

Acid-Base Disorders I: Anion Gap Metabolic Acidosis

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 - Research focus: Kidney physiology, PKD

Disclosures

- I have no financial disclosures

Objectives

- Review the diagnostic approach to acid-base disorders
- Review the causes and management of anion gap metabolic acidosis

Evaluation of acid-base disorders

1. Arterial pH

- $\text{pH} < 7.37$ Acidemia
- $\text{pH} > 7.43$ Alkalemia

Evaluation of acid-base disorders

2. Use P_{CO_2} and HCO_3^- to identify the underlying primary disorder(s)

$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.03 P_{CO_2}}$$

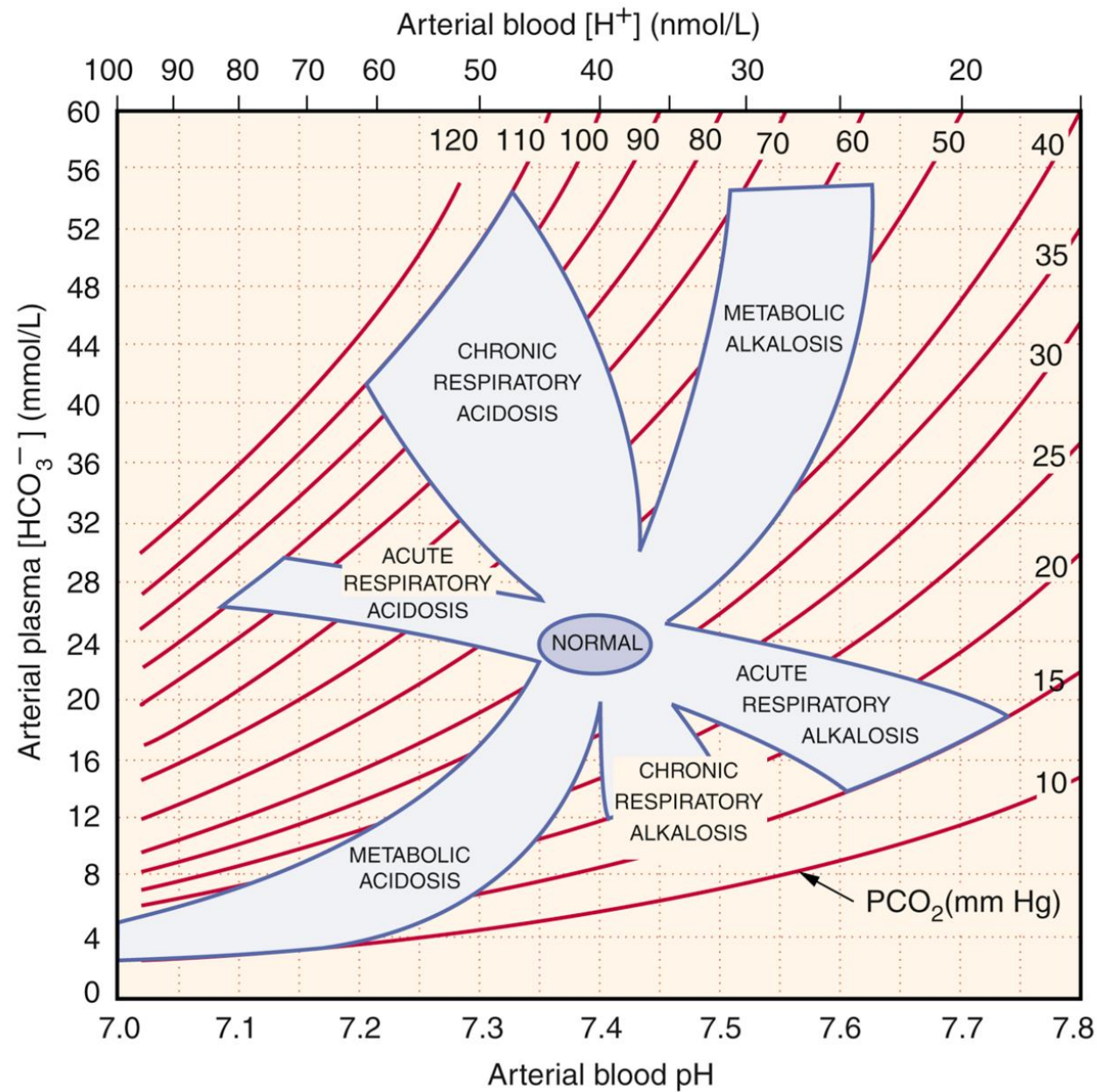
Arterial pH	P _{CO2} and HCO ₃ ⁻	Primary disturbance
Acidemia	↓ HCO ₃ ⁻	Metabolic acidosis
	↑ P _{CO2}	Respiratory acidosis
Alkalemia	↑ HCO ₃ ⁻	Metabolic alkalosis
	↓ P _{CO2}	Respiratory alkalosis

Evaluation of acid-base disorders

3. Look for abnormal compensatory response to diagnose mixed metabolic & respiratory disorder

Determine whether the magnitude and direction of the compensatory response is appropriate.

Primary disorder	Expected compensation
Metabolic acidosis	Each 1 mEq/L $\downarrow$ $\text{HCO}_3^- \rightarrow 1.2 \text{ mm Hg } \downarrow \text{P}_{\text{CO}_2}$
Metabolic alkalosis	Each 1 mEq/L $\uparrow$ $\text{HCO}_3^- \rightarrow 0.7 \text{ mm Hg } \uparrow \text{P}_{\text{CO}_2}$
Respiratory acidosis	
Acute	Each 1 mm Hg $\uparrow \text{P}_{\text{CO}_2} \rightarrow 0.1 \text{ mEq/L } \uparrow \text{HCO}_3^-$
Chronic	Each 1 mm Hg $\uparrow \text{P}_{\text{CO}_2} \rightarrow 0.3 \text{ mEq/L } \uparrow \text{HCO}_3^-$
Respiratory alkalosis	
Acute	Each 1 mm Hg $\downarrow \text{P}_{\text{CO}_2} \rightarrow 0.2 \text{ mEq/L } \downarrow \text{HCO}_3^-$
Chronic	Each 1 mm Hg $\downarrow \text{P}_{\text{CO}_2} \rightarrow 0.4 \text{ mEq/L } \downarrow \text{HCO}_3^-$



Compensatory mechanisms

- Remember the *direction* of compensation
- Remember that compensation is almost never complete
- Remember Winter's formula

In a metabolic acidosis, the predicted $p\text{CO}_2$ is:

$$(1.5 \times \text{HCO}_3^-) + 8 \pm 2$$

Example 1

- pH 7.34
- PCO_2 55 mm Hg
- HCO_3^- 30 mEq/L

What is nature of this acid-base disturbance?

Primary respiratory acidosis

Example 2

- pH 7.65
- PCO_2 30 mm Hg
- HCO_3^- 35 mEq/L

What is the acid-base disturbance?

Combined metabolic alkalosis
and respiratory alkalosis

Polling question 1

Which of the following is the most likely cause of the following acid-base disturbance?

pH 7.40, PCO_2 22 mm Hg, HCO_3^- 14 mEq/L

- A. Panic attack
- B. COPD
- C. Seizure
- D. Salicylate poisoning
- E. Diarrhea

Metabolic acidosis

Serum anion gap

$$[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$$

(Normal range: 8 - 12)

How does the serum anion gap work?

Total anions = Total cations

$$\begin{array}{ccc} \text{Measured anions} & & \text{Measured cations} \\ + & = & + \\ \text{Unmeasured anions} & & \text{Unmeasured cations} \end{array}$$

$$\begin{array}{ccc} \text{Unmeasured anions} & & \text{Measured cations} \\ - & = & - \\ \text{Unmeasured cations} & & \text{Measured anions} \end{array}$$

Serum anion gap

Unmeasured anions

Albumin

PO_4

SO_4

Lactate

Pyruvate

Unmeasured cations

K

Ca

Mg

Immunoglobulins

Correction of the anion gap

Add 2.5 mEq/L for every 1 g/dL fall in serum albumin.

Cause of anion-gap acidosis

Lactic acid

Cause of anion-gap acidosis



Cause of anion-gap acidosis



Buffered



Cause of anion-gap acidosis

"Unmeasured"
anion



Buffered



Decrease in
[HCO₃⁻]

Cause of anion-gap acidosis

$$\text{Anion gap} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$$

Decrease in
[HCO₃⁻]

↓
↑AG

Surrogate indicator of
the presence of an
"unmeasured" anion

Anion gap metabolic acidosis: GOLD MARK

Glycols (ethylene & propylene)

Oxoproline

L-lactic acidosis

D-lactic acidosis

Methanol

Aspirin

Renal Failure

Ketoacidosis (diabetic & alcoholic)

What is the unmeasured anion?

ethylene Glycol

Oxalate

propylene Glycol

Lactate

5-Oxoproline

Pyroglutamic acid

Methanol

Formate

Aspirin

Ketoacids & lactate

Renal failure

Sulfate

Phosphate

+ Toluene (Hippurate)

Urate

Ketoacidosis

Acetoacetate

β -hydroxybutyrate

Evaluation of acid-base disorders (anion gap metabolic acidosis)

4. Calculate the $\Delta AG/\Delta$ bicarbonate ratio (“delta-delta”)

Determine whether the increase in anion gap in a high anion gap metabolic acidosis is appropriate for the degree of acidosis

Principle of the delta-delta

- For every 1 mEq/L of acid added to circulation, the serum bicarbonate should decrease by 1 mEq/L, and the anion gap should increase by 1 mEq/L.
- Thus, the $\Delta \text{anion gap} / \Delta \text{HCO}_3^-$ should (theoretically) be 1

Calculation of the delta-delta

$$\Delta AG / \Delta HCO_3^- = \frac{AG - 10}{24 - HCO_3^-}$$

Interpretation of the delta-delta

$$\Delta AG / \Delta HCO_3^-$$

1	Simple AG acidosis
< 1	Superimposed non-gap acidosis
> 1	Superimposed metabolic alkalosis

Polling question 2

A 21 yo male intoxicated with ethanol presents with a history of repeated vomiting and is obtunded.

Na 136, K 3.5, Cl 90, HCO_3^- 18

pH 7.20, PCO_2 45 mm Hg

What is nature of this acid-base disturbance?

- A. Mixed anion-gap and non-gap metabolic acidosis
- B. Anion-gap metabolic acidosis with respiratory alkalosis
- C. Anion-gap metabolic acidosis and respiratory acidosis
- D. Anion-gap metabolic acidosis, metabolic alkalosis and respiratory acidosis**
- E. Metabolic acidosis, respiratory acidosis and respiratory alkalosis

Na 136, K 3.5, Cl 90, HCO₃ 18

pH 7.20, PCO₂ 45 mm Hg

$$\text{Anion gap} = 136 - 90 - 18 = 28$$

$$\Delta\text{Anion gap} = 28 - 10 = 18 \text{ mM}$$

$$\Delta\text{HCO}_3^- = 24 - 18 = 6 \text{ mM}$$

$$\Delta\text{AG}/\Delta\text{HCO}_3^- = 18/6 = 3$$

Alternatively:

Adding the ΔAG of 18 to the HCO₃⁻ of 18 corrects it to 36 mM.

Pitfalls in interpretation of the Δ/Δ

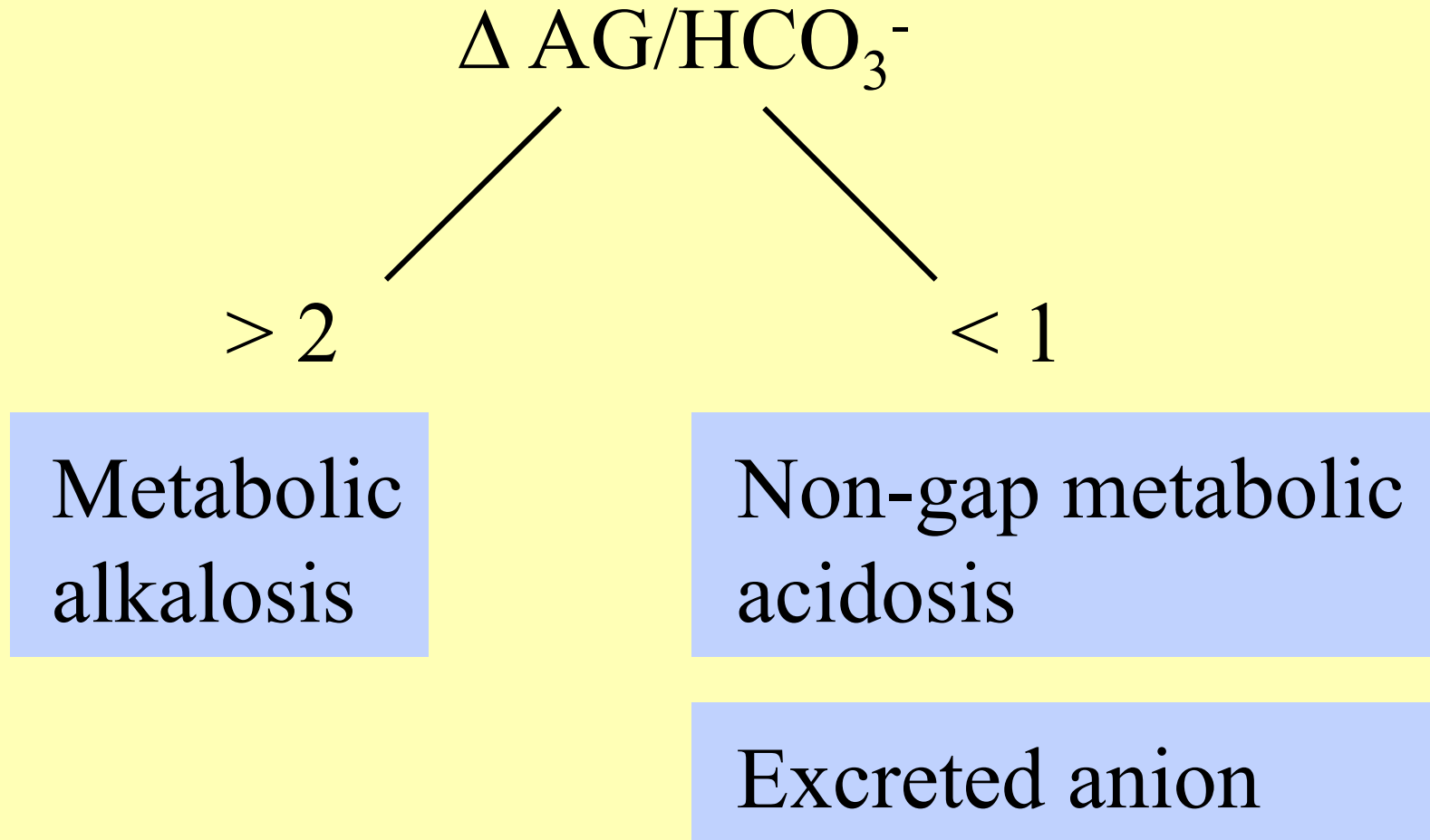
Average Δ/Δ of lactic acidosis is 1.6

Up to half of acid load is buffered intracellularly and not by serum HCO_3^-

Δ/Δ in DKA varies from 2 (early) to 0 (late)

Many unmeasured acid anions are rapidly renally excreted

Rational use of the delta-delta



Evaluation of acid-base disorders (anion gap metabolic acidosis, suspected intoxication)

5. Calculate the osmolal gap

Is there any evidence for the presence of unmeasured osmotically active substances in the blood?

Serum osmolal gap

$$\text{Osmolal gap} = \text{Measured } S_{\text{osm}} - \text{Calc } S_{\text{osm}}$$

Calculated S_{osm} :

$$2 [\text{Na}^+] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

Serum osmolal gap

$$\text{Osmolal gap} = \text{Measured } S_{\text{osm}} - \text{Calc } S_{\text{osm}}$$

Calculated S_{osm} :

$$2 [\text{Na}^+] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

**Contribution of alcohols and ketones in mOsm/kg
(from concentration in mg/dL):**

[Ethanol]/4.6

[Ethylene glycol]/6.2

[Methanol]/3.2

[Isopropanol]/6

[Acetone]/5.8

Polling question 3

The 21 yo male described previously who was intoxicated with ethanol has the following additional labs.

Na 136, K 3.5, Cl 90, HCO₃ 18, glucose 86, BUN 35, Cr 1.6, Osm 318, ethanol 124 mg/dL

Which of the following statements is correct?

- A. There is no osmolal gap
- B. There is an osmolal gap that is due solely to ethanol
- C. There is an osmolal gap that is only partially attributable to ethanol
- D. Ethanol does not contribute to the osmolal gap
- E. The osmolal gap cannot be calculated with the available laboratory data

$$\begin{aligned}\text{Calculated } S_{\text{osm}} &= 2 [\text{Na}^+] + [\text{glucose}]/18 + [\text{BUN}]/2.8 \\ &= 2(136) + 86/18 + 35/2.8 = 289\end{aligned}$$

Measured osmolality = 318

$$\text{Osmolal gap} = 318 - 289 = 29 (< 10)$$

Contribution of ethanol

$$= \text{Ethanol concentration (mg/dL)} / 4.6$$

$$= 124 / 4.6 = 27$$

Therefore ethanol accounts for the entire osmolal gap

Anion gap acidosis	Osmolal gap	
+	Normal	Salicylates
+	High	Ethanol Ethylene glycol* Propylene glycol* Methanol*
-	High	Isopropanol

*Metabolized to acids

Ethylene glycol poisoning

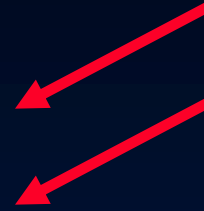
- Inebriated without alcoholic fetor
- CHF, ARDS, ATN
- Absence of optic disc edema or blindness
- Anion and osmolar gap acidosis
- Minor elevation in serum lactate
- Hypocalcemia
- Microscopic hematuria
- Calcium oxalate dihydrate (envelope-shaped) crystalluria (50% sensitive)
- Urine fluoresces under Wood's (UV) lamp



Ethylene glycol



Alcohol
dehydrogenase



Ethanol

Fomepizole

Glycolic acid

Toxic

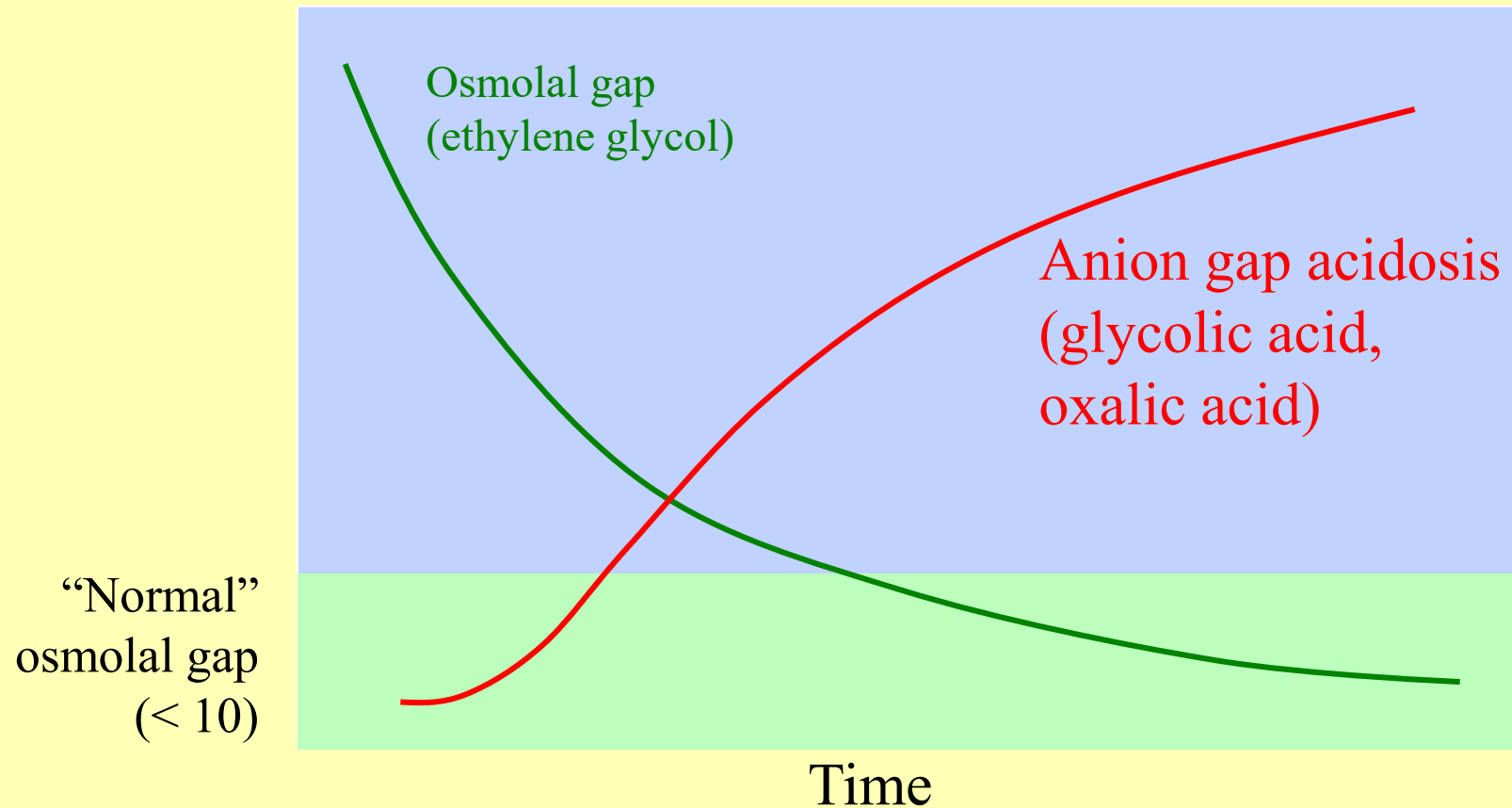


Glyoxylic acid



Oxalic acid

Anion and osmolal gaps are not 100% sensitive for ethylene glycol & methanol poisoning



Management of (suspected) ethylene glycol poisoning

- GI decontamination (little role)
- Sodium bicarbonate (urine acid trapping)
- Inhibit alcohol dehydrogenase
 - Ethanol
 - Fomepizole
- Do not treat asymptomatic hypocalcemia
- Hemodialysis
- (Thiamine & pyridoxine)

Methanol intoxication

- Alcoholic fetor
- Dilated pupils, retinal and optic disc edema and blindness
- Anion and osmolar gap
- Undetectable serum ethanol
- No hypocalcemia, hematuria or crystalluria
- Can have myoglobinuric AKI, abdominal pain due to acute pancreatitis



Methanol poisoning: Management

Similar to ethylene glycol except:

- Acidemia treated more aggressively (keep arterial pH > 7.3) because formic acid is more toxic than formate
- Avoid heparin with hemodialysis (risk of intracerebral hemorrhage)

Salicylate intoxication

- N/V/D, tinnitus, deafness, vertigo, diaphoresis, hyperpyrexia, hyperventilation, tachycardia, non-cardiac pulmonary edema, seizures, coma
- Acid-base disturbances
 - 56% Respiratory alkalosis + metabolic acidosis* in adults
 - 22% Pure respiratory alkalosis
 - 2% Respiratory and metabolic acidosis (co-ingested sedative)

*Due to lactate and ketoacids, hence increased anion gap

Salicylate intoxication: Management

- Stabilization: avoid intubation for “respiratory fatigue”. If truly in respiratory failure, intubate and hyperventilate to maintain alkalemia
- Gastric decontamination (multi-dose charcoal)
- Alkalinization (level >30 mg/dL or any signs of intoxication)
 - Decrease CNS penetration
 - Increase urine trapping and excretion
 - Goal urine pH 7.5, arterial pH ≤ 7.60
 - Use NaHCO_3 (e.g. 1 L D5W with 3 amps HCO_3), *not* acetazolamide
- Correct hypokalemia (inhibits renal HCO_3 excretion), include glucose
- Extracorporeal therapy

Alcoholic ketoacidosis

- Nausea, vomiting or abdominal pain (2/3), abdominal tenderness (50%)
- Normal glucose
- Serum Acetest/acetoacetate negative or borderline
- Serum β -hydroxybutyrate positive
- Serum ethanol may or may not (1/3) be present
- Lactate (usually < 6 mmol/L)
- Rx is dextrose-containing fluids

D-lactic acidosis

Cause: Short bowel syndrome +/- malabsorption incl. bariatric surgery

Pathogenesis: Carbohydrates in gut + bacterial overgrowth in colon -> generation of D-lactic acid

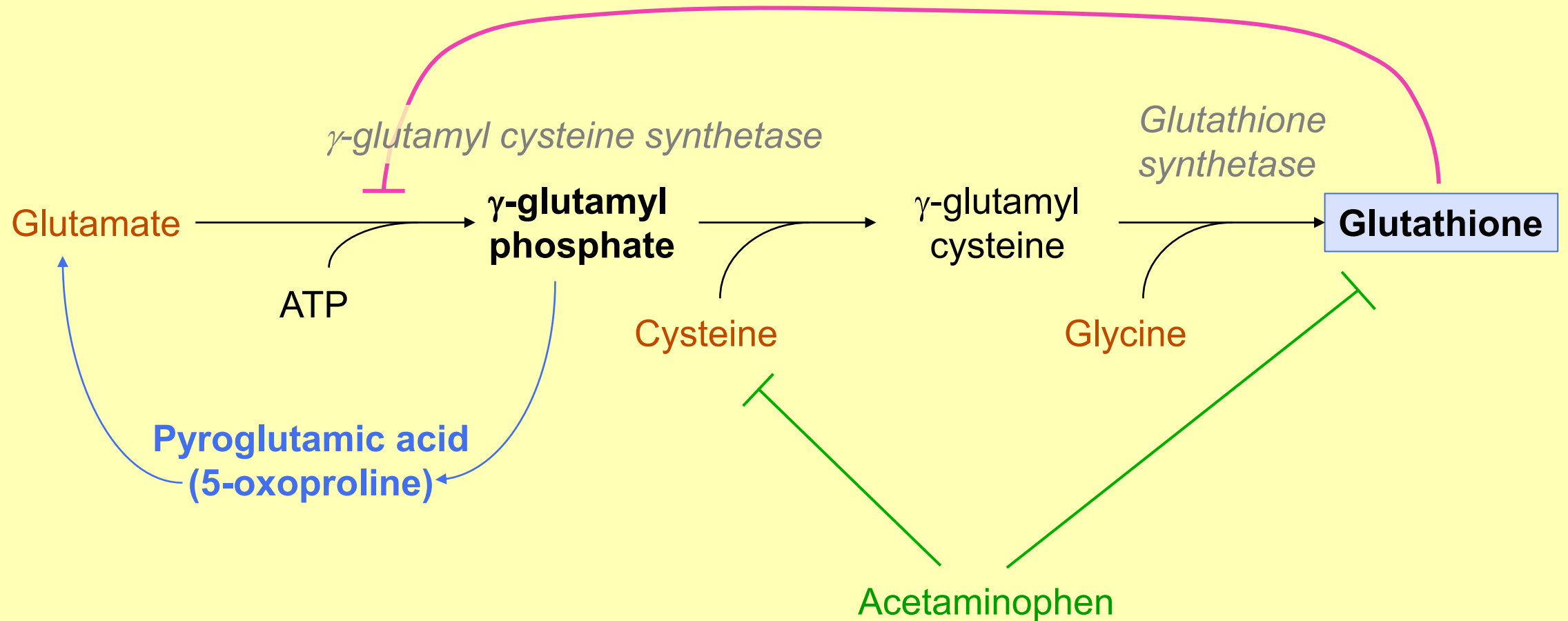
Presentation: Episodes of Δ MS associated with CHO intake; AG metabolic acidosis with elevated D-lactate; spontaneous resolution if NPO

Treatment: Low CHO diet, poorly absorbable oral Abx

Pyroglutamic acidemia (5-oxoprolinemia)

- $\frac{3}{4}$ of cases are female, usually critically ill or malnourished
- Main risk factor is chronic treatment with acetaminophen
- All have anion gap acidosis with elevated blood and urine pyroglutamic acid
- Discontinue acetaminophen, supportive care

Pyroglutamic acidemia (5-oxoprolinemia)



Suggested additional reading

- Seifter J. L. **Acid-Base Disorders**. In Goldman-Cecil Medicine 27th Edition, 2024: Eds. Goldman L., Cooney K. A. Elsevier, Philadelphia PA p. 752–765
- Hamm L, DuBose, T.D., Jr. **Disorders of Acid-Base Balance**. In Brenner & Rector's The Kidney, 11th Edition, 2020: 496-536, Elsevier, Philadelphia PA