PEER REVIEWED

The Practitioner's Acid–Base Primer
Differential Diagnoses & Treatment

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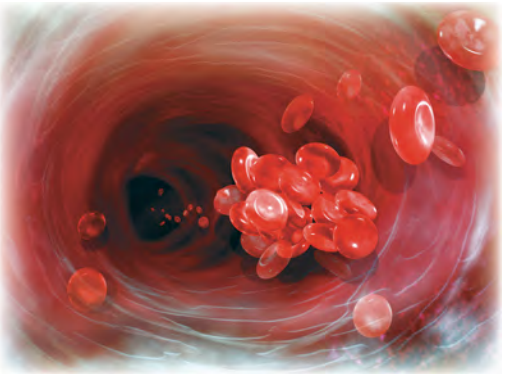


This article is the second in the 2-part series: The Practitioner's Acid–Base Primer. The first article, **Obtaining & Interpreting Blood Gases** (May/June 2013) addressed techniques for obtaining blood gases and interpretation of metabolic and respiratory disturbances. Read Part 1 at **tvpjournal.com**. This article will further investigate metabolic and respiratory disturbances, identifying:

- Clinical signs
- Differential diagnoses
- Treatment options.

Acid–base alterations can lead to:

- Altered cardiovascular, neurologic, and respiratory function
- Altered response to various drug therapies.

Blood gases, either arterial or venous, evaluate acid–base status, and also test respiratory function (with arterial samples superior to venous), more specifically:

- Oxygenation
- Ventilation.

METABOLIC ACIDOSIS

Clinical Signs & Consequences

Severe acidosis can lead to:

- **Cardiovascular:** Vasodilation, hypotension, arrhythmias, decreased cardiac contractility
- **Metabolic:** Insulin resistance
- **Neurologic:** Mental dullness
- **Respiratory:** Increased respiratory effort

Differential Diagnoses

Increased Anion Gap Metabolic Acidosis (Normochloremic)

- Lactate
- Ketones (eg, diabetic ketoacidosis)
- Uremic acids (eg, elevated sulfates and phosphates in marked azotemia)
- Toxins (eg, metabolites of ethylene glycol, salicylates)

Normal Anion Gap Metabolic Acidosis (Hyperchloremic)

- Renal tubular acidosis
- HCO_3^- loss through diarrhea

Therapeutic Measures

Treatment of metabolic acidosis should be aimed at correcting the underlying problem.

Increased Anion Gap Metabolic Acidosis

In patients with increased anion gap (AG) metabolic acidosis, unmeasured organic anions, such as ketones or lactate, can be metabolized to HCO_3^- during recovery.

- If metabolic acidosis is due to lactate from hypovolemia, take appropriate measures—intravascular volume resuscitation using IV fluids—to restore adequate oxygen delivery to tissues.
- If lactic acidosis is due to decreased arterial oxygen content (see **Decreased Oxygen Delivery**), administer red blood cells via transfusion and/or provide supplemental oxygen.
- If severe, persistent metabolic acidosis (pH < 7.1) is due to a cause other than lactate, consider sodium bicarbonate administration (see **Sodium Bicarbonate Administration**, page 26). However, only consider sodium bicarbonate administration in:
  - » Cases of increased AG metabolic acidosis refractory to fluid therapy
  - » Cases with evidence of cardiovascular compromise secondary to metabolic acidosis.

Normal Anion Gap Metabolic Acidosis

Patients with a normal AG metabolic acidosis have experienced a loss of bicarbonate, either through gastrointestinal (GI) tract from diarrhea or via the kidneys from renal tubular acidosis. These patients often need sodium bicarbonate therapy to correct metabolic acidosis.

DECREASED OXYGEN DELIVERY

Decreased tissue oxygen delivery (causing lactic acidosis due to anaerobic metabolism) can occur as a result of:

- **Decreased stroke volume due to decreased preload** (eg, hypovolemia)—the most common cause of lactic acidosis in veterinary patients
- **Decreased arterial oxygen content** (due to anemia or hypoxemia) ***and/or***
- **Decreased cardiac output** (eg, from decreased stroke volume or, much less commonly, pathologic arrhythmias).

DEFINING THE ANION GAP

Anions & Cations

Calculation of the anion gap (AG) is helpful for differentiating causes of metabolic acidosis. The AG is the difference in the sum of commonly measured:

- **Anions:** Negatively charged ions—chloride (Cl^-) and bicarbonate (HCO_3^-)
- **Cations:** Positively charged ions—sodium (Na^+) and potassium (K^+)

$$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

Unmeasured Anions & Cations

The AG is an artificial, calculated measure because the patient always has equimolar amounts of anions and cations to maintain electroneutrality. The unmeasured anions (UA) and cations (UC) maintain the balance of positive and negative charges:

$$Na^+ + K^+ + UC = Cl^- + HCO_3^- + UA$$

Therefore, the anion gap is the difference between the number of unmeasured anions and unmeasured cations:

$$AG = UA - UC = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

- **Unmeasured anions:** In healthy (normal) animals, the majority of UAs are plasma proteins, with albumin contributing a larger portion than the globulins.
- **Unmeasured cations:** The UCs are calcium and magnesium, which normally do not vary enough to cause appreciable changes in the AG because their serum concentrations are tightly regulated.

Differences in Anion Gap

- **Decreases in AG** are most commonly associated with hypoalbuminemia.
- **Increases in AG** are seen with many causes of metabolic acidosis in which additional UA are present in plasma, such as:
  - » Lactic acidosis
  - » Ketoacidosis
  - » Uremia
  - » Ethylene glycol or salicylate intoxication.
- **Normal AG acidosis** is often referred to as *hyperchloremic acidosis* because AG remains normal due to an increase in Cl^- (rather than addition of UA) when HCO_3^- is decreased.
  - » Most commonly seen in animals with large bowel diarrhea and renal tubular acidosis
  - » Also seen with parenteral (or systemic) administration of carbonic anhydrase inhibitors (eg, acetazolamide) and acidifying agents (eg, ammonium chloride, oral calcium chloride).

METABOLIC ALKALOSIS

Clinical Signs & Consequences

Consequences of metabolic alkalosis include:

- **Cardiovascular:** Cardiac arrhythmias, decreased oxygen delivery to tissues (via shifting of oxygen hemoglobin curve to the left)
- **Neurologic:** Neuromuscular dysfunction
- **Metabolic** (in acute, severe alkalosis only)**:** Muscle twitching due to decreased serum ionized calcium concentration caused by increased binding of calcium ions to albumin, hypokalemia as H^+ ions shift out of cells and K^+ moves into them.

In humans, these signs are described as malaise, lethargy, and weakness, and can progress to confusion, stupor, muscle twitching, tetany, seizures, and coma.

Differential Diagnoses

- GI obstruction in the upper GI tract (stomach or proximal duodenum), that results in loss of H^+, K^+, and, most important, Cl^- in the vomitus
- Furosemide administration
- Administration of alkali (sodium bicarbonate)

SODIUM BICARBONATE ADMINISTRATION

When treating with sodium bicarbonate, calculate the amount to administer by using the following equation:

Base excess (BE) **x body weight** (kg) **x 0.3 = Bicarbonate deficit** (mEq)

Depending on the needs of the patient, usually ¼ to ⅓ of the calculated dose is given at a time:

- By slow bolus over 5 to 10 minutes (only to correct life-threatening acidosis) ***or***
- Through IV fluids over several hours.

Careful monitoring of pH, HCO_3^-, BE, carbon dioxide (CO_2), and Na^+ should occur when sodium bicarbonate is administered.

Side effects of sodium bicarbonate therapy should be considered, and include:

- **Cardiovascular:** Shifting of oxyhemoglobin curve to the left if alkalosis occurs, making it more difficult for hemoglobin to unload oxygen to the tissues
- **Metabolic:**
  - » Hypernatremia
  - » Hyperosmolality
  - » Development of alkalosis (after organic anions are metabolized)
  - » Hypokalemia (K^+ ions shift back into intracellular spaces as hydrogen [H^+] ions move out)
  - » Decreased serum ionized calcium concentration caused by increased binding of calcium ions to albumin
- **Neurologic:** Paradoxical central nervous system acidosis caused by diffusion of CO_2 into cerebral spinal fluid
- **Respiratory:** Secondary respiratory acidosis if patient is unable to blow off CO_2 formed from the administered bicarbonate.

- Post chronic hypercarbia (rare)
- Primary hyperaldosteronism (rare)
- Hyperadrenocorticism (rare)

Therapeutic Measures

As with metabolic acidosis, treatment of metabolic alkalosis should be aimed at correcting the underlying problem. Metabolic alkalosis is typically associated with hypokalemia, and the most common causes of metabolic alkalosis are GI obstruction with loss of H^+, K^+, and Cl^- in the vomitus, and furosemide administration.

In patients with upper GI losses of Cl^-:

- Treatment should be aimed at:
  - » Correcting intravascular volume depletion and Cl^- concentrations
  - » Eliminating GI obstruction
  - » Addressing hypokalemia, if present.
- Initial IV boluses, if indicated, should be 0.9% sodium chloride, but without potassium due to risk for bradycardia.
- Once any boluses have been completed, fluid therapy of choice is:
  - » 0.9% sodium chloride due to its high Cl^- concentration
  - » Potassium chloride supplementation.

If metabolic alkalosis is due to diuretic administration:

- It will usually correct itself once:
  - » Diuretic therapy has been discontinued ***or***
  - » Diuretic dose is reduced and patient is eating again.
- Administration of oral potassium chloride improves alkalosis by correcting chloride deficits and hypokalemia.
- Including potassium-sparing diuretics can also reduce or eliminate metabolic alkalosis in these patients.

RESPIRATORY ACIDOSIS (Hypoventilation)

Clinical Signs & Consequences

Respiratory acidosis is associated with:

- Increased pCO_2 and bicarbonate levels
- Decreased pH
- Reduced ventilation, which decreases pO_2; hypoxemia makes the condition life-threatening.

Acute hypercarbia can have cardiovascular, metabolic, and neurologic sequelae.

- **Cardiovascular:** Hypercarbia causes catecholamine release, which, along with concurrent acidosis, hypoxia, and electrolyte derangements, can result in tachyarrhythmias, including ventricular fibrillation.
- **Metabolic:** Acidosis causes a shift of H^+ ions into the cells, resulting in extracellular movement of K^+.
- **Neurologic:** Complications include cerebral vasodilation from hypercarbia, which can result in increased intracranial pressure; neurologic signs can range from agitation and restlessness to depression and coma.

Differential Diagnoses

- *Impairment of respiratory center:* Drug induced (narcotics, barbiturates), neurologic disease (brainstem or high cervical cord)
- *Airway obstruction:* Foreign body, mass, tracheal collapse, laryngeal paralysis, brachycephalic airway disease, asthma, obstructed endotracheal tube
- *Neuromuscular disease:* Myasthenia gravis, botulism, tick paralysis, polyradiculoneuritis, severe hypokalemia, drugs (neuromuscular blockers, organophosphates)
- *Restrictive disorders preventing lung expansion:* Pleural space disease
- *Severe primary pulmonary disease:* Pneumonia, pulmonary edema
- *Increased CO_2 production with decreased alveolar ventilation:* Cardiopulmonary arrest, heat stroke, malignant hyperthermia

Therapeutic Measures

Respiratory acidosis can rapidly become life-threatening and requires immediate recognition and treatment. Treatment is aimed at correcting the:

- Underlying problem, particularly airway obstruction or restrictive disease
- Concurrent hypoxia.

If anesthetic or sedative agents have been administered and are causing hypercarbia due to depression of brain respiratory centers:

- Anesthetic plane should be lightened ***or***
- Reversal agents administered.

If the cause of hypoventilation *cannot* be rapidly corrected, the following are indicated:

- Intubation (**Figure**)
- Support with positive pressure ventilation.

RESPIRATORY ALKALOSIS (Hyperventilation)

Clinical Signs & Consequences

- Hypocapnia can result in cerebral vasoconstriction and, therefore, decreased perfusion; however, this

Figure. *Tracheostomy tubes can be used to treat hypoventilation and respiratory acidosis in dogs with upper airway obstruction.*

CASE STUDY 1

Diagnostic Results & Interpretation

A 2-year-old, castrated male domestic shorthair cat is presented with a few-day history of lethargy, anorexia, and occasional vomiting. **Table 1** provides pertinent laboratory results; **Table 2** provides interpretation of results.

Differential Diagnosis

Differentials for this severe, normochloremic (when the slightly low Cl^- is corrected for the low Na^+, it is in the normal range), high AG metabolic acidosis should include:

- Uremia
- Ketoacidosis
- Lactic acidosis
- Exogenous toxins, such as metabolites of ethylene glycol.

Ketosis is unlikely given the normal glucose, and lactate is normal. However, BUN and creatinine (248 and 20.6 mg/dL, respectively) indicate that the cat is severely azotemic.

Diagnosis & Treatment

- **Diagnosis** is lily toxicity as the owners revealed that the cat chewed on a bouquet of flowers containing lilies a few days before clinical signs were noted.
- **Treatment** should consist of IV fluids: 0.9% sodium chloride ***or*** balanced electrolyte replacement solution, such as Plasma-Lyte 148 (baxter.com).
- If hyperkalemia is persistent, insulin and dextrose ***or*** bicarbonate therapy can be considered.

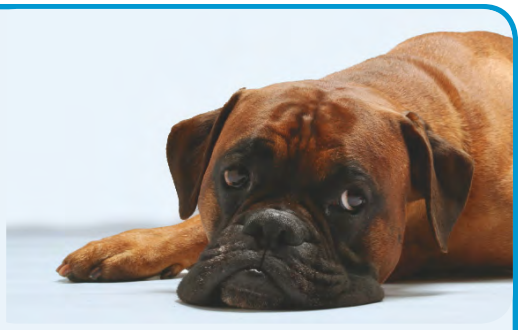
TABLE 1. CASE STUDY 1 PERTINENT LABORATORY RESULTS

VALUE	RESULT	REFERENCE INTERVAL
VENOUS BLOOD GAS ANALYSIS		
Base excess/deficit (mmol/L)	-20.2	-5.7 ± 5
Bicarbonate (HCO_3^-) (mmol/L)	9.3	19.4 ± 4
Partial pressure of CO_2 (mm Hg)	28.4	41.8 ± 9
Partial pressure of O_2 (mm Hg)	65	38.6 ± 11
pH	7.12	7.3 ± 0.08
ELECTROLYTE RESULTS		
Chloride (Cl) (mmol/L)	110.9	116–126
Potassium (K) (mmol/L)	6.43	3.5–4.8
Sodium (Na) (mmol/L)	141.3	146–157
OTHER		
Blood urea nitrogen (BUN) (mg/dL)	248	15–32
Creatinine (mg/dL)	20.6	1–2
Glucose (mg/dL)	75	70–168
Lactate (mmol/L)	1.7	< 2

TABLE 2. CASE STUDY 1 INTERPRETATION OF BLOOD GAS ANALYSIS

STEP-BY-STEP PROCESS	INTERPRETATION
Step 1. Determine if venous or arterial sample.	**Venous**
Step 2. Assess for acidemia or alkalemia.	pH of 7.12 indicates **acidemia**
Step 3. Perform additional assessments for acidosis.	BE of -20.2 mmol/L indicates **metabolic acidosis**
Step 4. Perform additional assessments for alkalosis.	**Respiratory alkalosis** present (pCO_2 of 28.4 mm Hg)
Step 5. Assess oxygenation.	Oxygenation **high** for venous sample; causes could include: • Patient is receiving O_2 supplementation • Decreased O_2 extraction by tissues (poor perfusion) • Sample has been exposed to room air.
Step 6. Determine if compensation has occurred. HCO_3^- is approximately 10 mmol/L lower than normal for a cat. For every 1 mmol/L decrease in HCO_3^-, pCO_2 should decrease by 0.7 mm Hg (**Table 5**, page 30). Therefore, a decrease of 7 mm Hg is expected. • Normal venous pCO_2 for a cat is approximately 42 mm Hg; therefore, pCO_2 should be 35 mm Hg if compensation was the only process affecting pCO_2. • However, this cat's pCO_2 of 28 mm Hg is lower than expected. • Since overcompensation does not occur, other possible causes of hypocarbia include: » Air contamination of the sample since venous O_2 is high (CO_2 diffused out and O_2 diffused in) or » Concurrent primary respiratory alkalosis.	

CASE STUDY 2



Diagnostic Results & Interpretation

A 4-year-old, castrated male boxer is presented with a 4- to 5-day history of vomiting multiple times daily. **Table 3** provides pertinent laboratory results; **Table 4** provides interpretation of results.

Diagnosis & Treatment

- **Diagnosis** is a mixed acid–base disorder:
  - » This patient is losing Cl^- and K^+ in the vomitus and is volume depleted.
  - » Metabolic alkalosis has developed secondary to the loss of Cl^- and K^+.
  - » The increased lactate indicates concurrent metabolic acidosis—a second primary metabolic acid–base disorder, likely caused by hypovolemia due to vomiting.
- **Treatment** should consist of:
  - » Volume expansion with 0.9% sodium chloride
  - » Supplementation of potassium chloride in the fluids once any boluses have been given
  - » Determining the underlying cause for the vomiting.
- Abdominal radiographs revealed a proximal GI obstruction.
- After stabilization with fluid therapy, an exploratory laparotomy was performed; a cloth foreign body was removed from the proximal duodenum.
- The acid–base and electrolyte abnormalities resolved over 24 to 48 hours.

TABLE 3. CASE STUDY 2 PERTINENT LABORATORY RESULTS

VALUE	RESULT	REFERENCE INTERVAL
VENOUS BLOOD GAS ANALYSIS		
Base excess/deficit (mmol/L)	+22.9	-4 ± 2
Bicarbonate (HCO_3^-) (mmol/L)	44.8	21–24
Partial pressure of CO_2 (mm Hg)	50.2	34–41
Partial pressure of O_2 (mm Hg)	48.3	48–56
pH	7.561	7.35–7.44
ELECTROLYTE RESULTS		
Chloride (Cl) (mmol/L)	81	109–120
Potassium (K) (mmol/L)	2.6	4–5.2
Sodium (Na) (mmol/L)	117	140–150
OTHER		
Lactate (mmol/L)	4.6	< 2

TABLE 4. CASE STUDY 2 INTERPRETATION OF BLOOD GAS ANALYSIS

STEP-BY-STEP PROCESS	INTERPRETATION
Step 1. Determine if venous or arterial sample.	**Venous**
Step 2. Assess for acidemia or alkalemia.	pH of 7.561 indicates **alkalemia**
Step 3. Perform additional assessments for acidosis.	**Respiratory acidosis** present (pCO_2 of 50.2 mm Hg)
Step 4. Perform additional assessments for alkalosis.	BE of 22.9 mmol/L indicates **metabolic alkalosis**
Step 5. Assess oxygenation.	**Adequate**
Step 6. Determine if compensation has occurred. HCO_3^- is 44.8 mmol/L, which is an increase of approximately 25 mmol/L above normal values. For every 1 mmol/L increase in HCO_3^-, pCO_2 should increase by 0.7 mm Hg; therefore, an increase of 17 mm Hg is expected (**Table 5**, page 30). • Normal pCO_2 for a dog is 40 mm Hg; the dog's pCO_2 of 50 mm Hg indicates that only partial compensation is present because the expected pCO_2 would be 57 mm Hg.	
Other abnormalities: • Lactate is increased, indicating concurrent primary metabolic acidosis. • Significant electrolyte abnormalities are present, including hypochloremia and hypokalemia.	

TABLE 5. EXPECTED COMPENSATORY CHANGES[1]

DISORDER	CHANGES	COMPENSATORY RESPONSE
Metabolic acidosis	↓ HCO_3^-	0.7 mm Hg *decrease* in pCO_2 for each 1 mEq/L *decrease* in HCO_3^-
Metabolic alkalosis	↑ HCO_3^-	0.7 mm Hg *increase* in pCO_2 for each 1 mEq/L *increase* in HCO_3^-
Acute respiratory acidosis	↑ pCO_2	1.5 mEq/L *increase* in HCO_3^- for each 10 mm Hg *increase* in pCO_2
Chronic respiratory acidosis	↑ pCO_2	3.5 mEq/L *increase* in HCO_3^- for each 10 mm Hg *increase* in pCO_2
Acute respiratory alkalosis	↓ pCO_2	2.5 mEq/L *decrease* in HCO_3^- for each 10 mm Hg *decrease* in pCO_2
Chronic respiratory alkalosis	↓ pCO_2	5.5 mEq/L *decrease* in HCO_3^- for each 10 mm Hg *decrease* in pCO_2

degree of hyperventilation rarely occurs except in patients with significant intracranial disease.
- In humans with acute respiratory alkalosis due to hyperventilation, lightheadedness and confusion are often reported.
- Extremely high pHs (> 7.6) may be associated with metabolic, cardiac, and neurologic consequences as listed under **Metabolic Alkalosis**.

Differential Diagnoses

- Hypoxemia
- Pulmonary disease: Stimulation of nociceptors, independent of hypoxia
- Central nervous system disease: Trauma, neoplasia, infection, inflammation
- Sepsis/systemic inflammatory response syndrome (SIRS)
- Drugs: Corticosteroids, progesterone (pregnancy), methylxanthines (aminophylline)
- Liver disease
- Hyperadrenocorticism
- Exercise
- Stress and/or pain (common in patients arriving at the hospital)
- Excessive mechanical ventilation

Therapeutic Measures

Treatment is aimed at correcting the underlying process that is driving the hyperventilation.
- In hypoxic patients: Oxygen supplementation
- In stressed or painful patients: Sedation/analgesia corrects the majority of cases of respiratory alkalosis.
- In exceptional cases of documented hypocapnia: Rebreathing CO_2 using a paper bag may be required, analogous to first-aid therapy applied to humans for hyperventilation.

SUMMARY

Interpretation of venous and arterial blood gases can be essential to treatment of many patients. Blood gas analysis has important implications with regard to:
- When fluid therapy is indicated
- What fluid types are the best choices
- When oxygen and mechanical ventilation are needed, including when the patient can be weaned off this support. ■

AG = anion gap; BE = base excess/deficit; BUN = blood urea nitrogen; Cl^- = chloride; CO_2 = carbon dioxide; GI = gastrointestinal; H^+ = hydrogen; HCO_3^- = bicarbonate; K^+ = potassium; Na^+ = sodium; O_2 = oxygen; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; SIRS = systemic inflammatory response syndrome; UA = unmeasured anions; UC = unmeasured cations

References

1. DiBartola SP. Introduction to acid–base disorders. In DiBartola SP(ed): *Fluid, Electrolyte, and Acid–Base Disorders in Small Animal Practice*, 4th ed. St. Louis: Elsevier Saunders, 2012, pp 231-252.

Suggested Reading

De Morais HA, Leisewitz AL. Mixed acid–base disorders. In DiBartola SP (ed): *Fluid, Electrolyte, and Acid–Base Disorders in Small Animal Practice*, 4th ed. St. Louis: Elsevier Saunders, 2012, pp 302-315.

DiBartola SP. Metabolic acid–base disorders. In DiBartola SP (ed): *Fluid, Electrolyte, and Acid–Base Disorders in Small Animal Practice*, 4th ed. St. Louis: Elsevier Saunders, 2012, pp 253-286.

Johnson RA, De Morais HA. Respiratory acid–base disorders. In DiBartola SP (ed): *Fluid, Electrolyte, and Acid–Base Disorders in Small Animal Practice*, 4th ed. St. Louis: Elsevier Saunders, 2012, pp 287-301.

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