+ 25 meq/L	K^+ 15 meq/L
Cl^- <1 meq/L	Cl^- 2 meq/L

Playing the delta, or disparate, charge game again, patient 1 has a disparity of approximately 59 mEq between cations (60 total) and anions (<1 total). Unlike the values in normal anion gap acidemia, this delta gap requires that unmeasured anions be identified. Patient 2 has a lesser disparity in charge (cations, 21; anions, 2), but still has 19 excess cations. Therefore this patient also has an unidentified, unmeasured anion. The best hint to the “missing” anion is the urinary pH of 7.5.

The kidney has already been accused of slower adjustments to acid-base disturbances than the lungs (see the Rules and the compensation for respiratory acidemias). The situation that transpires with vomiting or nasogastric suction is similar. Initially there is a remarkable bicarbonate diuresis, so much so that despite the volume contraction, Na^+ is dragged along with the excreted bicarbonate. After 48 hours the kidney increases bicarbonate reabsorption, and as a contingent, urine Na^+ also decreases. There is still bicarbonate in the urine, but not as much. Urine 1 has significantly more bicarbonate than urine 2 (± 60 mEq vs 19 mEq). Patient 1 has had upper gastrointestinal tract acid loss for less than 48 hours. This patient has unique urine electrolytes. The pathophysiologic response to early gastrointestinal volume and acid loss is the only time that urine Na^+ and Cl^- “dissociate,” as they do here. They are otherwise low or high simultaneously.

Finally, there is at least one more situation in which the urine delta gap is

helpful,⁵ namely, in the diagnosis of toluene poisoning, as might be seen in persons who sniff glue. The metabolism of glue produces hippurate, an organic anion. So, analogous to the excretion of either ketoacids or citrate, sample urine lytes in such clinical situations would be Na^+ 45 mEq/L, K^+ 55 mEq/L, and Cl^- 20 mEq/L, and urine pH 6.

Note that the delta is 100 positive charges versus 20 negative charges, with a urine pH that is acidic. The disparity, or delta, is composed of hippurate, a negative organic acid, accompanied in its urinary excretion by Na^+ and K^+ .

A number of questions arise in the context of evaluating the initial information. Is there any benefit of adding K^+ to anion gap calculation? Not really, most calculations no longer use it; therefore the anion gap calculation throughout this monograph does not use K^+ concentration. The K^+ level will become important for reasons related to algorithmic combinations using hypokalemia, acidemia, and alkalemia. Does compensation for a primary disturbance bring pH back to normal? No, it does not. Compensation mitigates the primary pH change, but does not normalize pH. If an acid-base disturbance is present and pH is normal, there is a mixed acid-base disorder, not a compensated one.

How far should values stray from normal before the Rules are applied? Probably about ± 2 units, for example, pH 7.40 to 7.38, or PaCO_2 26 mm Hg when the calculated prediction is 28 mm Hg. If clinicians are concerned about subtler changes based on clinical intuition, the blood gas values should be determined again to identify evolving situations.

Does blood gas value interpretation benefit from patient context? Absolutely, it does. Contraction alkalemia may be betrayed by orthostatic blood pressure changes, D-lactate acidemia by multiple surgical scars discovered at abdominal examination in the setting of Crohn disease, and chronic respiratory acidemia by pulmonary function tests and a history of right-sided heart failure as a result of cor pulmonale. In fact, blood gas analysis complements history and physical examination. Like echocardiograms supplemented with history, physical examination, and electrocardiogram, blood gas values add texture to the whole clinical picture.

Finally, can one avert arterial puncture and rely on oximetry and venous blood gas values (Box 4)?

BOX 4. HOW ACCURATE ARE VENOUS BLOOD GAS VALUES?¹⁰⁻¹³

How can one be negative about arterial blood gas values in a monograph about acid-base problem solving? To be fair, clarifications should be added. First, arterial puncture is not the least morbid procedure. It can be painful, certainly

more painful than venous puncture, and the risks increase when repeated punctures or arterial lines become necessary. Adverse outcomes may include laceration, pseudoaneurysm formation, or needle stick injury to the healthcare provider. So how good a substitute is venous gas values plus oximetry? That is an issue to address.

Recent studies have demonstrated a strong correlation between arterial and venous blood pH and bicarbonate levels in patients with diabetic ketoacidosis and uremia. In these studies the difference between arterial and venous pH varied from 0.04 to 0.05, and the difference in bicarbonate levels varied from -1.72 to 1.88 . In an emergency room study, in patients with either acute respiratory disease or a suspected metabolic derangement, the correlation for pH was again strong at -0.04 .

Now comes the “rub,” so to speak. The correlation for PCO_2 with regard to arterial and venous samples is poor. An elevated venous PCO_2 level (>45 mm Hg) is useful only as a screen, and requires further documentation with an arterial sample. In populations in whom acid-base interpretation is critical, such as patients with hemodynamic instability or circulatory collapse, there is significant discordance between arterial and venous samples.

Is there a bottom line in this arena? Yes. Bicarbonate can be useful from venous samples in specific populations, such as patients with diabetic ketoacidosis or uremia. It is possible to initially draw both arterial and venous samples, and if correlation is strong, if the clinical condition does not change for the worse (instability), follow up with venous samples. However, in patients with respiratory disorders, although oximetry is good for PaO_2 , an arterial sample is required for pH and PCO_2 .

Sometimes yes; usually no. Studies have demonstrated correlations between venous and arterial PaCO_2 and pH. Such accuracy has been documented in diabetic ketoacidemia when perfusion of the extremity from which the venous blood is drawn is good. However, experience in other diseases, particularly if organ perfusion is compromised, is not adequate to obviate arterial blood gas values with the combination of venous blood and oximetry.

The Rules of Five (see Box 1)

Rule 1 interprets arterial pH. If the pH is less than 7.40 (by a factor of ± 2 or more), acidemia is present, and if pH is greater than 7.44, alkalemia is present. Why not acidosis or alkalosis, respectively? Because, like the important difference between hypoxemia and hypoxia, the distinction of $-emia$ and $-osis$ has more than semantic import. A patient with pH 7.46 has alkalemia. If this same patient has an anion gap of 20, acidosis is also present, but not acidemia. It is also important to note that normal pH does not rule out a significant acid-base disturbance! If two or three competing

processes, rather than compensation for a primary process, are operative, pH may be normal. One example is simultaneous metabolic acidosis and alkalosis (note, because arterial pH is normal, not acidemia or alkalemia), which simultaneously balance the addition to serum of bicarbonate from alkalosis, with titration of bicarbonate downward with the addition of acid. Such a disturbance may be manifested with a pH of 7.40, but with an elevated anion gap.

Rule 2 builds on Rule 1. If acidemia or alkalemia is present, is the primary disturbance metabolic or respiratory, or possibly both? If pH is 7.30, acidemia is present. If the bicarbonate concentration is less than normal, the acidemia is metabolic; if PaCO₂ is increased, the acidemia is respiratory. If both the bicarbonate concentration is decreased and PaCO₂ is increased, both respiratory and metabolic causes are present simultaneously. Conversely for alkalemia, bicarbonate and carbon dioxide (PaCO₂) move in opposite directions to acidemia (bicarbonate up, PaCO₂ down). If pH is 7.50, for example, and the bicarbonate concentration is increased and PaCO₂ is decreased, both mechanisms, metabolic and respiratory, contribute to alkalemia. If only the bicarbonate concentration is increased (ie, PaCO₂ is normal or increased), metabolic alkalemia is the primary disturbance.

Rule 3 cautions, Always calculate the anion gap: $([Na^+] - [Cl^- + HCO_3^-])$! This is a critical calculation even when pH is normal, because an acid-base disturbance may still be present. Do not forget to adjust the calculated gap for the albumin level as soon as the albumin concentration is known. Also, a low anion gap also has diagnostic utility in the absence of an acid-base disorder (Box 2).

Rule 4 predicts appropriate compensation for the primary disturbance discovered by Rule 2. Do not let Rule 4 daunt progress. If necessary, carry a “cheat sheet” until formulas become second nature. Metabolic acidemia is a starting point, because one formula covers every contingency. If the metabolic disorder causing acidemia is acute or chronic, with or without an anion gap, the compensation is the same. The primary disturbance during metabolic acidemia is a decline in bicarbonate secondary to the addition of an acid. The lung must compensate for the primary process by removing an acid, namely, CO₂, by ventilation. So for every 1 mEq/L decline in bicarbonate (the primary metabolic process), the lung, by increasing ventilation, blows off or lowers PaCO₂ by a factor of 1.3 mm Hg. For example, if the bicarbonate concentration decreases from 25 to 15 mEq/L, a decrease of 10 mEq/L, PaCO₂ should decrease by 13 (1.3 × 10), from a normal of 40 mm Hg to 27 mm Hg. If PaCO₂ is higher than 27 mm Hg (±2), a component of respiratory acidosis has been added; if

lower than 27 mm Hg, respiratory alkalosis is also present with primary metabolic acidemia. Is this degree of detail important? If a geriatric patient has metabolic acidemia and respiratory compensation is inadequate, that is, the patient has additional respiratory acidosis, elevated PaCO_2 may represent fatigue and limited reserve, and may deteriorate further into a respiratory arrest. Such a negative outcome can be obviated by careful attention to predicted compensation.

It would be nice if metabolic alkalemia were a mirror image of metabolic acidemia. It is not, but the reason will become apparent. For the primary process, that is, metabolic alkalemia, the HCO_3^- concentration rises and primary metabolic alkalemia ($\text{pH} > 7.44$) develops. The lung hypoventilates and increases acid (PaCO_2) to compensate for the primary metabolic disorder. Therefore the PaCO_2 rises 0.6 mm Hg for every 1 mEq/L increase in bicarbonate. The compensation factor is less than that for metabolic acidemia (0.6 vs 1.3). However, because compensation for metabolic alkalemia requires a decrease in either tidal volume or frequency of respiration, and tissue perfusion demands maintenance of the oxygen concentration, the compensation formula for metabolic alkalemia is the least useful. The geriatric patient with restrictive lung disease and decreased vital capacity cannot afford to compensate for primary metabolic alkalemia. Also, inpatients with metabolic alkalemia (eg, postoperative, with nasogastric suction) have multiple reasons (hypoxemia, sepsis, pulmonary embolic events) to have respiratory alkalosis or alkalemia with concurrent metabolic alkalemia.¹⁴ Therefore the pH will be higher than expected for metabolic alkalemia, but for explicable reasons.

Compensation for the respiratory disturbances of alkalemia and acidemia adds one more layer of complexity. Unlike the metabolic disturbances already reviewed, "one size (or in this case, one formula) does not fit all." Each respiratory disturbance will have an acute formula (the respiratory disturbance, either acidemia or alkalemia, has been present for ≤ 48 hours) and a chronic formula (respiratory disturbance present for > 48 hours). The reason for the doubling of compensatory formulas is that the kidney adds to the acute compensation with adjustments that further increase bicarbonate (compensation for respiratory acidemia) or that further decrease bicarbonate (compensation for respiratory alkalemia). The "early" compensations represent changes that occur by titration, according to the Henderson-Hasselbach equation.

In the respiratory acid-base disturbances, the primary disorder is retention of PaCO_2 , an acid (acute and chronic respiratory acidemia), or lowering of PaCO_2 , loss of acid (acute and chronic respiratory alkalemia).

After 48 hours the kidney adds to the initial compensation (see below), increasing bicarbonate, a base, in respiratory acidemia, and decreasing bicarbonate during respiratory alkalemia. Thus for every 10 mm Hg increase in PaCO₂ (acidemia), bicarbonate increases 1 mEq/L (acute) or 4 mEq/L (chronic). For example, if PaCO₂ increases from a normal concentration of 40 mm Hg to 60 mm Hg acutely, the bicarbonate concentration will increase 2 mEq/L (a bicarbonate concentration of 28 mEq/L will increase to 30 mEq/L), and chronically will increase 8 mEq/L (from 28 mEq/L to 36 mEq/L). For every 10 mm Hg decrease in PaCO₂ (alkalemia), the bicarbonate concentration decreases 2 mEq/L (acute) or 5 mEq/L (chronic). If during respiratory acidemia the bicarbonate concentration is higher than the formula predicts, simultaneous metabolic alkalosis is present, and if the bicarbonate concentration is lower, metabolic acidosis is present. The converse is true for the formulas as applied to respiratory alkalemia. Also note that despite difference in compensation for respiratory disturbances (1 and 4 mEq/L bicarbonate for acidemia; 2 and 5 mEq/L bicarbonate for alkalemia), the renal addition or subtraction of bicarbonate after 48 hours is represented as 3 “more” mEq/L of bicarbonate in the appropriate direction (up for acidemia; down for alkalemia).

Some call Rule 5 the “delta” gap, some the 1:1 relationship. This Rule is to be used if metabolic alkalemia or alkalosis has not been diagnosed up to this point or if both varieties of metabolic acidosis are suspected, that is, a combination of anion gap and normal anion gap metabolic disturbances. Rule 5, like the anion gap (Box 2), relies on the law of electroneutrality. If an anion gap increases by 10 (from a normal of 10 to an elevated level of 20), to maintain electroneutrality the bicarbonate must decrease by the same number (from 25 mEq/L to 15 mEq/L). If the bicarbonate is higher than predicted by the 1:1 relationship or delta gap, for example, at a level of 20 mEq/L rather than 15 mEq/L, simultaneous metabolic alkalosis is present. Because the law of electroneutrality cannot be broken, it is assumed that the bicarbonate did indeed decrease by the same number (10) that the anion gap increased, but to do this it had to start at a higher level, decreasing from 30 mEq/L to 20 mEq/L. Conversely, if the bicarbonate concentration is lower than predicted by the anion gap increase (anion gap increase by 10, from 10 to 20, but bicarbonate decrease from 25 mEq/L to 10 mEq/L, a decrease of 15), an additional normal anion gap metabolic acidosis is present also.

The 1:1 relationship, or delta gap, has previously been used to diagnose metabolic alkalemia or alkalosis in the context of normal anion gap acidosis. For example, with similar reasoning as before, if chloride

increases from 100 mEq/L to 112 mEq/L, the bicarbonate should decrease by an equal amount, that is, from 25 mEq/L to 13 mEq/L (delta, 12). This application is left over from the flame photometry era, and has not been critically evaluated in the ion-specific era. Although it may have continued validity, it is not so reliable as the 1:1 relationship or delta gap in the setting of an elevated anion gap.

The next two clinical sections address the Rules in the context of metabolic acid-base disorders. Case 1 explicates a single metabolic acid-base disorder. The cases that follow become more difficult, demonstrating double and triple disturbances, and their differential diagnoses.

CASE 1. METABOLIC ALKALEMIA WITH AN EATING DISORDER

Metabolic alkalemia may seem an unlikely starting point for clinical acid-base problem solving. On the contrary, it may represent the best initiation. In clinical studies, half of all acid-base disorders are metabolic alkalemia or alkalosis.¹⁴ The mortality with metabolic alkalosis is prohibitive. For arterial blood gas values with pH 7.55 or greater, the mortality rate is 45%; and for pH greater than 7.65, the mortality rate is 80%. For these reasons, cases in addition to Case 1 will also deal with this prevalent disorder.

A 30-year-old woman was admitted to the psychiatry service with an “eating disorder.”^{15,16} She had a history of bulimia nervosa, manifested by self-induced vomiting and previous metabolic alkalemia, but said she had not induced vomiting for the last 3 weeks.^{17,18} Although she was cachectic, she adamantly denied other efforts to control her weight, including laxative or diuretic abuse. At physical examination, height was 5 feet 5 inches, and weight was 81 lb. The patient was afebrile; blood pressure was 90/65 mm Hg; pulse was 98 and regular; respiratory rate was 12/min. When the patient was asked to sit up, pulse increased to 112, blood pressure decreased to 86/62 mm Hg, and she complained of lightheadedness. The oral mucosa was moist, and the neck veins flat. Temporal wasting was apparent. Cardiovascular examination yielded normal findings. The lungs were clear. Findings at abdominal examination were normal. Guaiac test results were negative. The remainder of the examination was unremarkable. Laboratory data were obtained at admission (Table 1).

Rules of Five

Rule 1: Alkalemia is present; pH (7.50) is greater than 7.44 by a factor greater than 2.

TABLE 1. Case 1: Laboratory data

Arterial Blood Gases	Serum Electrolytes	Spot Urine Lytes	Urinalysis
pH, 7.50	Na ⁺ , 141 mEq/L	Na ⁺ , 48 mEq/L	pH, 6.5; dipstick negative
Pco ₂ , 45 mm Hg	K ⁺ , 3.1 mEq/L		
Bicarbonate, 34 mEq/L	Cl ⁻ ; 98 mEq/L	K ⁺ , 48 mEq/L	
PaO ₂ , 92 mm Hg	BUN, 35 mg/dL Creatinine, 1.0 mg/dL	Cl ⁻ , 84 mEq/L	

BUN, Blood urea nitrogen.

- Rule 2: The primary process that led to alkalemia is metabolic; bicarbonate concentration has increased to 34 mEq/L, and PCO₂ has not decreased in the direction of alkalemia (ie, not <40 mm Hg). Therefore there is no respiratory contribution to the primary process. The patient has metabolic alkalemia.
- Rule 3: The anion gap is normal ($141 - [98 + 34] = 9$). Later, the albumin level returned at 2.8 g/dL, and an adjustment to the anion gap was required. The anion gap decreased about 1 g/dL, so 2.5 should be added to the calculation. The gap would then be $9 + 2.5 = 11.5$, less than 2 greater than normal. Thus there is no increase in anion gap.
- Rule 4: The compensation formula for metabolic alkalemia can be applied: for every 1 mEq/L increase in bicarbonate (the primary process in metabolic alkalemia), PCO₂ (an acid) may increase by 0.6, if the patient can tolerate hypoventilation or if additional respiratory alkalosis is not concurrent. Therefore, $0.6 \times (34 - 25) = 5.4$. The PCO₂ here is slightly above the normal range, and represents compensation for primary metabolic alkalemia.
- Rule 5: The 1:1 relationship, or delta gap, is unnecessary, because primary metabolic alkalemia has already been diagnosed with Rule 1.

Addressing the information obtained from the spot urine electrolytes may help determine the cause of the metabolic alkalemia. The first question is whether metabolic alkalemia is due to low urine chloride (<20 mEq/L; saline-responsive) or high urine chloride (>20 mEq/L; saline-unresponsive). In this instance it is high urine chloride metabolic alkalemia (spot urine chloride >20 mEq/L).

This patient had a “simple” acid-base disorder, that is, primary metabolic alkalemia with secondary respiratory compensation (Box 5¹⁴).

BOX 5. METABOLIC ALKALOSIS: A DIFFERENTIAL DIAGNOSIS¹⁴

Low urine chloride variety (volume or saline–responsive)

Gastric volume loss (vomiting, nasogastric suction, bulimia nervosa)

Diuretics

Posthypercapnia

Villous adenoma (uncommon)

Cystic fibrosis, if there has been excessive sweating with resultant high sweat chloride concentration

High urine chloride variety (not saline–responsive)

With hypertension

Primary and secondary hyperaldosteronism

Apparent mineralocorticoid excess

Liddle's syndrome

Conn's Syndrome (aldosteronoma)

Cushing disease

Without hypertension

Bartter syndrome

Gitelman syndrome

Excess bicarbonate administration

However, other aspects of the diagnosis are not so straightforward. For instance, the physiologic parameters, including orthostatic tachycardia with postural blood pressure decrease and prerenal azotemia (BUN-creatinine ratio, 35), strongly suggest low urine chloride metabolic alkalemia that is saline–responsive. Both Na^+ and Cl^- (both values in the spot urine should be low) should be retained as a result of volume contraction. So what process is responsible for the metabolic alkalemia? Inappropriate salt wasting causing volume contraction may be due to one of three reasons or a combination thereof. Underlying renal disease or Addison disease may be responsible, or the kidney may be influenced by a diuretic. The differential diagnosis for low urine chloride metabolic alkalemia includes vomiting or nasogastric suctioning, chloride-rich diarrhea, cystic fibrosis, or recovery after hypercapnia.

High urine chloride metabolic alkalemia includes states of excess mineralocorticoids, real or apparent (Conn's Syndrome, Cushing disease, increased aldosterone) or tubular abnormalities (Bartter syndrome, Gitelman syndrome, Liddle syndrome). Also, depending on the diuretic involved (short half-life, eg, furosemide; long half life, eg, thiazide) and

how recently it was taken (after 1 hour furosemide will still cause salt wasting), the urine Na^+ and Cl^- can be either low or high during contraction metabolic alkalemia. Diuretic abuse is a distinct possibility in this patient. The history is replete with other efforts to lose weight.

An assay for diuretics in the urine was positive.¹⁹ The patient admitted to taking thiazides, furosemide, and spironolactone with the intent of decreasing her body weight. Normal saline was administered intravenously to replete volume. When the effect of the diuretic disappeared after 24 hours, pulse, blood pressure, metabolic alkalemia, and prerenal azotemia all returned to normal. The patient's eating disorder is complicated. She has bulimia nervosa, and has attempted weight loss through bulimia, purging, and most recently diuretic abuse.

To demonstrate the utility of urine electrolytes for acid-base problem solving, hypothetical values are discussed in the context of the same patient (Box 3). For example, if the spot urine concentrations were Na^+ 42 mEq/L, K^+ 40 mEq/L, and Cl^- 5 mEq/L, with urine pH 7.5, the cause of metabolic alkalemia would be different. First, the primary process would be low, not high, urine chloride metabolic alkalemia. In addition, the cation-anion disparity ($[\text{Na}^+ + \text{K}^+] - \text{Cl}^-$, or $42 + 40 = 82$ cations and 5 anions) would suggest another cause. There are 77 excess cations in this spot specimen of urine. In reality, the balancing anion is bicarbonate. This specific spot urine picture in the clinical scenario presented is diagnostic for vomiting. The urine pH is alkaline as a result of the presence of bicarbonaturia.

CASE 2. METABOLIC ACIDEMIA WITH DISORIENTATION

This case continues education about metabolic alkalosis and alkalemia and introduces metabolic acidemia. It also adds a second, simultaneous disturbance to problem solving.

A 52-year-old man suddenly had disorientation and confusion. His wife provided the history, and related that in the last few days the patient was "irritable and not acting himself." In addition, during the same period he was vomiting and had three episodes of diarrhea. Past medical history was significant for Crohn's disease, with a surgical history of three substantial small bowel resections in the last 10 years. Physical examination revealed a temperature of 99°F, blood pressure was 98/62 mm Hg supine (he could not sit up); pulse was 110 and regular; respiratory rate was 22/min. The patient was lethargic, dysarthric, and had impressive nystagmus on lateral gaze in both directions. There was no asterixis. Laboratory values are shown in Table 2.

TABLE 2. Case 2: Laboratory data

Arterial Blood Gases	Serum Electrolytes	Urine Electrolytes
pH, 7.34	Na ⁺ , 143 mEq/L K ⁺ , 3.8 mEq/L	Available later
Pco ₂ , 31 mm Hg	Cl ⁻ , 102 mEq/L BUN, 18 mg/dL	
Bicarbonate, 16 mEq/L	Creatinine, 1.2 mg/dL	
PaO ₂ , 97 mm Hg	Glucose, 72 mg/dL	

BUN, Blood urea nitrogen.

Rules of Five

Rule 1: Acidemia is present; pH is less than 7.40.

Rule 2: The primary process responsible for the acidemia is metabolic; the bicarbonate concentration is decreased, and PCO₂ is not elevated.

Rule 3: The anion gap was elevated ($143 - [16 + 102] = 25$); albumin was 2.6 gm/dL, so the actual anion gap was 25 plus at least 2.5, or 27.5 or greater.

Rule 4: Compensation. The primary process is metabolic acidemia. Therefore the PCO₂ should decrease 1.3 for each 1 mEq/L decline in bicarbonate concentration: $1.3 \times (25 - 16) = 11$. PCO₂ has decreased by 9 mm Hg, which is appropriate.

Rule 5: The 1:1 relationship, or delta gap. In the setting of anion gap metabolic acidemia the Rule states that the change in anion gap (increase from normal) should be equivalent to the decline in bicarbonate concentration. The increase in anion gap is $28 - 10$, or 18, but the bicarbonate concentration decreased by only 9 ($25 - 16$). Therefore there is underlying metabolic alkalosis also.

The diagnosis is a double disorder, namely, anion gap metabolic acidemia with appropriate respiratory compensation (no respiratory acidosis or alkalosis) and metabolic alkalosis. Further laboratory data obtained are shown in Table 3.

As discussed in Case 1, the urine electrolytes categorize primary metabolic alkalosis as due to low urine chloride (saline-responsive) or high urine chloride. In this patient the urine chloride level was low. Additional laboratory data were obtained to further characterize the increased anion gap (Box 6).

TABLE 3. Case 2: Additional laboratory data

Spot Urine Electrolytes	Urinalysis
Na ⁺ , 18 mEq/L	Specific gravity, 1.017
K ⁺ , 30 mEq/L	pH, 5
Cl ⁻ , 7 mEq/L	Dipstick negative

BOX 6. FINDING THE CAUSE OF ANION GAP METABOLIC ACIDEMIA

When the senior author was a student, the easiest way to learn the differential diagnosis of the Anion Gap Metabolic Acidemias was to memorize the mnemonic MUDPILES. The letters represented *m*ethanol, *u*remia, *d*iabetic ketoacidosis (also, alcoholic ketoacidemia), *p*araldehyde, *i*soniazid (INH), *l*actic acidemia, *e*thylene glycol toxicity, and, finally, *s*alicylates. Over time, certain parts of the differential diagnosis disappeared from clinical practice. For example, paraldehyde was used in the 1970s for alcohol withdrawal. It is gone today. Also, other drugs and toxins have been associated with anion gap acidemia, and INH-associated occurrences are few and far between. But it would be such a shame to lose such a tried and true mnemonic.

Paraldehyde can be replaced with *p*ropylene glycol.²⁰ The change is easy to remember, because anion gap metabolic acidemia occurs in the same clinical context, alcohol withdrawal. Propylene glycol is a solvent in which diazepam is dissolved before intravenous administration. Large doses of diazepam are associated with concurrent propylene glycol. Approximately 55% of the propylene glycol is metabolized to lactic acid. In addition, the large dose of the solvent can cause hyperosmolality and a significant increase in the osmolar gap.²¹

Since the addition of INH to the differential diagnosis is unnecessary, the I can now be ingestions, such as Ecstasy or cocaine (see Case 3).

The other components of MUDPILES that require comment include lactic acid and poisoning with methanol and ethylene glycol.

Lactic acidemia is a common cause of anion gap acidemia in the critically ill. The lactatemia can be classified into two groups, types A and B. Type A results from an increase in lactate secondary to hypoxia; type B is not due to hypoxia. Type A is secondary to causes such as sepsis and tissue hypoperfusion, end-stage lung disease, and carbon monoxide poisoning. Type B may be secondary to biguanides (eg, metformin or phenformin), seizures, or liver failure. A recent addition to the type B category is thiamine deficiency.²² Severe thiamine deficiency, as might be seen in hyperalimentation without adequate thiamine replacement, can cause type B lactic acidemia. Both A and B lactates are the L-stereoisomer of lactic acid (see Case 2). There is also a D-stereoisomer of

lactic acid, and it is a more recent addition to the causes of metabolic acidemias with an anion gap.

Both methanol and ethylene glycol as causes of anion gap acidemia are unusual, but treatable if diagnosed. They can lead to blindness, renal failure, and death if not diagnosed. Ethylene glycol is the colorless, odorless component of antifreeze. It is metabolized to glycolic acid and oxalate. The diagnosis of poisoning with anion gap acidemia can be tricky. Two techniques can assist, but both lack sensitivity and specificity. First, the urine may contain oxalate crystals. In fact the “octahedral” variety is more specific for poisoning.⁵ However, the crystals can be seen in urine from healthy persons as well, as after vitamin C ingestion. Second, the so-called osmol gap may lead to diagnosis. Because ethylene glycol is an antifreeze, its chemical composition is of high osmotic activity. Normal plasma osmolality is primarily composed of electrolytes, blood urea nitrogen (BUN), and glucose, and may be estimated with the formula $2 (Na^+) + glucose/18 + BUN/2.8 = osmolality \text{ in } mOsm/kg/H_2O$. Normally there is less than 10 mOsm/kg/H₂O difference between calculated and measured osmolality. The difference will increase with ingestion of either methanol or ethylene glycol. Again, sensitivity and specificity are lacking. The best diagnostic method is a high index of suspicion in the right population (persons who abuse alcohol who run out of alcohol). Empty bottles found by family or friends may cinch the diagnosis in the setting of severe anion gap acidemia.

Glycolate may cause large but artifactual elevations in lactate measurements.²¹ The treatments of acidemia due to lactate and ethylene glycol are different, so the distinction between the two must be made.

Finally, large anion gap elevations (>30) usually suggest a multifactorial cause, which can include ingestions, renal failure, lactate, and exogenous phosphate intoxication.²³

The osmolality was calculated as $2(143)+18/2.8+72/18=297$; the ethanol level was zero. Serum osmolality was measured at 302 mOsm/kg/H₂O. A difference of 5 is not significant. Serum determinations were negative for other organic acids including lactate, acetone, ketoacids (β -hydroxybutyrate/acetoacetate), and salicylates.

How can anion gap metabolic acidemia be present without the presence of a measurable organic acid? Further history obtained from the patient’s wife revealed that the symptoms began after he finished a carbohydrate-rich meal. Remember also that he had a history of short bowel syndrome as a result of surgical intervention to treat Crohn’s disease.

In the setting of short bowel syndrome,^{24–26} carbohydrates that are not absorbed by the small bowel are delivered to the colon in high concentration. As the glucose is metabolized by colonic bacteria, two isomers of lactate are produced: L-lactate and D-lactate. Human beings possess only the isomer-specific enzyme L-lactate dehydrogenase, and are therefore

only able to rapidly metabolize L-lactate. As a result, with a short bowel the excess D-lactate accumulates, causing metabolic acidemia with anion gap, but is not detected with the assay for the more common L-lactate. For this to occur, patients have a short bowel, eat a carbohydrate load, and flood the colon with unmetabolized sugars. In fact, D-lactic acidemia occurs after carbohydrate malabsorption, colonic motility disorders, or impaired metabolism of D-lactate. Patients with this syndrome have varying degrees of encephalopathy, thought to be secondary either to the D-lactate itself or to other bacterial toxins.

Assay of the patient's serum for L-lactate was negative. Then the serum was assayed for D-lactate with a specific test, and was 12 mEq/L. Treatment was supportive. The D-lactate will eventually be metabolized by the host. Treatment with antibiotic agents such as oral vancomycin, metronidazole, or neomycin may reduce the symptoms. However, this therapy may also cause overgrowth of *Lactobacillus*, a bacterium that produces D-lactate, and lead to further episodes.

CASE 3. ACID-BASE DISORDER WITH AGITATION

This case scenario continues metabolic acid-base disorders, but is the first triple acid-base disorder. It also enables discussion of a contemporary "toxin" associated with a primary anion gap metabolic disturbance.²⁷

A 22-year-old man who had been previously healthy was brought to the emergency room early on a Monday morning, with agitation, fever, tachycardia, and hypertension. He was confused and incapable of providing a meaningful history. His friends seemed concerned, but were evasive as to his activities the preceding weekend except to say that he had been "partying" with them. They denied illicit drug use, and insisted that the patient had been drinking alcoholic beverages but not driving.

Examination revealed pulse 124 and regular; respirations 30; blood pressure 180/118; and temperature 101.6°F. Pulse oximetry was consistent with oxygen saturation of 90%. The patient appeared anxious and confused. The pupils were dilated, and a symmetric tremor was noted during movement. The rest of the examination was unremarkable. Fifteen minutes after his arrival in the emergency room the patient had a 3-minute generalized tonic-clonic convulsion. Initial laboratory values for blood drawn after the seizure are reported in [Table 4](#).

Rules of Five

Rule 1: Acidemia is present; pH less than 7.40.

TABLE 4. Case 3: Initial laboratory data

Arterial Blood Gases	Electrolytes
pH, 7.27	HCO ₃ ⁻ , 18 mEq/L
Pao ₂ , 84 mm Hg	Na ⁺ , 128 mEq/L
Paco ₂ , 40 mm Hg	Cl ⁻ , 88 mEq/L

- Rule 2: This is a metabolic disturbance, because the bicarbonate value is lower than normal (18 mEq/L). However, one would suspect that with primary metabolic acidemia the PCO₂ should be lower than normal, moving in the appropriate direction for compensation. PCO₂ is not decreased, and absence of compensation for the primary disturbance is proved by Rule 4.
- Rule 3: Calculation of anion gap: $128 - [88 + 18] = 22$. The anion gap is elevated, and the systemic pH is less than 7.4; therefore anion gap metabolic acidemia is present. Later the albumin value was measured at 4.2 g/dL. No further adjustment to the elevated anion gap was required.
- Rule 4: PCO₂ should decline 1.3 for every 1 mEq/L that the bicarbonate concentration decreases below normal as a result of primary metabolic acidemia. Bicarbonate decreased by 7, or from 25 to 18; PCO₂ should be $40 - (1.3 \times 7)$, or approximately 31 ± 2 mm Hg. This is the expected compensation for metabolic acidemia. PCO₂ has not reached this level; therefore additional respiratory acidosis is present.
- Rule 5: Should be applied. Metabolic alkalemia or alkalosis has not been diagnosed yet. The Rule states that for every 1 that the anion gap rises (in this instance, from a normal of 10 to a level of 22, a delta, or difference, of 12) the bicarbonate concentration should decrease by the same amount, that is, from 25 to 13. The bicarbonate concentration is higher than the predicted value; therefore the patient also has metabolic alkalosis. After application of the five Rules, this patient has anion gap metabolic acidemia, respiratory acidosis, and metabolic alkalosis. A triple acid-base disturbance is present.

Let us approach the primary disturbance, the anion gap metabolic acidemia. Use Box 6 again for the differential diagnosis of anion gap metabolic acidemia. The following additional laboratory tests were ordered: osmolar gap (serum electrolytes, glucose, ethanol levels, measured osmolality), toxicology samples for cocaine and so-called club

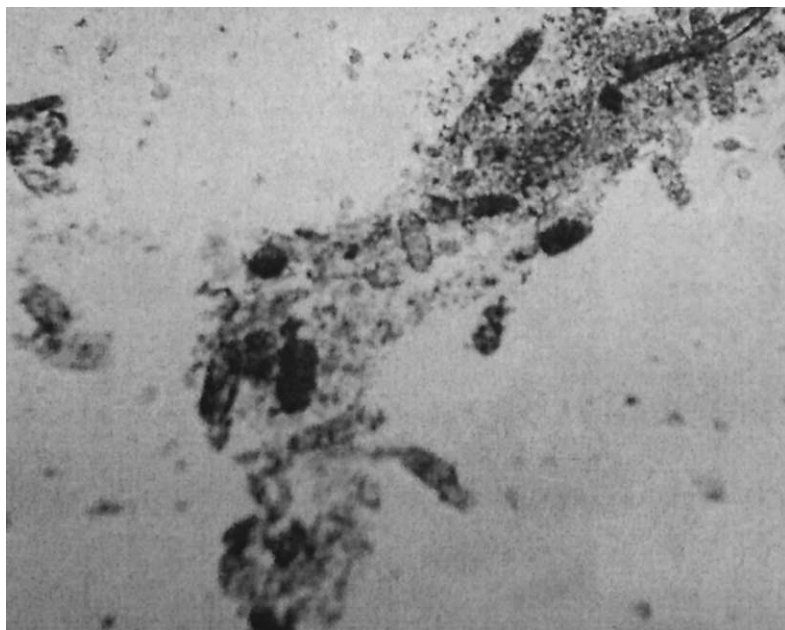


FIG 1. Urinalysis (dipstick) revealed blood (4+). The microscopic sediment, however, contained no red blood cells or crystals, but had many coarsely granular, pigmented casts.

drugs, MDMA (Ecstasy),²⁸ γ -hydroxybutyrate, flunitazepam, and ketamine hydrochloride; lactate levels; blood urea nitrogen (BUN) and creatinine concentrations; and salicylate levels. The first values to return enabled calculation of the osmolar gap (less than 10 mOsm/kg/H₂O), and included BUN value (32 mg/dL) and creatinine concentration 3.0 mg/dL. Urinalysis (dipstick) revealed blood (4+). The microscopic sediment, however, contained no red blood cells or crystals, but had many coarsely granular, pigmented casts (Figure 1). The suspicion was that this patient with a triple acid-base disorder also had rhabdomyolysis and myoglobinuria, and, as expected, the creatine kinase–muscle type level was 43,000 U/L. Rhabdomyolysis is a known complication of many drugs, including MDMA and cocaine.^{29,30} In addition, MDMA (Ecstasy) increases the release of neurotransmitters, altering visual perceptions, enhancing libido, and increasing energy. The downside of ingestion includes agitation, anxiety, tachycardia, hypertension, hyperthermia, and, as in this patient, rhabdomyolysis with resultant renal failure. The toxicology report returned positive for MDMA, but not for cocaine.

Creatine kinase (66,000 U/L), BUN (55 mg/dL), and creatinine (5.8

TABLE 5. Case 4: Initial laboratory data

Arterial Blood Gases	Electrolytes	Other
PaO ₂ , 58 mm Hg	Na ⁺ , 120 mEq/L	Glucose, 824 mg/dL
Paco ₂ , 59 mm Hg	Cl ⁻ , 62 mEq/L	BUN, 112 mg/dL
	HCO ₃ ⁻ , 45 mEq/L	Creatinine, 4.1 mg/dL
pH, 7.50	K ⁺ , 2.6 mEq/L	Calcium, 5.9 mg/dL

BUN, Blood urea nitrogen.

mg/dL) peaked after volume repletion, supportive measures, and alkalinization of the urine. The patient later admitted to MDMA use, and all abnormal values returned to baseline after about 1 week. The presumed causes of the anion gap metabolic acidemia were the U and I of MUDPILES (*m*ethanol, *u*remia, *d*iabetic ketoacidosis, *p*araldehyde, *i*soniazid, *l*actic acidemia, *e*thylene glycol toxicity, *s*alicylates), that is, uremia and renal failure from rhabdomyolysis, and ingestion of MDMA, which caused the hyperpyrexia and rhabdomyolysis.

Although one of the preceding cases added the complexity of a respiratory acid-base disturbance to the primary metabolic disturbance, the two cases that follow will increase the challenge in this regard. Case 4 adds respiratory acidosis, and Case 5 discusses a chronic respiratory disturbance common in primary care and specialty practice.

CASE 4. RESPIRATORY ACIDOSIS

A 40-year-old man with a history of alcohol abuse, diabetes mellitus type 1, and frequent admissions to treat diabetic ketoacidemia came to the emergency room after protracted alcohol drinking, during which he stopped eating and taking insulin. He was agitated on arrival; vital signs included temperature 99.6; pulse 110 and regular; blood pressure 112/78; respirations 20/min and unlabored; and oxygen saturation 88% at oximetry. There was no history of pulmonary disease or smoking. Initial laboratory work was ordered (Table 5).

Rules of Five

Rule 1: Alkalemia was present, because the arterial pH was greater than normal; it had increased from 7.40 to 7.44, to 7.50.

Rule 2: The alkalemia is metabolic because the bicarbonate concentration is elevated (45 mEq/L). It is not respiratory, because PCO₂ is 59 mm Hg, the direction of acidemia. PCO₂ would have to be decreased, not increased, to cause alkalemia.

Rule 3: The anion gap ($\text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^+]$) is 13, slightly above normal. Later, the albumin concentration was 2.9 gm/dL; thus the corrected anion gap was $13 + 2.5$ (1 g below normal; Box 2), or approximately 15 to 16. This qualifies as an additional component of anion gap metabolic acidosis (not acidemia!). This could be secondary to ketoacidemia, because the patient has diabetes, but the cause should be documented (refer to Cases 2 and 3) because the gap could be secondary to lactate or ingestion of ethylene glycol (antifreeze for radiators), for example. Some patients with metabolic alkalemia have an elevated anion gap from alkalemia per se. Alkalemia causes hydrogen ions to move from albumin to plasma as part of the buffering process. The albumin relative negativity that results increases albumin as an unmeasured anion. In this patient, however, serum ketones were consistent with the increased anion gap.

Rule 4: Determining whether compensation has occurred takes us to an interesting arena. The primary process is metabolic alkalemia. Remember that for primary metabolic alkalemia the compensation requires hypoventilation to increase PCO_2 . This occurs at the expense of PaO_2 , so compensation may be absent. Also, patients with metabolic alkalemia often have, in addition, respiratory alkalosis, which precludes compensation. In this patient, however, there has been significant CO_2 retention (PCO_2 is 59 mm Hg). Does the elevated PCO_2 represent compensation? Or does the patient have a mixed acid-base disorder with metabolic alkalemia, anion gap metabolic acidosis, and respiratory acidemia? Inasmuch as PCO_2 is higher than predicted by the compensation formula (for every 1 mEq/L that bicarbonate increases, PCO_2 might increase by 0.6), it was suspected that the patient also had respiratory acidosis. Normal PCO_2 before the present acute illness could help rule out chronic CO_2 retention; however, previous blood gas values were not available.

Rule 5: Since metabolic alkalemia has already been diagnosed with Rule 1, Rule 5 need not be applied.

Because the patient was initially tolerating the three acid-base disturbances without incident, administration of intravenous insulin, potassium, and calcium was begun. Ten minutes later the patient had a generalized tonic-clonic convulsion; a nasotracheal tube was placed, and mechanical ventilation was given. Because both hypokalemia (2.6 mEq/L) and hypocalcemia (5.9 mg/dL) were present, blood was drawn for determi-

TABLE 6. Case 4: Repeat laboratory data

Arterial Blood Gases	Electrolytes	Other
P _O ₂ , 436 mm Hg	HCO ₃ ⁻ , 47 mEq/dL	Glucose, 320 mg/dL
P _{CO} ₂ , 47 mm Hg	Na ⁺ , 128 mEq/dL	
pH, 7.62	Cl ⁻ , 72 mEq/dL	

nation of magnesium and parathyroid hormone levels. Hypomagnesemia can cause both hypokalemia (by renal tubular potassium wasting) and hypocalcemia (by decreased parathyroid hormone release and end-organ effect). Hypomagnesemia is common in persons who abuse alcohol, particularly if they are malnourished. This patient also lost magnesium through the osmotic diuresis of hyperglycemia. It was demonstrated later that the magnesium concentration was decreased (1.5 mEq/L). Consistent with hypomagnesemia as the cause for hypocalcemia, the parathyroid hormone level was also slightly decreased. The seizure ceased spontaneously, and blood gas analysis was repeated (Table 6).

What happened to account for the change from the first set of blood gas values?

- Rule 1: Alkalemia is still present; that is, the pH is greater than 7.44, actually measured at 7.62. In fact, the patient is more alkalemic than previously.
- Rule 2: The alkalemia is metabolic, because the bicarbonate concentration is increased and the CO₂ level, at 52 mm Hg, available from repeated blood gas analysis, would be responsible for acidemia, not alkalemia.
- Rule 3: The anion gap has decreased to 9 ($128 - [72 + 47]$) + 2.5 (actual value, 11 to 12, when adjusted for the decrease in albumin). The anion gap is now normal.
- Rule 4: The presence of compensation is still somewhat problematic. The PCO₂ has improved (that is, it is lower) with ventilator support, and the pH has progressed further in the direction of alkalemia (7.47-7.60). The rise in pH is clearly secondary to the decrease in PCO₂ (an acid) mediated by ventilation therapy. The bicarbonate value is within (\pm) 1 to 2 of the last value, so an explanation similar to that with the first set of blood gas values will suffice.
- Rule 5: This Rule is not required for the same reason as before; the primary disturbance is metabolic alkalemia.

The ventilator was adjusted to decrease tidal volume and fraction of inspired oxygen, and as a result the next PO_2 reading decreased to 106 mm Hg. The hyperglycemia was treated, and the patient was weaned from the ventilator over the next 36 hours. The anion gap was explained by ketoacids (acetoacetic acid, β -hydroxybutyric acids) resulting from poorly controlled diabetes mellitus. The low magnesium level was corrected, and the potassium and calcium levels were normalized. There were no further seizures. In addition, approximately 5 to 6 L of intravenous fluid (normal saline solution; later, 5% Dextrose with half normal saline solution).

After treatment and recovery, predischARGE blood gas values were pH 7.43, PCO_2 40 mm Hg, PO_2 92 mm Hg, and bicarbonate 26 mEq/L. Because blood gas values were normal after the acute events, chronic lung disease as a cause of CO_2 retention was eliminated. Serum alcohol level was 2.5 times the legal limit. In addition, toxicology results were positive for diazepam and barbiturates. It appears that this patient retained CO_2 for two reasons. He compensated for metabolic alkalemia, and also appeared to have toxic (alcohol, diazepam, barbiturates) respiratory depression. There was no evidence of either ethylene glycol or methanol intoxication (crystals at urinalysis, increased osmolar gap, levels of toxic metabolites such as formic acid), and salicylates were absent. Although it was not proved, the metabolic alkalemia was probably contraction (low urine chloride value on a spot sample was not obtained), consistent with the patient's poor oral intake followed by protracted nausea and vomiting previously. Glucose-induced diuresis would have spuriously elevated chloride excretion in a spot urine value. The elevated systemic pH, corrected with fluid repletion, supports a volume-responsive state.

CASE 5. A PRIMARY RESPIRATORY ACID-BASE DISORDER^{31,32}

A 50-year-old man with known chronic obstructive pulmonary disease came to the emergency room with shortness of breath and impending ventilatory failure. He had smoked more than 55 pack-years. During his last admission, pulmonary function tests were consistent with a moderately severe, irreversible obstructive defect, by ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC), or $FEV_{1\%}$, lack of bronchodilator response, increased residual volume, and decreased carbon monoxide diffusion in the lung (DLCO). Findings on a previous chest computed tomography (CT) scan were consistent with a diagnosis of emphysema. At that time

TABLE 7. Case 5: Laboratory data

Arterial Blood Gases	Electrolytes		Urine Electrolytes
pH, 7.24	Na ⁺ , 136 mEq/L	Glucose, 122 mg/dL	Na ⁺ , 48 mEq/L
Pao ₂ , 76 mm Hg	K ⁺ , 3.6 mEq/L	BUN, 13 mg/dL	Cl ⁻ , 60 mEq/L
Paco ₂ , 52 mm Hg	HCO ₃ ⁻ , 22 mEq/L	Creatinine, 0.9 mg/dL	
	Cl ⁻ , 108 mEq/L		

BUN, Blood urea nitrogen.

arterial blood gas values were not obtained, but oxygen saturation at oximetry was decreased (86%), and the serum bicarbonate concentration (24 mEq/dL) did not suggest PCO₂ retention. If PCO₂ was elevated, one would expect an increase in HCO₃⁻ as compensation. Past medical history included bladder cancer, cured 6 years previously with cystectomy with urinary drainage via an ileal conduit.

On arrival at the emergency room the patient had tachypnea (24/min) and was febrile (100.6). Rhonchi were present, and cough produced thick green sputum. There was no elevation in jugular pulse, and no other evidence of cor pulmonale. After blood gas values were obtained, continuous positive airway pressure was started. A chest x-ray film was normal. Blood pressure was 112/88 mm Hg; pulse was 110, and regular. Laboratory values were obtained (Table 7).

Rules of Five

Rule 1: The patient has acidemia (pH is 7.24, <7.40).

Rule 2: There is a respiratory component; PCO₂ is increased. We do not know yet whether the increase in PCO₂ is acute or chronic. The bicarbonate concentration is decreased, albeit minimally (<25 mEq/dL), and is consistent with additional metabolic acidosis.

Rule 3: The anion gap is 6 ($Na^+ - [Cl^- + HCO_3^-] = 136 - [108 + 22] = 6$). The albumin concentration was normal, and no further adjustment to the anion gap was necessary.

Rule 4: Because there are two processes, one respiratory and one metabolic, compensation is not present.

Rule 5: With non-anion gap metabolic acidemia, the 1:1 relationship is not so helpful in ruling in metabolic alkalosis. However, if it were applied, chloride increased about 4 mEq/L (from 104 mEq/L to 108 mEq/L), and the bicarbonate concentration decreased about 3 mEq/L (from 25 mEq/L to 22 mEq/L). These values suggest the absence of metabolic alkalosis.

The patient has respiratory acidemia³¹ (Boxes 7 and 8).

BOX 7. CAUSES OF RESPIRATORY ACIDOSIS (HYPOVENTILATION)

Central nervous system depression

- Anesthesia, sedation, toxins
- Ischemic, traumatic, infectious injury
- Brain tumor

Neuromuscular disorders

- Spinal cord injury
- Guillain-Barré syndrome
- Anesthesia, sedation, toxins
- Hypokalemic periodic paralysis
- Myasthenia gravis
- Poliomyelitis
- Multiple sclerosis
- Muscular dystrophy
- Amyotrophic lateral sclerosis
- Myopathy
- Diaphragmatic impairment

Respiratory disorders (impairment in ventilation)

- Pulmonary parenchymal disease (eg, chronic obstructive pulmonary disease, interstitial fibrosis)
- Laryngospasm or vocal cord paralysis
- Obstructive sleep apnea
- Obesity
- Kyphoscoliosis

BOX 8. CAUSES OF RESPIRATORY ALKALOSIS (HYPERVENTILATION)

Central nervous system stimulation

- Anesthesia, toxins
- Ischemic, traumatic, infectious injury
- Brain tumor
- Salicylate (may also cause anion gap metabolic acidosis)
- Xanthines

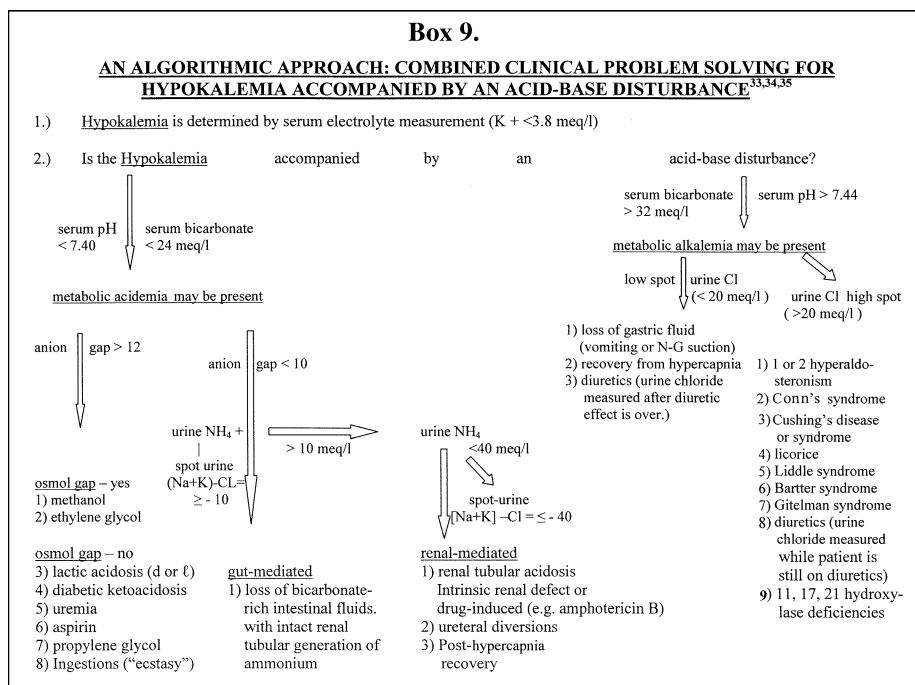
Progesterone
Pain, anxiety
Fever
Respiratory disorders
 Parynchymal lung disease (eg, pneumonia)
 Hypoxia
 Pulmonary embolism
 Pulmonary edema
 Flail chest
Sepsis or circulatory failure
Pregnancy
Cirrhosis
Hyperthyroidism

There is ample reason for this acid-base disturbance, inasmuch as the patient has severe obstructive pulmonary disease from cigarette smoking. If blood gas values had been determined at his last admission, the question as to chronicity could have been answered. In lieu of previous blood gas values, when the patient recovers from the present exacerbation a persistently increased PCO_2 level will be evidence of chronic respiratory acidemia. The decrease in bicarbonate is interesting. Renal compensation for respiratory acidemia would be reflected by an increase in the bicarbonate concentration (1 mEq/L for every 10-mm increase in PCO_2 acutely; 4 mEq/L chronically). In this patient the bicarbonate concentration is decreased without an elevated anion gap, consistent with normal anion gap metabolic acidosis. Could this patient have gastrointestinal loss of bicarbonate (diarrhea), or is renal tubular acidosis responsible for the acidosis (Box 3)? It may be that he has neither. The urine is being excreted from the kidneys into contact with active transport processes of the ileum. Gastrointestinal tissue transport can modify urinary electrolytes substantially. Ileal or colonic epithelia actively reabsorb urinary chloride and excrete bicarbonate.³³ This activity leads to normal anion gap metabolic acidosis.

The patient improved subjectively before discharge. PCO_2 remained elevated, consistent with chronic respiratory acidemia from emphysema. Acidosis from the conduit persisted also. The final values were pH 7.30, PCO_2 49 mm Hg, and PaO_2 84 mm Hg.

POTASSIUM IN THE SCHEME OF ACID-BASE PROBLEM SOLVING, OR KILLING TWO BIRDS WITH ONE STONE

The differential diagnosis for potassium depletion is extensive. It would be helpful to economize the list on the basis of abnormal values concurrent with hypokalemia. Approaching problem solving in this manner is called “concept sorting.” For example, hypokalemia can be secondary to diuretic therapy, renal tubular acidosis, diarrhea, vomiting, Conn’s Syndrome (aldosteronoma), or magnesium depletion, among potential causes. But renal tubular acidosis and diarrhea as a “concept sort,” as well as Conn’s Syndrome (aldosteronoma) and vomiting, have more in common than the presence of hypokalemia. These grouped diseases are characterized by hypokalemia with a distinctive acid-base picture. For example, the hypokalemias of renal tubular acidosis and diarrhea are accompanied by normal anion gap metabolic acidemia or acidosis; conversely, with vomiting and Conn’s Syndrome (aldosteronoma) the potassium depletion is accompanied by metabolic alkalemia or alkalosis³⁴ (Box 9).



Urine electrolytes also assist in problem solving with combined hypokalemia and acid-base disturbance (Box 3). For example, in patients with hypokalemia and normal anion gap acidemia there are only two organs that potentially waste potassium and bicarbonate simultaneously, namely, the gut (as a result of bicarbonate and potassium wasting with diarrhea, as in Case 5) and the kidney (bicarbonate and potassium wasting from renal tubular acidosis, types 1 and 2). The “fingerprints” that enable us to find the culprit organ for bicarbonate and potassium loss (gut vs kidney) are found in the “unmeasured” cations present in spot urine values. The sign of “hidden” urine NH_4^+ ($[\text{Na}^+ + \text{K}^+] - \text{Cl}^- = >10$) can differentiate the cause in patients with hypokalemia and normal anion gap acidemia. Conversely, there are only two kinds of hypokalemic metabolic alkalosis, low urine chloride (saline-responsive) and high urine chloride (saline-unresponsive). Vomiting can be differentiated from Conn’s Syndrome (aldosteronoma) (low and high urine chloride metabolic alkalosis, respectively) by the level of urine chloride (low, <20 mEq/L; high, >20 mEq/L). In essence, combining problem solving for potassium and an acid-base disorder can “economize” diagnosis. The simplification is especially helpful in the difficult terrain of hypokalemic, high urine chloride metabolic alkalosis. The high urine chloride group can be subdivided with application of two pieces of additional information. Blood pressure (normotensive vs hypertensive) and the renin and aldosterone levels (low or high, respectively) are discerning in this regard. Two cases will illustrate how the combination of blood pressure, potassium, acid-base status, renin and aldosterone levels, and urine electrolytes facilitate problem solving.

CASE 6. POTASSIUM AND ACID-BASE

Does this patient with hypertension, hypokalemia and metabolic alkalemia have hyperaldosteronism or renal artery stenosis, or does she just eat too much licorice?

A 36-year-old woman was seen with hypertension, hypokalemia, and metabolic alkalemia. Blood pressure was 160/108 mm Hg; serum potassium was 2.9 mEq/L; and bicarbonate concentration was elevated to 38 mEq/L. The hypertension is of recent onset, and electrolyte values obtained 1 year previously were normal. There is no family history of hypertension, and the patient had no preeclampsia with three previous pregnancies. She denies diuretic use or abuse, and is otherwise healthy. Previous urinalyses have all been normal.

The first question is whether she has metabolic alkalemia with hypokalemia. Does the answer to this question require the documentation of

TABLE 8. Case 6: Laboratory data

Arterial Blood Gases	Electrolytes
pH, 7.57	HCO ₃ ⁻ , 38 mEq/L
Pao ₂ , 95 mm Hg	Na ⁺ , 144 mEq/L
Paco ₂ , 44 mm Hg	Cl ⁻ , 101 mEq/L

arterial pH with blood gas values? In lieu of blood gas values, is this an instance in which venous values can suffice for diagnosis?

An elevated bicarbonate level can be the result of two underlying acid-base disturbances, metabolic alkalemia or the result of compensation for primary respiratory acidemia (see Case 5). The laboratory data for this patient suggest a metabolic disturbance rather than compensation for lung disease. The patient is healthy and has no history of pulmonary disease. Many would assume that she has metabolic alkalemia or alkalosis, on the basis of an elevated bicarbonate level, without blood gas values. On the other hand, adding blood gas values to the clinical evaluation is not wrong, and these may be obtained to document elevated arterial pH. Blood gas analysis is imperative for inpatients, such as the preceding cases discussed. In ambulatory patients with a suggestive clinical picture, etiologic disturbance may be assumed from venous electrolytes in selected instances. If doubt exists, that is, when hypokalemia is accompanied by either an elevated or decreased bicarbonate level, arterial blood gas values should be obtained. The case presented here will be approached in both ways, that is, with and without arterial blood gas values (Table 8).

If arterial gas values are obtained, the Rules of Five would be applied as follows.

Rule 1: Alkalemia is present; pH is 7.57.

Rule 2: The disturbance is metabolic (bicarbonate, 38 mEq/L), not respiratory (PCO₂, 44 mm Hg).

Rule 3: The anion gap is normal ($144 - [101 + 38] = 5$).

Rule 4: Compensation is absent (HCO₃⁻ increased from 25 mEq/L to 38 meq/L, a total of 13 mEq/L. PCO₂ should increase by 0.6×13 , or from 40 to approximately 48. This is the least reliable compensation!

Rule 5: This Rule need not be applied, because metabolic alkalemia has been diagnosed.

Now let us apply the algorithm for hypokalemia with metabolic

alkalemia. The sequence would be as follows: What is the urine chloride value? Is hypertension present or absent? What are the renin and aldosterone concentrations?

A spot urine sample was sent to the laboratory, and was found to contain chloride of 42 mEq/L, diagnostic of high urine chloride metabolic alkalemia. The patient had hypertension (blood pressure 160/108 mm Hg).

Plasma renin and aldosterone concentrations were obtained (urine or serum aldosterone levels may be used), and were as follows: renin, 0.5 ng/mL/hr (range, 0.65-1 ng/mL/hr, low; 1.1-3.1 ng/mL/hr, normal; and 3.2 ng/mL/hr, high). Aldosterone was elevated (urine, 42 ng/dL). This specific pattern, namely, hypokalemia, metabolic alkalemia with elevated urine chloride and hypertension, low renin concentration, and high aldosterone concentration, is consistent with primary hyperaldosteronism³⁷ (see algorithm). Further workup is dedicated to differentiating among adrenal adenoma, hyperplasia, and glucocorticoid-remediable varieties.³⁸ The workup includes attempts to suppress aldosterone with an intravenous saline solution infusion, to prove that the aldosterone secretion is autonomous, and efforts to stimulate the low renin, including upright posture, salt restriction, and furosemide, to verify that the low renin level is not a result of excess volume.

If hypertension is present in the same patient, that is, with hypokalemia and high urine chloride metabolic alkalemia, but with elevated renin and aldosterone levels, the diagnosis is secondary hyperaldosteronism, not primary hyperaldosteronism. The elevated renin and aldosterone levels might be secondary to renal artery stenosis, a renin-secreting tumor (rare), or primary renin stimulation of aldosterone as a result of ineffective circulation or volume contraction.

Another algorithm combination might include hypokalemia, metabolic alkalemia, high urine chloride, and hypertension, with low renin and aldosterone levels. This entity is called apparent mineralocorticoid excess.³⁹ This combination would suggest a hormonal or tubular abnormality capable of causing salt retention, hypertension, and renal potassium wasting. What are the candidates? Licorice abuse is an interesting syndrome in this regard. Licorice contains glycyrrhetic acid, which inhibits 11- β -hydroxysteroid dehydrogenase, the enzyme that converts cortisol to cortisone. Cortisol has significantly more mineralocorticoid activity than cortisone. The excess cortisol present after licorice ingestion inhibits the 11- β enzyme and thereby causes volume expansion, hypertension, renal potassium wasting, and hypokalemia. Renin and aldosterone would both be suppressed. The excess cortisol and its mineralocor-

ticoid activity increase volume and blood pressure, thereby suppressing renin and aldosterone.

One caveat is added to the use of the potassium acid-base algorithm. Not all patients with primary aldosteronism have hypokalemia. Approximately a third of patients with this disorder have normal potassium levels. Diagnosis in this group is more difficult, and requires a higher level of suspicion. But low renin and high aldosterone levels are still diagnostic.

Molecular biology and genetic cloning have enhanced the understanding of a variety of disorders. These advances have enabled investigators to define the underlying cause of many renal transport disorders, including those with clinical presentation of normotensive hypokalemic metabolic alkalosis, such as Bartter syndrome and Gitelman syndrome.^{40,41,44}

Bartter syndrome clinically mimics findings after administration of loop diuretic agents. Mutations in the genes that encode at least three transport proteins in the medullary thick ascending limb of the loop of Henle lead to the phenotypic presentation of hypokalemic metabolic alkalosis. Abnormalities of the $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter, the apical renal outer medullary potassium channel, and the basolateral chloride channel all may cause salt wasting similar to that with recent loop diuretic use. This impaired salt reabsorption (with elevated urinary chloride) results in volume contraction (normotension or even hypotension), stimulating the renin-angiotensin-aldosterone system (high renin, high aldosterone). This secondary hyperaldosteronism and increased distal flow causes distal hydrogen and potassium secretion, manifested as hypokalemic metabolic alkalosis. Bartter syndrome results from any of these impaired transport proteins. As Bartter syndrome is phenotypically identical to the effect of loop diuretic agents, a careful history, including family history of tubular disorders or history of diuretic use, should be sought. Often, if the diagnosis is still in question, sending a urinary diuretic screen (see Case 1) or serum for one of the above specific tubular defects is necessary.

Genetic defects in the thiazide-sensitive sodium chloride transporter in the distal tubule are the underlying cause of Gitelman syndrome. As expected, Gitelman syndrome mimics thiazide diuretic use, giving rise to normotensive chloride (saline)-nonresponsive hypokalemic metabolic alkalosis. Again, a family history of tubular defects or a history of diuretic use is helpful in making the diagnosis. As both Bartter (loop diuretics) and Gitelman (thiazide diuretics) may have similar clinical findings (normotension, hypokalemia, elevated urine chloride metabolic alkalosis, high renin and aldosterone levels), other signs are helpful to differentiate the disorders. Hypercalciuria is often present in Bartter syndrome, just as

TABLE 9. Case 7: Laboratory data

Arterial Blood Gases	Electrolytes	Urine Electrolytes
pH, 7.35	Na ⁺ , 138 mEq/L	Na ⁺ , 28 mEq/L
PaCO ₂ , 30 mm Hg	K ⁺ , 1.8 mEq/L	K ⁺ , 34 mEq/L
HCO ₃ ⁻ , 16 mEq/L	Cl ⁻ , 114 mEq/L	Cl ⁻ , 60 mEq/L
PaO ₂ , 87 mm Hg		

it is with loop diuretic use, as opposed to the hypocalciuria seen in Gitelman syndrome and thiazide use. Patients with Bartter syndrome may have nephrocalcinosis from the hypercalciuria, especially those with Na⁺-K⁺-2Cl⁻ and renal outer medullary potassium channel mutations. Gitelman syndrome may also present with severe magnesium wasting, although this particular pathophysiologic finding is not well understood. Lastly, Bartter syndrome often arises in early childhood, whereas the autosomal recessive Gitelman syndrome typically arises later in childhood or even in adulthood.

CASE 7. HYPOKALEMIA WITH NORMAL ANION GAP METABOLIC ACIDEMIA AND WEAKNESS

A 16-year-old woman was admitted to the hospital with profound weakness of 1 month's duration. However, the weakness had progressed over the last week, until she could not arise from bed. Her family brought her to the emergency room. She denied drug use, and had been previously healthy. Physical examination revealed blood pressure of 105/68 mm Hg; pulse 98 and regular; respirations 22 and labored; and temperature 99.0°F. The patient was oriented, and had no mental status abnormalities. Cardiac, pulmonary, abdominal, and skin examinations were unremarkable. She could not move any of her extremities, and said it was difficult for her to breathe. Oxygen saturation was 86%. She had symmetric reflexes, and sensation was intact to pin and vibration. The presumptive diagnosis was Guillain-Barré syndrome. A chest x-ray film was normal. X-ray examination of the kidneys, ureters, and bladder KUB revealed a surprising finding, multiple calcifications in the kidneys! Laboratory tests were ordered (Table 9).

Rules of Five

Rule 1: Acidemia is present; pH is 7.35.

Rule 2: The acidemia is metabolic; bicarbonate concentration is decreased, and PCO₂ is decreased, not increased as it would be with acidemia.

- Rule 3: The acidemia is of the normal anion gap variety ($Na^+ 138 - [Cl^- 114 + HCO_3^- 16] = 8$). The albumin level was normal.
- Rule 4: The bicarbonate decline is $25 - 16 = 9 \times 1.3 = 12$, or $40 - 12 = 28$. This is consistent with a single acid-base disorder, normal anion gap metabolic acidemia.
- Rule 5: The 1:1 relationship is less reliable without an anion gap. However, if it were applied, the bicarbonate concentration decreased by 9, and chloride increased from 104 mEq/L to 114 mEq/L, approximately 10 mEq/L. Metabolic alkalosis is absent. The potassium algorithm can now be applied.

In this patient the disorder, a metabolic acidemia but with normal anion gap, can be the result of dysfunction in one of two organs. The gut can waste bicarbonate with diarrhea, or the kidney can lose bicarbonate with renal tubular acidosis. If the gut is responsible, the kidney will compensate by excreting acid. Because this acid must be buffered, it is “packaged” by the kidney as titratable acid in the form of NH_4^+ . How can this titratable NH_4^+ be discovered in the spot urine? Remember that the cations or positive charges in the urine must be balanced by negative anions. In this patient, Na^+ plus K^+ provides a total of 62 positive charges. However, there are 60 negative charges, as represented by the spot urine Cl^- . In the presence of significant acidemia the renal tubules are not producing NH_4^+ in sufficient quantity (>15 mEq/L). This patient has distal renal tubular acidosis (proximal renal tubular acidosis differs, and is reviewed in the following section). The surprise kidneys-ureters-bladder x-ray finding was nephrocalcinosis, which occurs in distal renal tubular acidosis. Substantial amounts of intravenous potassium were administered slowly. After the potassium concentration rose (>3.0 mEq/dL), bicarbonate tablets were given orally. The patient’s strength improved over 72 hours. At discharge, the patient was given 1 mEq/kg of oral bicarbonate per day.

ACID-BASE DISORDERS IN THE SETTING OF THREE DISEASES

Recent discoveries regarding contemporary diseases have placed a number of them in an acid-base context. For example, the light-chain disease variant of an M protein disorder may manifest as proximal renal tubular acidemia.⁴² In addition to the normal anion gap disturbance, glucose, amino acids, and phosphate are wasted into the urine. In addition, Sjögren syndrome, traditionally diagnosed with sicca complex, antinuclear antibody positivity, and anti-Ro and anti-La antibodies, can be

TABLE 10. Case 8: Laboratory data

Arterial Blood Gases	Electrolytes	
pH, 7.30	Na ⁺ , 142 mEq/L	BUN, 18 mg/dL
Pco ₂ , 25 mm Hg	K ⁺ , 4.2 mEq/L	Creatinine, 1 mg/dL
HCO ₃ ⁻ , 12 mEq/L	Cl ⁻ , 106 mEq/L	CPK, 102 μ/L
PaO ₂ , 92 mm Hg		Osmolality, 299 mOsm/kg/H ₂ O
		Glucose, 82 mg/dL

BUN, Blood urea nitrogen; *CPK*, creatine phosphokinase.

associated with distal renal tubular acidosis.⁴³ Finally, acquired immune deficiency syndrome occurs with distinctive acid-base derangements.

CASE 8. TYPE B LACTIC ACIDEMIA

A 45-year-old man went to his physician with complaints of malaise, myalgias, anorexia, and nausea of 5 days' duration. He is positive for human immunodeficiency virus (HIV), and is receiving stavudine, lamivudine, and didanosine. Two months previously, electrolytes were evaluated; bicarbonate concentration was 23 mEq/L, with an anion gap of 12 (adjusted for albumin). He denies any drugs or toxin exposure. Temperature is 99.6°F, pulse is 104 and regular, respiratory rate is 20, and blood pressure is 96/60 mm Hg. Physical examination reveals clear lungs and a diffusely tender abdomen without rebound or guarding, or hepatosplenomegaly. Heart and neurologic examinations are unremarkable. There is no edema. Laboratory studies were ordered (Table 10).

Rules of Five

Rule 1: Acidemia is present; pH is less than 7.40.

Rule 2: The primary acidemic process is metabolic; the bicarbonate concentration has decreased appropriately for acidemia, the PCO₂ has not.

Rule 3: The anion gap is elevated ($142 - [106 + 12] = 24$). The albumin concentration is normal.

Rule 4: The compensation for primary metabolic acidemia is a decline in PCO₂ of 1.3 mm Hg for every 1 mEq/L decrease in HCO₃⁻. Therefore the bicarbonate level has decreased 13 mEq/L (25 - 12), so the PCO₂ should decline to 23 ± 2 ($1.3 \times 13 = 17$; $40 - 17 = 23$). The patient compensated for the primary process appropriately.

Rule 5: For the 1:1 relationship, the anion gap changed by 14 (24 - 10), equal to the decrease in bicarbonate (13). Therefore there is no hidden metabolic alkalosis.

This 45-year-old man with HIV infection undergoing HAART has anion gap metabolic acidemia with appropriate respiratory compensation. An osmolar gap was absent, as his calculated osmolality ($2[142] + 18/2.8 + 82/18 = 295 \text{ mOsm/kg/H}_2\text{O}$) was within $\pm 4 \text{ mOsm/kg/H}_2\text{O}$ of measured osmolality ($299 \text{ mOsm/kg/H}_2\text{O}$). Ketone and salicylate levels were not elevated. However, the serum lactate level was 13 mmol/L (normal range, $0.5\text{-}1.7 \text{ mmol/L}$).

Lactic acidemia evolves from either overproduction or underutilization of lactic acid.⁴⁵ Type A lactic acidosis is responsible for most lactic acidemia in hospitalized patients. The type A form is associated with profound tissue hypoxia, is most commonly seen with shock, and there is overproduction of lactate as a result. Type B lactic acidemia arises from underutilization of lactic acid, and is occasionally seen in patients like this one, who take antiretroviral agents.^{45,46} Mitochondrial dysfunction has been implicated in the pathogenesis of the type B variant seen with HAART. In this setting, the ratio of mitochondrial to nuclear DNA is lower in patients in whom lactic acid excess develops from nucleoside analogs when compared with either HAART naive patients or control patients without HIV infection.⁴⁷ In addition, when the antiretroviral agents are stopped, the ratio of mitochondrial to nuclear DNA increases. Hepatomegaly, hepatic steatosis, liver failure, and myopathy may be associated findings. Riboflavin deficiency may contribute to the mitochondrial dysfunction in affected patients, because the acidemia improves after administration of riboflavin.⁴⁸

This patient had type B lactic acidemia from antiretroviral agents, specifically stavudine and didanosine. This combination is rarely used in modern medicine because of the risk of lactic acidosis with both agents. The medications were withheld after the diagnosis was made, and with supportive treatment the lactic acidemia resolved over the next 48 hours.

CONCLUSION

Given arterial blood gas values, serum and urine electrolytes, and a few other noninvasive values such as albumin, renin concentrations, and osmolality, clinicians can apply acid-base problem-solving skills to many diseases. In addition, drugs and poisons of successive generations (eg, phenformin and Ecstasy) have characteristic acid-base findings. Systemic application of the Rules of Five, the assorted gaps, and a potassium algorithm provide clinical tools to solve complex scenarios in disparate subspecialties. This observation has been accurate in the changing environment of medicine for more than 30 years.

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