Diagnosis and Management of Acid-Base Disorders

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KEYWORDS

- Acid-base disorder • Metabolic acidosis • Metabolic alkalosis • Respiratory acidosis
- Respiratory alkalosis

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Mixed acid-base disorders are common in hospitalized patients. A stepwise approach helps clinicians identify mixed acid-base disorders.
2. A compensatory response does not normalize the pH completely. Always calculate the anion gap when the mixed acid-base disorders are suspected.
3. Patients with low albumin levels with a normal uncorrected anion gap (such as patients with end-stage liver disease) could have a high anion gap after correction. The anion gap decreases by 2.5 mEq/L for each 1 g/dL decrement of serum albumin.
4. If the urine anion gap is positive, this is caused by either high unmeasured anions (such as drug anions, toluene poisoning) or low unmeasured cations (such as renal tubular acidosis [RTA] related to a defect in urine ammonium excretion).
5. Milk-alkali syndrome is characterized by hypercalcemia, alkalosis, and renal failure.
   a. There are 3 types of RTA. The most important clue is to look at the serum potassium level. If the serum potassium level is low, type 1 (distal RTA) and type 2 (proximal RTA) are likely the cause. If the serum potassium level is high, type 4 RTA is likely.

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    b. Lactic acidosis is one of the most common causes of metabolic acidosis in the hospitalized patient, and sometimes, the first indicator of decreased tissue perfusion. The initial serum lactate level is a predictor of survival in septic shock. It is important to restore tissue perfusion and stop possible offending agents.

    c. Experts suggest that patients with lactic acidosis and pH lower than 7.1 need to be treated with bicarbonate therapy to prevent or treat the possible effects of profound acidemia on hemodynamic instability. It is important to treat the underlying cause of the acidemia.

    d. Venous blood measurements can be a good alternative to arterial blood measurements, but can be misleading when patients are in shock.

How do you diagnose acid-base disorders? What are the steps in making a diagnosis?

- It helps to use a stepwise approach in identifying acid-base disorders (**Box 1**).
- First, consider the clinical settings that are commonly associated with acid-base disorders. Hospitalized patients often have more than 1 acid-base process occurring simultaneously. Pay particular attention if a patient has gastrointestinal (GI) (vomiting, diarrhea), respiratory (hyperventilation, hypoventilation, severe chronic obstructive pulmonary disease [COPD]), or renal (renal failure) problems.
- Second, obtain an analysis of arterial blood gas (ABG) and serum electrolytes. Clinicians could make a wrong diagnosis by determining the acid-base disorder solely based on blood gas. It is easy to miss mixed acid-base disorder when electrolyte values are not taken into consideration.

Box 1
Stepwise approach to acid-base disorder

Step 1: consider clinical settings

  Common settings: gastrointestinal (vomiting, diarrhea), pulmonary (hyperventilation caused by pneumonia/hepatic encephalopathy/sepsis, hypoventilation caused by neuromuscular disorder/central nervous system depression/severe pneumonia, advanced chronic obstructive pulmonary disease), renal (renal failure, rhabdomyolysis), ketoacidosis, toxin, drugs

Step 2: identify primary disorder(s)

  Determine primary disorder based on P_{CO_2} and bicarbonate

  a. acidemic (pH<7.37) or alkalemic (pH>7.43)

  b. compare HCO_3^- from blood gas and from serum electrolytes

    If difference is greater than 3, repeat laboratory measurements

Step 3: check mixed disorders

  Compensation does not normalize pH

  a. If metabolic acidosis, apply the Winter formula or rule of 15 (addition of 15 to HCO_3^- = P_{CO_2} and the last 2 digits of pH) to assess compensation

  b. Calculate anion gap. If greater than 20, metabolic acidosis exists regardless of pH and bicarbonate

  c. Measure δ-δ (>1 [or >2, practically], superimposed metabolic alkalosis; <1, superimposed nongap acidosis; 1, simple gap acidosis)

Next, determine the primary acid-base disorder using the pH, P_{CO_2}, and bicarbonate values. Acidemia (pH<7.37) or alkalemia (pH>7.43) reflects a net effect of underlying acid-base disturbances.[1] So, it is important to know that acidemia and alkalemia are different from acidosis and alkalosis. The processes that increase or decrease the H^+ concentration are called acidosis and alkalosis, respectively.[1]

Once you have determined whether the acid-base disorder is acidemic or alkalemic, determine if the P_{CO_2} and bicarbonate move in the direction of pH. (See What is the Henderson-Hasselbalch equation? What is it used for? regarding how to identify primary disorder.)

- Third, determine if a mixed acid-base disorder exists or not. (See What is the Winter formula? How can you tell if the compensatory mechanism is appropriate or inappropriate?)

What is the Henderson-Hasselbalch equation? What is it used for?

$$pH = 6.10 + \log \frac{\left[HCO_3^-\right]}{0.03 PCO_2}$$

- Even although the Henderson-Hasselbalch equation is frequently mentioned in textbooks, the equation itself is not frequently used in clinical practice. But looking at the equation can help us understand the primary acid-base disorder.

The changes in blood pH result from the ratio of bicarbonate to P_{CO_2}.[2]

As shown in this equation, a high pH (alkalemia) is caused by high bicarbonate concentration (metabolic alkalosis) or low P_{CO_2} (respiratory alkalosis). Conversely, a low pH (acidemia) is caused by low bicarbonate concentration (metabolic acidosis) or high P_{CO_2} (respiratory acidosis). Determine if the P_{CO_2} or bicarbonate moves in the direction of the pH, and the primary acid-base disorder can be determined. However, there can be more than 1 primary acid-base disorder occurring concurrently.[2]

Consider an example of pH 7.46, HCO_3^- 30, P_{CO_2} 44. The pH indicates that there is alkalemia. The primary acid-base disorder is caused by an increased bicarbonate concentration (because P_{CO_2} is not low), so this is a primary metabolic alkalosis.

Let us see another example: pH 7.59, HCO_3^- 28, P_{CO_2} 30. PH also indicates alkalemia. Because the bicarbonate level is high and P_{CO_2} low, both metabolic alkalosis and respiratory alkalosis exist as primary disorders. As shown in this example, 2 primary acid-base disorders can coexist.

Another use of the Henderson-Hasselbalch equation is when assessing the quality of measurements of blood gas and electrolytes. The value of HCO_3^- from blood gas is calculated, whereas the value from the electrolyte panel is measured. If the values from these 2 sources differ by more than 3, repeat measurement of blood gas and electrolytes is recommended to reduce the error.[3] If the difference is large, it is usually because either ABG and serum electrolytes were drawn at different times or there may be quality issues with the blood gas analyzer.[3]

What is the Winter formula? How can you tell if the compensatory mechanism is appropriate or inappropriate?

- The compensatory response is almost never complete.[3] Compensation moves the pH toward normal but does not normalize the pH completely.[3] One good

case example to assess whether there is appropriate compensatory mechanism is metabolic acidosis. In metabolic acidosis, the appropriate compensatory response should be a decrease in P_{CO_2}, which can be calculated by the Winter formula [$P_{CO_2} = (1.5 \times HCO_3^-) + 8 \pm 2$]. If measured P_{CO_2} is higher than calculated (expected) P_{CO_2} from the Winter formula, it indicates that there is a superimposed respiratory acidosis. If measured P_{CO_2} is lower, then, there is a superimposed respiratory alkalosis. The Winter formula can be applied only to metabolic acidosis.[4] Another way to determine the expected compensation is simply adding 15 to the bicarbonate value, which equals P_{CO_2} and the last 2 digits of pH.[5] This formula is valid if the bicarbonate value is between 10 and 40 mEq/L. For example, if the bicarbonate value is 17 mEq/L, adding 15 to 17 (bicarbonate value) equals P_{CO_2} 32 mm Hg, and the last 2 digits of pH (7.32).

How common are mixed acid-base disorders? What is the approach that should be taken to diagnose the presence of a mixed disorder? How can one tell if there is only a simple anion gap acidosis, or if there is superimposed nongap acidosis or metabolic alkalosis?

- Mixed acid-base disorder is common in inpatient settings, because patients' illness often involves multiple organ systems.
- There are 2 principles to remember when assessing mixed disorders:
  1. Compensatory response does not normalize the pH completely and
  2. Calculate the anion gap regardless of what the pH shows.
- Compensatory response does not normalize pH completely.[3] If a patient presents with severe vomiting and the blood gas shows a normal pH, this suggests the presence of a mixed disorder, because the respiratory compensation for primary metabolic alkalosis (from vomiting) is not complete and should not normalize the pH. In this scenario, the presence of a mixed acid-base disorder is likely. When a patient has active GI, respiratory, renal, or neurologic problems, but the pH is normal or near normal, it is likely that a mixed acid-base condition is present.
- When a patient's history and physical examination suggest the presence of an acid-base disorder, calculate the anion gap even if blood gas shows a normal pH. For example, if the ABG and electrolyte values show pH 7.40, P_{CO_2} 42, bicarbonate 23, sodium 145, and chloride 97, even although pH, P_{CO_2}, and bicarbonate are all within a normal range, the anion gap shows the presence of an underlying anion gap metabolic acidosis.[3]
- After the anion gap has been calculated, the δ-δ should be checked to assess if there is a superimposed disorder. δ-δ is based on the fact that an addition of each 1 mEq/L of acid to the blood circulation decreases the bicarbonate value by 1 mEq/L and increases the anion gap by 1 mEq/L. For example, in a case in which the anion gap is 24 and HCO_3^- is 17, the δ anion gap (calculated as anion gap – 10) is 14 and δ HCO_3^- (calculated as 24 – HCO_3^-) is 7. In a simple anion gap metabolic acidosis, the δ anion gap equals δ HCO_3^-. However, if the δ anion gap is greater than the δ HCO_3^-, it suggests that there is a superimposed metabolic alkalosis leading to higher than expected HCO_3^- level. Let us see another example: anion gap 15, HCO_3^- 14. δ anion gap (AG – 10) is 5, δ HCO_3^- is (24 – HCO_3^-) 10. δ anion gap is smaller than δ HCO_3^-, which suggests a superimposed nongap acidosis leading to a larger HCO_3^- loss.

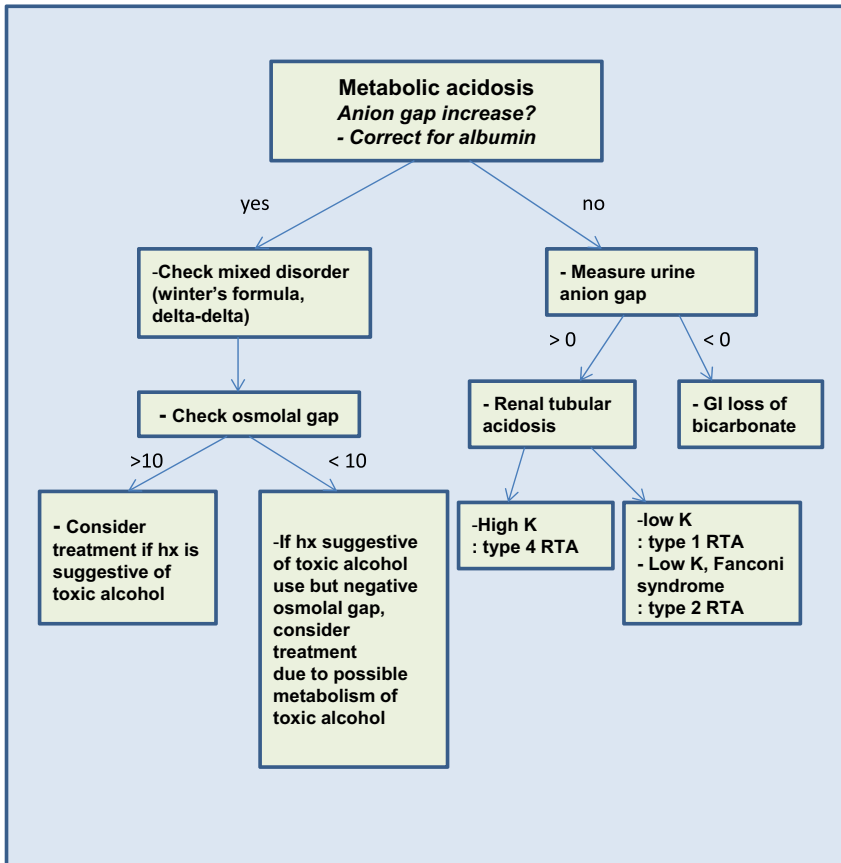See Fig. 1 for an overall stepwise approach to acid-base disorder.

Fig. 1. Approach to metabolic acidosis.

What are some special scenarios to be aware of when interpreting acid-base disorders?

a. Calculating anion gap in a patient with hypoalbuminemia?

Anionic charges of circulating proteins are responsible for much of the serum anion gap. It has been reported that there is a direct correlation between changes in serum albumin level and the anion gap. The anion gap decreased by 2.5 mEq/L for each 1 g/dL decrement of serum albumin.[6,7]

Consider an example: Na 133, Cl 105, HCO_3^- 18, albumin 1 g/dL. The calculated anion gap is $(Na - (Cl^- + HCO_3^-)) = 10$.

Applying the albumin correction to determine the reduction in normal anion gap shows: $(4 - 1) \times 2.5 = 7.5$.

The adjusted anion gap is $12 - 7.5 = 4.5$.

The calculated anion gap of 10 is higher than the adjusted anion gap of 4.5.

So, the albumin correction of anion gap shows high anion gap metabolic acidosis, even although the uncorrected anion gap looks normal.

Patients with low albumin levels with a normal uncorrected anion gap (such as patients with end-stage liver disease) could have a high anion gap after correction.

b. What is pyroglutamic acidemia?

Pyroglutamic acidemia (5-oxoprolinemia) is a rare cause of high anion gap metabolic acidosis, which is associated with the use of medications like acetaminophen and flucloxacillin.[8] This acidemia generally occurs in the setting of sepsis, liver failure, or renal failure.[8] In the case of acetaminophen-induced pyroglutamic acidemia, the mechanism is believed to involve the depletion of liver glutathione stores, which causes accumulation of γ-glutamylcysteine. γ-Glutamylcysteine is metabolized to 5-oxoprolinemia.[9] Pyroglutamic acidemia can occur with the therapeutic doses of acetaminophen.[8] Altered mental status is a main clinical feature. The diagnosis can be made by measuring 5-oxoproline level from plasma or urine after other causes are ruled out.[8] Treatment of the pyroglutamic acidemia is to discontinue associated drugs such as acetaminophen and flucloxacillin, and provide supportive care.[9] N-Acetylcysteine may be an effective treatment.[9] Consider pyroglutamic acidemia in patients with high anion gap metabolic acidosis when other causes are ruled out and when acetaminophen (or flucloxacillin) is used in the setting of sepsis, liver failure, or renal failure.[9,10]

c. What is milk-alkali syndrome?

Milk-alkali syndrome is characterized by hypercalcemia, alkalosis, and renal failure.[11] This syndrome occurs in patients taking excessive amounts of calcium and absorbable alkali such as calcium carbonate.[12] The incidence of this syndrome is increasing as more people are taking calcium-based therapy for osteoporosis and treatment of secondary hyperparathyroidism in patients with chronic kidney disease.[11]

Symptoms include nausea, vomiting, and altered mental status caused by hypercalcemia.[11] Diagnosis can be made based on clinical history (including the use of calcium-containing drugs) after other causes of hypercalcemia are ruled out.[11] Treatment is to discontinue the offending drug and improve hypercalcemia with hydration and furosemide.[11]

d. If both anion gap and osmolal gap are increased, what do you need to do next?

Causes that increase both anion gap and osmolal gap include methanol, ethylene glycol, propylene glycol, ethanol, lactic acidosis, ketoacidosis, and renal failure.[13,14] Even although the osmolal gap is generally higher in toxic alcohols than other causes like diabetic ketoacidosis (DKA), it is not always the case.[15] The serum osmolal gap and anion gap change over time. Even if the osmolal gap is high initially, the osmolal gap decreases over time as the offending alcohol is metabolized to organic acids (which increases anion gap).[14]

So, it is particularly important to obtain a thorough history and exclude the use of toxic alcohol in all patients with high anion gap metabolic acidosis, even if the osmolal gap is not high. See **Fig. 1** for a stepwise approach to metabolic acidosis.

What are the causes of different types of acid-base disorders? (**Table 1**)

a. Anion gap acidosis?

Increased anion gap acidosis can result from 4 key causes:
- Ketoacidosis, often caused by diabetes, alcohol, or starvation
- Lactic acidosis caused by type A lactic acidosis (impaired perfusion) or type B lactic acidosis (impaired carbohydrate metabolism)
- Renal failure, resulting in uremic acidosis or acute renal failure
- Toxins (ethylene glycol, methanol, salicylates)

Table 1
Causes of acid-base disorders

Acid-Base Disorder	Subclassification	Causes/Differential Diagnosis
Metabolic acidosis	Anion gap	DKA Chronic kidney disease Lactic acidosis Aspirin toxicity Alcoholic ketoacidosis Poisoning from methanol, ethylene glycol
Metabolic acidosis	Nonanion gap	Bicarbonate loss from GI tract (diarrhea) Bicarbonate loss from renal (proximal, type 2 RTA) Impaired H+ secretion from nephron (distal, type 1 RTA) Impaired ammoniagenesis (type IV RTA) Fanconi syndrome (phosphaturia, glucosuria, uricosuria, and aminoaciduria) Use of carbonic anhydrase inhibitors
Metabolic alkalosis		Vomiting (loss of hydrochloric acid) Diuretics use (loss of hydrogen caused by increased distal sodium delivery and volume contraction) Hypokalemia Primary mineralocorticoid excess Posthypercapnia Gitelman syndrome, Bartter syndrome
Respiratory acidosis		Central nervous system depression: sedatives Neuromuscular disorders Inhibition of medullary respiratory center Disorders of the chest wall and respiratory muscles Airway obstruction Gas exchange disorders across pulmonary capillaries Obesity hypoventilation syndrome Mechanical ventilation issues
Respiratory alkalosis		Anxiety Hypoxia Lung disease (pneumonia) Central nervous system disease (ie, hemorrhage, stroke) Drug use (aspirin, caffeine) Pregnancy Sepsis Hepatic encephalopathy Mechanical ventilation

b. Nonanion gap (hyperchloremic) acidosis?

Normal anion gap acidosis has 2 main causes:

- Renal causes: usually attributed to RTA or medications such as carbonic anhydrase inhibitors
- GI causes: severe diarrhea, urinary diversion using ileal or colonic segments, drainage of pancreatic or biliary secretions or small bowel fistulas[16]

When should the urine anion gap be used and how is it interpreted?

The urine anion gap (UAG) can be calculated to help determine whether a hyperchloremic metabolic acidosis is of extrarenal origin (usually, GI loss of bicarbonate) or renal

origin (usually RTA).[17] The UAG is used to measure the urine ammonium levels.[17] In the presence of metabolic acidosis, urinary acid excretion (in the form of ammonium) is normally increased to compensate for low serum bicarbonate levels.[17] However, this compensatory mechanism is impaired in the setting of RTA because of a defect in urinary ammonium excretion.[17] Calculating the UAG and then noting if the UAG is positive or negative helps clarify if the metabolic acidosis is of renal or extrarenal origin. Follow these simple steps:

- UAG = ([urine sodium] + [urine potassium]) − [urine chloride] = unmeasured anions (such as bicarbonate, organic anions) − unmeasured cations (such as ammonium)
- UAG is normally between 30 and 50 mEq/L
- If UAG is positive, this is caused by either high unmeasured anions (such as drug anions, toluene poisoning) or low unmeasured cations (such as RTA related to a defect in urine ammonium excretion)
- If UAG is negative, this suggests increased urinary ammonium excretion and an extrarenal origin (commonly, a GI source like diarrhea)

How can you distinguish different types of RTA? (Fig. 2, Table 2).

When UAG is positive, it may represent the presence of an RTA, and the next step is to determine the type of RTA. There are 3 types of RTA.

The most important clue is to look at the serum potassium level. If the serum potassium level is low, type 1 (distal RTA) and type 2 (proximal RTA) are likely the cause. If the serum potassium level is high, type 4 RTA is likely. Hypokalemia is caused by hyperaldosteronism and renal potassium wasting.[18,19] Bicarbonate loss is believed to cause volume contraction and leads to hyperaldosteronism, even although its mechanism is not clear.[18,19] On the contrary, type 4 RTA is characterized by hyporenin, hypoaldosteronism that causes hyperkalemia.[20] Hyperkalemia suppresses ammonium synthesis, leading to the defect of urinary acidification.[20] When hypokalemia is present, one should look for evidence of urinary loss of phosphate, amino acids, glucose, and uric acid (Fanconi syndrome), because it is rare to have isolated bicarbonate loss with proximal RTA (like carbonic anhydrase inhibitors).[19] Drug-induced Fanconi syndrome is a common cause of proximal RTA and includes ifosfamide, valproic acid, and tenofovir.[21]

How do you treat patients with RTA? (see Fig. 2, Table 2).

Proximal RTA (type 2 RTA): a type 2 RTA can cause the loss of large amounts of bicarbonate, and hence, the doses needed to replace bicarbonate are sizable and often range from 10 to 20 mmol/kg per day to correct this type of RTA, because of large urinary loss of bicarbonate.[17] The addition of a thiazide diuretic (eg, hydrochlorothiazide 25–50 mg daily) increases the efficacy of bicarbonate treatment.[17] It is important to provide potassium replacement, because a bicarbonate replacement with thiazide diuretic can worsen hypokalemia. Polycitra (Cytra-3, Cypress pharmaceutical) is a mixture of sodium and potassium citrate and is a useful treatment option. Closely monitoring electrolyte levels in these patients is important.[17,21]

Distal RTA (type 1 RTA): distal tubular acidosis occurs when the kidney is unable to remove acid into the urine properly. Therefore alkali therapy in the amount of 1 to 2 mmol/kg daily is usually needed to correct the metabolic acidosis and balance H+ production.[17] The hypokalemia should be corrected before correcting the acidosis in these patients. Potassium citrate can be used as a monotherapy.[17]
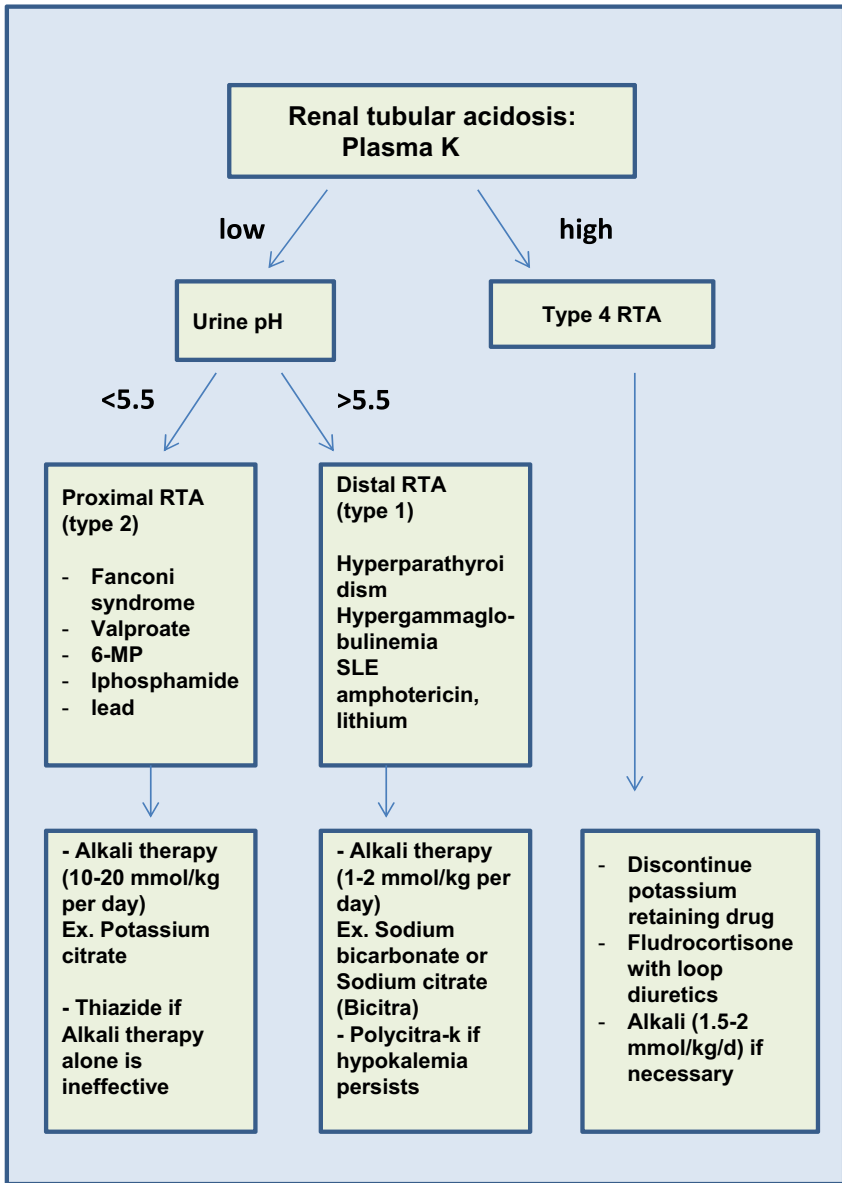
Fig. 2. Approach to RTA.

Hyperkalemic distal RTA (type 4 RTA): treatment differs depending on the underlying cause. It is important to correct hyperkalemia in type 4 RTA, because this treatment in itself often leads to the correction of acidosis. Alkali therapy with bicarbonate often treats acidosis and hyperkalemia as well. Potassium-retaining drugs (such as spironolactone) should be discontinued. Hyporeninemic hypoaldosteronism may be treated with fludrocortisones. The use of a loop diuretic like furosemide is recommended for patients with low glomerular filtration rate (<30 mL/min) to avoid volume overload.[17]

Table 2
Summary of types of RTA

	Type 1	Type 2	Type 4
Hyperchloremic acidosis	Yes	Yes	Yes
Minimum urine pH	>5.5	<5.5 (but usually >5.5 before the acidosis becomes established)	<5.5
Plasma potassium	Low-normal	Low-normal	High
Kidney stone	Yes	Uncommon	Uncommon
Defect	Reduced H^+ excretion in distal tubule	Impaired HCO_3 reabsorption in proximal tubule	Impaired cation exchange in distal tubule
Treatment	Alkali therapy	Bicarbonate ± thiazide	Correct hyperkalemia Depending on cause, also ± alkali therapy, loop diuretics, or fludrocortisones

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What are the causes of lactic acidosis and what is the role of bicarbonate therapy?

a. Why is lactic acidosis important?

It is one of the most common causes of metabolic acidosis in the hospitalized patient, and sometimes the first indicator of decreased tissue perfusion. The initial serum lactate level is a predictor of survival in septic shock, and lactate clearance (>10%) is associated with improved outcomes.[22]

b. How is it diagnosed?

An increased anion gap with a plasma lactate concentration higher than 4 mEq/L, even in the absence of systemic acidosis.[23] See **Box 2** for stepwise approach to lactic acidosis.

c. What are type A and type B lactic acidosis?

As seen in **Table 3**, there are 2 types of lactic acidosis. Type A lactic acidosis is caused by tissue hypoperfusion. Type B lactic acidosis is generally caused by toxin-induced impairment of metabolism in the absence of tissue hypoperfusion.[23]

d. What is D-lactic acidosis?

D-Lactic acidosis occurs in patients with short bowel syndrome after GI surgery (eg, jejunoileal bypass). In this condition, ingested carbohydrate is not metabolized adequately in the small intestine because of its short length.[24] This situation leads to carbohydrate overload in the colon, which is metabolized by colonic anaerobes (such as *Lactobacillus* species) producing D-lactate (dextrorotary isomer of lactate). Unlike L-lactate, D-lactate is neurotoxic, so the patient often manifests symptoms such as altered mental status, psychosis, and ataxia. The toxic effect of D-lactate increases in the setting of renal failure because its clearance is limited.[25] To measure D-lactate, a special assay needs to be ordered, because a routine lactate test does not measure the D-isomer. Treatment includes a low-carbohydrate diet. The addition of an antimicrobial agent (such as metronidazole) to treat bacterial overgrowth may also be beneficial.[25]

Box 2
Stepwise approach to lactic acidosis

Step 1: evaluate for tissue hypoperfusion and restore adequate perfusion and evaluate for local tissue ischemia

- Shock (distributive, cardiogenic, hypovolemic, and obstructive), postcardiac arrest syndrome
- Tissue hypoperfusion should be initially assumed/considered until proved otherwise
- Mesenteric ischemia, limb ischemia, burns, trauma, compartment syndrome, necrotizing soft tissue infections
- Consider early surgical consultation as appropriate

Step 2: stop/reverse potential offending agents

- Pharmacologic agents: linezolid, nucleoside reverse transcriptase inhibitors, metformin, valproate, theophylline, epinephrine, propofol, isoniazid, and salicylates
- Drugs and toxins: cocaine, alcohols, carbon monoxide, and cyanide poisoning

Step 3: consider other causes (such as malnutrition, anaerobic metabolic activity) and metabolic derangements

- Thiamine deficiency and treat if suspected
- Malnutrition of any cause (often alcoholics): give intravenous thiamine
- Heavy exercise, seizures, excessive work of breathing
- DKA
- Mitochondrial disease
- Liver dysfunction

Data from Andersen LW, Mackenhauer J, Roberts JC, et al. Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc 2013;88:1127–40.

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e. Who should receive treatment with bicarbonate therapy?

The role of bicarbonate therapy is controversial in lactic acidosis, some experts would recommend that patients with lactic acidosis and pH less than 7.1 be treated. The theoretical benefit is that it may prevent or treat the possible effects of profound acidemia on hemodynamic instability, such as left ventricular contractility, arrhythmias, response to vasopressors, arterial vasodilation, and

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Table 3
Types of lactic acidosis

Types of Lactic Acidosis	Mechanism	Examples

Type A	Impaired tissue oxygenation leading to increased anaerobic metabolism
	Prognosis poor until tissue perfusion restored
		Shock from:
		  Sepsis
		  Cardiac failure
		  Hypovolemia
		  Cardiopulmonary arrest

Type B	No evidence for systemic hypoperfusion, usually mediated by toxin-induced impairment of metabolism or regional areas of ischemia	Diabetes Metformin toxicity Human immunodeficiency virus Malignancy Alcoholism Liver disease

venoconstriction. It is always important to treat the underlying cause of the acidemia.[26,27]

f. What are the potential harms of bicarbonate therapy?

Rapid infusions of bicarbonate therapy can increase the P_{CO_2}, accelerate lactate production, cause hypernatremia, decrease ionized calcium, and expand extracellular space.[27] Possible alternative buffering agents such as tromethamine, carbicarb, and dichloroacetate have been proposed, but none has shown significant benefit in patients with lactic acidosis.[27]

g. How do you administer bicarbonate therapy?

Give 1 to 2 mEq/kg of sodium bicarbonate as an intravenous bolus for adequately ventilated patients. Measure serum electrolyte levels and blood gas in 30 minutes. If pH is still less than 7.10, the sodium bicarbonate may be readministered.[27,28]

What are the benefits of measuring the venous blood gas (in place of ABG)?

Venous blood gas (VBG) can be calculated using a peripheral venous sample as opposed to arterial blood. Central VBGs are preferred because they are most well established in the literature. If a peripheral venous sample is obtained with a tourniquet, it should be released 1 minute before the sample to avoid changes induced by local ischemia.[29]

a. How do you interpret a VBG? In general…

Venous pH: .03 to .05 pH units lower than arterial pH

Venous P_{CO_2}: 4 to 5 mm Hg higher than arterial P_{CO_2}

Venous HCO_3: no different from arterial HCO_3

Venous O_2: no practical value; oxygen has already been extracted[29]

b. When is a VBG inaccurate?

If a patient is hypotensive, the VBG can be misleading. Numerous studies have found poor correlation of arterial and venous blood measurements (up to 3-fold difference) among patients with shock.[26,27]

CASE EXAMPLES OF ACID-BASE DISORDERS
Case 1

A 60-year-old woman with a history of hypertension, chronic kidney disease, COPD presented with fever, vomiting, and right-sided flank pain. Urinalysis findings were consistent with acute pyelonephritis. Vital signs showed blood pressure of 90/40 mm Hg, heart rate 118, respiratory rate 24; blood gas: pH 7.30, P_{CO_2} 40 mm Hg; serum chemistry: sodium 147 mEq/L, chloride 100 mEq/L, bicarbonate 15 mEq/L. Serum creatinine increased from baseline 2.0 mg/dL to 3.5 mg/dL.

This patient has severe sepsis secondary to acute pyelonephritis.

Let us apply the stepwise approach:

First, consider the clinical setting. Acute GI and renal problems suggest underlying acid-base disorder, possibly a mixed disorder.

Second, identify primary acid-base disorder using P_{CO_2} and bicarbonate.

pH is acidemic. Because the bicarbonate is low (P_{CO_2} is not low), it suggests a primary metabolic acidosis.

Third, check if compensatory response is appropriate and if mixed acid-base disorder exists.

We can apply the Winter formula or simply add 15 to bicarbonate.

The addition of 15 to HCO_3^- is 30 Winter formula [$P_{CO_2} = (1.5 \times HCO_3^-) + 8 \pm 2 = 30.5 \pm 2$], so expected P_{CO_2} is 30. Because measured P_{CO_2} is higher than 30, there is a superimposed respiratory acidosis.

Next, calculate anion gap and δ–δ. Measured anion gap is 32. δ anion gap is 32 – 10 = 22. δ bicarbonate is 24 – 15 = 9. δ/δ ratio is greater than 2, which indicates a superimposed metabolic alkalosis.

So, this patient has a mixed disorder with metabolic acidosis (renal failure, possibly lactic acidosis caused by sepsis), respiratory acidosis (COPD), and metabolic alkalosis (vomiting, contraction alkalosis).

Case 2

A 25-year-old woman with a history of type 1 diabetes mellitus came in to the emergency department with fever and confusion. The patient had had a productive cough for about 2 weeks. She had also had difficulty eating and drinking because of nausea and vomiting for several days before her presentation. Her insulin regimen was 20 units of glargine at night and a rapid-acting insulin analogue before each meal.

On examination, the patient was found to be tachypneic at a rate of 24 breaths per minute, tachycardic with a pulse rate at 114, blood pressure 85/60 mm Hg, and she was also found to have dry mucous membrane and poor skin turgor. In addition, her lung examination showed rhonchi in the right lower lung field.

Laboratory tests showed an increased white blood cell count 22 K/uL, hemoglobin 14.3 g/dL, glucose 520 mg/dL, blood urea nitrogen 55 mg/dL, creatinine 1.6 mg/dL, sodium 153 mEq/L, K 4.5 mEq/L, chloride 110 mEq/L. ABG showed a pH of 7.0, P_{O_2} 98 mm Hg, P_{CO_2} 27 mm Hg, and bicarbonate 8 mEq/L, O_2 100% saturation. Urine study was positive for ketones.

Given this constellation of symptoms and laboratory results (hyperglycemia, ketosis, and metabolic acidosis), this patient was shown to have DKA in the setting of a suspected respiratory infection. Blood gas showed high anion gap metabolic acidosis (with an anion gap of 31).

This patient with insulin-dependent diabetes had DKA, likely triggered by pneumonia. Acute infection increases stress hormones like glucagons, which leads to increased gluconeogenesis, glycogenolysis, and ketogenesis.[30] DKA often involves the mixed disorder.[31] It has high anion gap metabolic acidosis caused by increased ketone bodies (predominantly acetoacetic acid and β-hydroxybutyric acid). Lactic acidosis can coexist as a result of tissue hypoperfusion, especially with patients who present with prolonged periods of hypotension and severe dehydration.[32] Contraction alkalosis may exist as well, as a result of vomiting and dehydration. Patients with pneumonia and sepsis could have respiratory alkalosis.

After a patient is aggressively treated with isotonic solution (0.9% NaCl), hyperchloremic (nongap) metabolic acidosis may occur as high anion gap metabolic acidosis resolves.

Why do we need to check both anion gap and ketones for DKA?

As mentioned earlier, patients with DKA often have mixed acid-base disorder. Lactic acidosis could lower the ketone production (by decreasing acetoacetate), so clinicians may face a clinical situation that a patient with severe anion gap metabolic acidosis does not have a significantly high ketone level.[33] It is also possible that ketone levels increase as the patient clinically improves when lactic acidosis resolves. So, it is important to provide insulin and other treatment to close the anion gap as well as normalize ketone level.

To manage this patient, 1 liter of isotonic saline (0.9% NaCl) bolus infusion needs to be initiated immediately. The patient's potassium was near normal levels, and 20 to 30 mEq of potassium for every liter of replacement fluid is generally sufficient to maintain potassium within the range of 4 to 5 mEq/L.[34] It is important to delay insulin therapy until serum potassium level is more than 3.3 mEq/L. Serum potassium levels need to be checked every 2 to 4 hours initially. Isotonic saline is generally recommended as boluses of 15 to 20 mL/kg for the first 1 to 2 hours to restore intravascular/extravascular volume, and then, the rate can be decreased. As for insulin, a continuous infusion of regular insulin (0.1 unit/kg per hour) is administered after the initial bolus of regular insulin (0.15 units/kg).[34] Serum glucose levels must be frequently monitored. Insulin infusion dosage is adjusted to decrease glucose level by 50 to 75 mg/dL per hour. Even after blood glucose level decreases lower than 250 mg/dL, insulin infusion may need to be maintained. This treatment can usually be administered while also giving 5% dextrose in 0.45% to 0.75% NaCl.[34]

Case 3

A 50-year old man with alcoholic cirrhosis and end-stage liver disease was admitted to hospital with hepatic encephalopathy. His vital signs were temperature 38.5°C, blood pressure 90/60 mm Hg, respiratory rate 24 breaths/min, heart rate 100 beats/min. White blood cell count was 13 K/uL platelet count 50 K/uL. The patient was not able to say how he got to the hospital.

How would you approach treating this patient?

It is crucial that you suspect sepsis (given his systemic inflammatory response syndrome and possible infection) and find the underlying cause and treat early. One should appropriately evaluate for infection (such as diagnostic paracentesis, urine analysis, blood culture, and chest radiography). As part of the Surviving Sepsis Campaign best practice 3-hour bundle, a lactate and blood culture also need to be ordered.

The lactate level is 4.5. How would you interpret this finding?

The increased lactate level is an early sign of decreased organ perfusion. The mortality for septic patients with lactate greater than 4 is high,[22] and this patient should be treated early with antibiotics (ideally within 1 hour) and hydration (30 mL/kg goal because systolic blood pressure <90). Increased lactate level could occur with advanced liver disease, but that should not be the assumed explanation in this case.

Despite antibiotics and 3 L of normal saline, the patient becomes more hypotensive, with systolic blood pressure 80/40. You have called the intensive care unit for a transfer. You attempt to measure ABG and instead receive venous blood. How would you interpret the results? VBG: pH = 7.20, P_{CO_2} = 50.

Because the patient was hypotensive, the results can be misleading. With adjustments, one could estimate the ABG as pH 7.25 and P_{CO_2} = 45. However, studies have found that VBGs from patients in shock can have misleading results. Patients should be transferred to the intensive care unit and an arterial line placed to follow ABGs.

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