

# Acid-Base Disorders I: Anion Gap Metabolic Acidosis

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# 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 <sub>CO2</sub> and HCO <sub>3</sub> <sup>-</sup>	Primary disturbance
Acidemia	↓ HCO <sub>3</sub> <sup>-</sup>	Metabolic acidosis
	↑ P <sub>CO2</sub>	Respiratory acidosis
Alkalemia	↑ HCO <sub>3</sub> <sup>-</sup>	Metabolic alkalosis
	↓ P <sub>CO2</sub>	Respiratory alkalosis

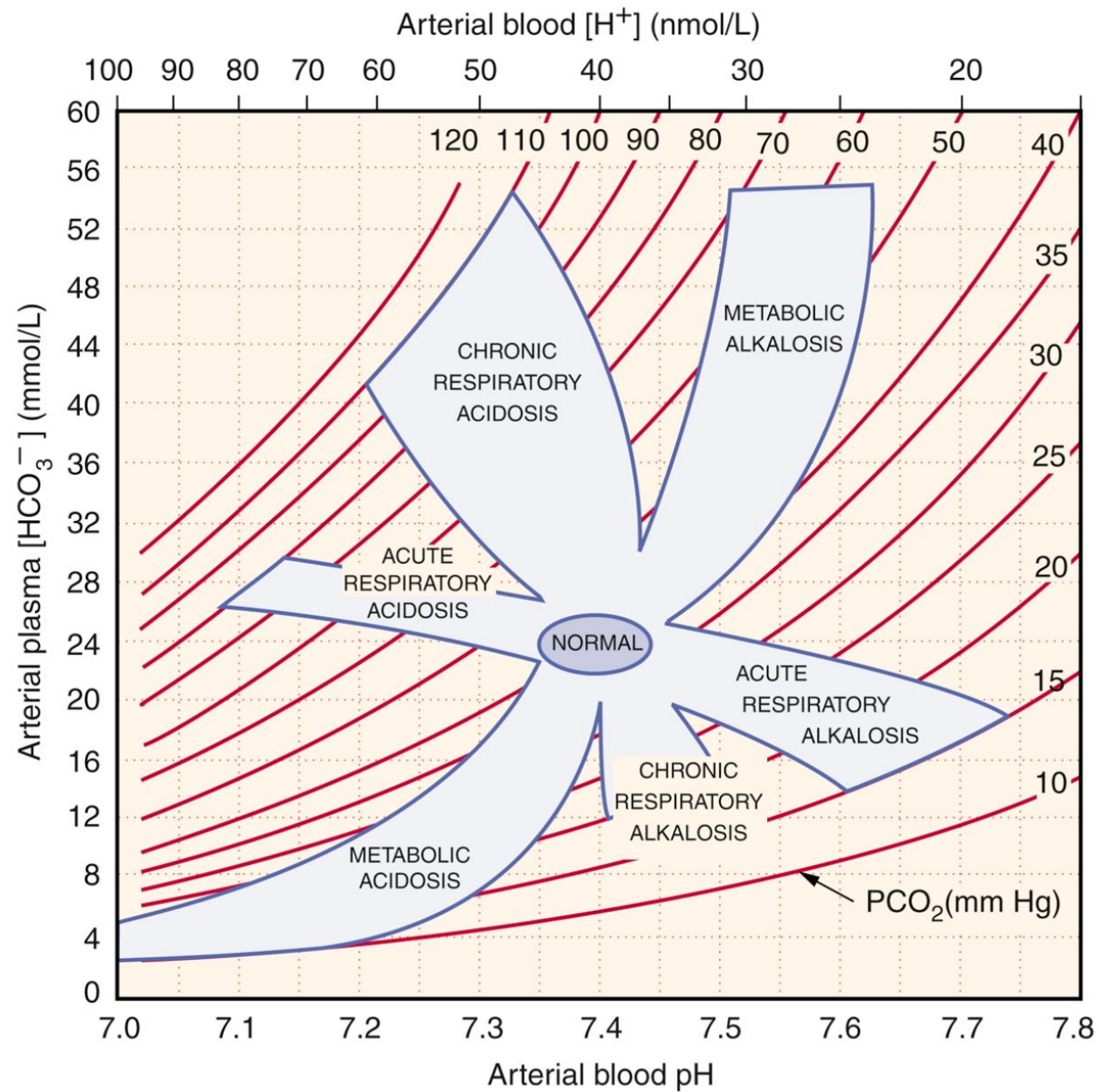
# Evaluation of acid-base disorders

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
- $\text{PCO}_2$  55 mm Hg
- $\text{HCO}_3^-$  30 mEq/L

What is nature of this acid-base disturbance?

Primary respiratory acidosis

## Example 2

- pH 7.65
- $\text{PCO}_2$  30 mm Hg
- $\text{HCO}_3^-$  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,  $\text{PCO}_2$  22 mm Hg,  $\text{HCO}_3^-$  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

$\text{PO}_4$

$\text{SO}_4$

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  
[HCO<sub>3</sub><sup>-</sup>]

# Cause of anion-gap acidosis

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

Decrease in  
[HCO<sub>3</sub><sup>-</sup>]

↓  
↑AG

Surrogate indicator of  
the presence of an  
"unmeasured" anion



# Anion gap metabolic acidosis: GOLD MARK

**G**lycols (ethylene & propylene)

**O**xoproline

**L**-lactic acidosis

**D**-lactic acidosis

**M**ethanol

**A**spirin

**R**enal Failure

**K**etoacidosis (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

$\beta$ -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

$$\Delta\text{AG} / \Delta\text{HCO}_3^-$$

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,  $\text{HCO}_3^-$  18

pH 7.20,  $\text{PCO}_2$  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,  $\text{HCO}_3^-$  18

pH 7.20,  $\text{PCO}_2$  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  $\Delta\text{AG}$  of 18 to the  $\text{HCO}_3^-$  of 18 corrects it to 36 mM.



# Pitfalls in interpretation of the $\Delta/\Delta$

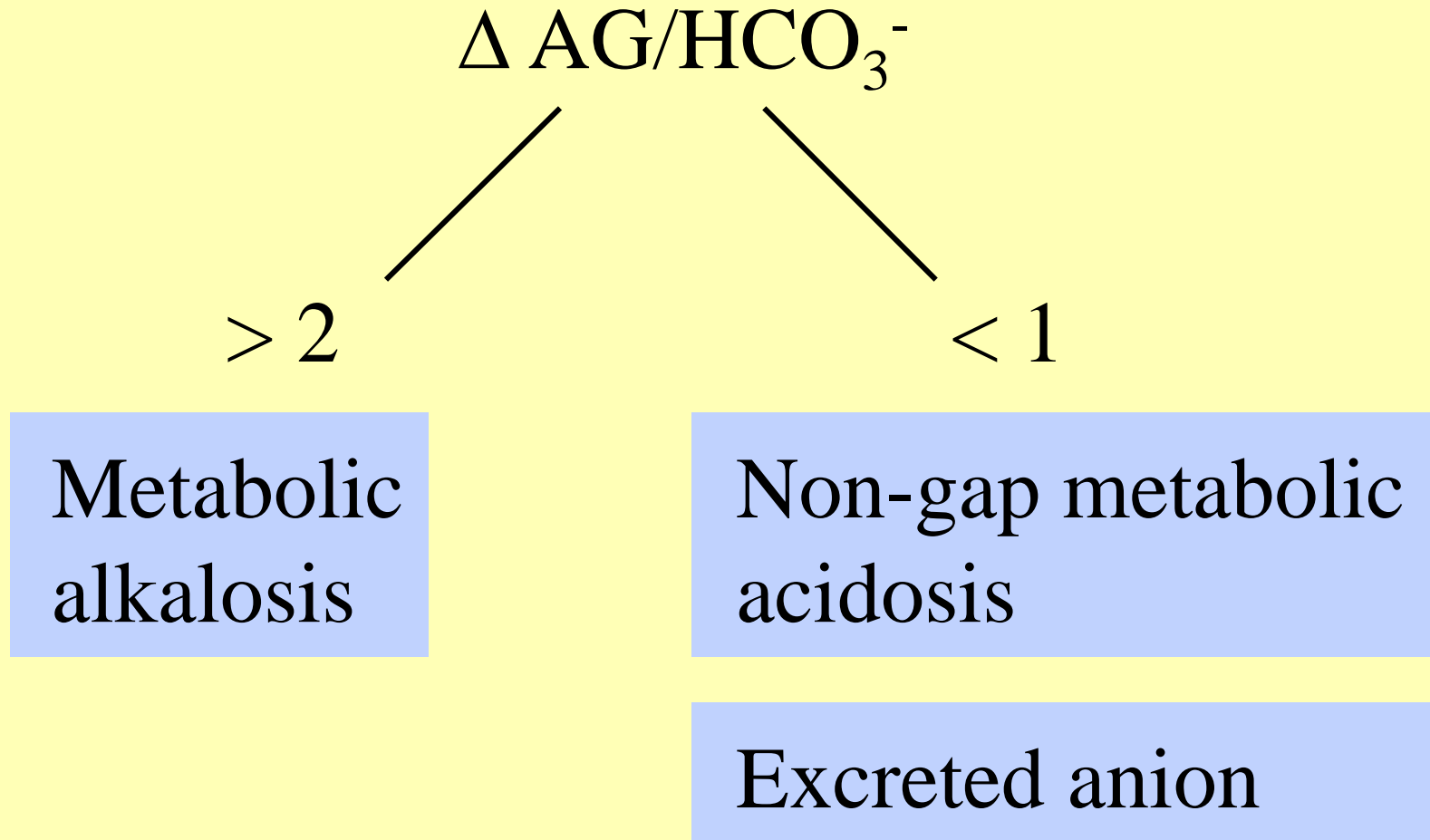
*Average  $\Delta/\Delta$  of lactic acidosis is 1.6*

Up to half of acid load is buffered intracellularly and not by serum  $\text{HCO}_3^-$

*$\Delta/\Delta$  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  $S_{\text{osm}}$  :

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

# Serum osmolal gap

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

Calculated  $S_{\text{osm}}$  :

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

**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,  $\text{HCO}_3$  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

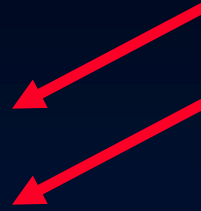
- Inebriated without alcoholic fetor
- CHF, ARDS, ATN
- Absence of optic disc edema or blindness
- Anion and osmolar gap acidosis
- Minor elevation in serum lactate
- Hypocalcemia
- Microscopic hematuria
- Calcium oxalate dihydrate (envelope-shaped) crystalluria (50% sensitive)
- Urine fluoresces under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



Ethylene glycol



Alcohol  
dehydrogenase



Ethanol

Fomepizole

Glycolic acid

*Toxic*

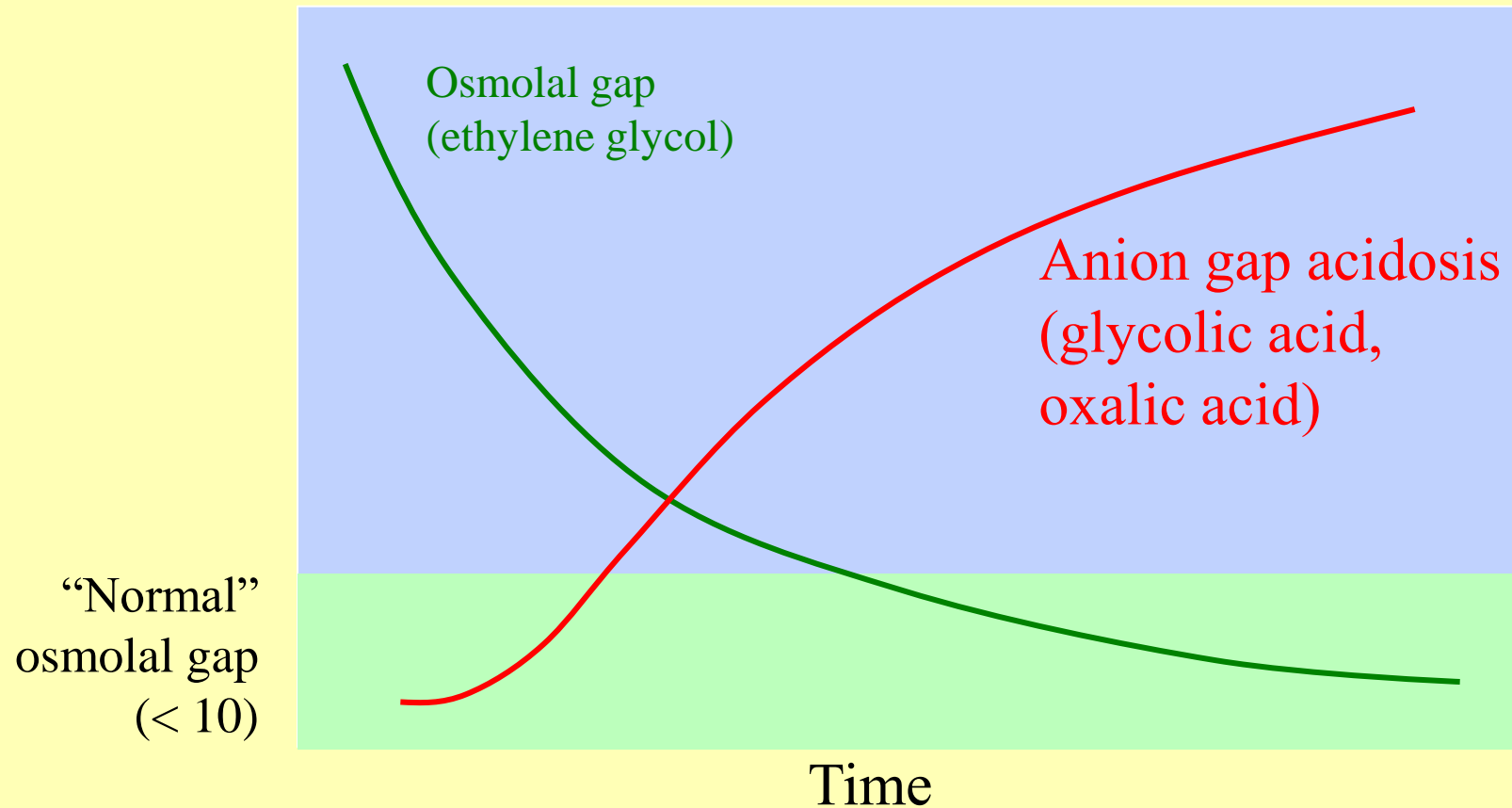


Glyoxylic acid



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  $\leq 7.60$
  - Use  $\text{NaHCO}_3$  (e.g. 1 L D5W with 3 amps  $\text{HCO}_3$ ), *not* acetazolamide
- Correct hypokalemia (inhibits renal  $\text{HCO}_3$  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  $\beta$ -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

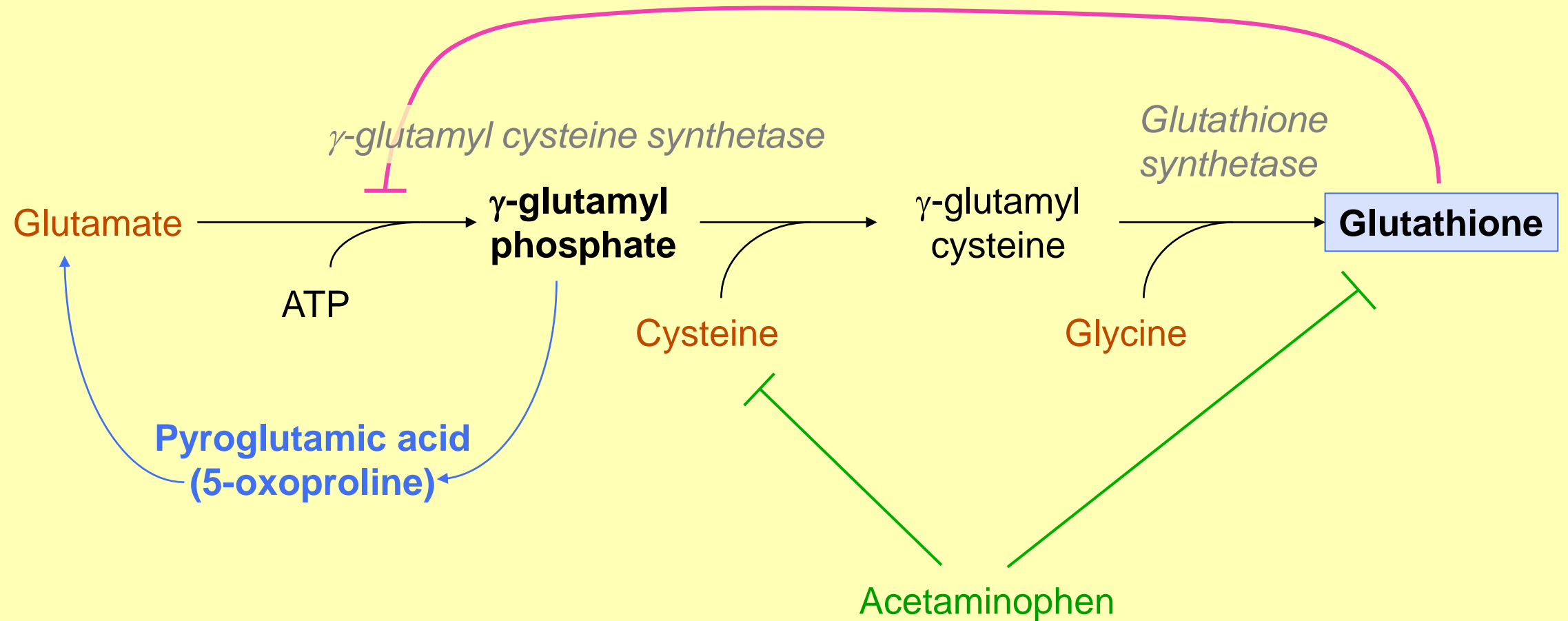
**Presentation:** Episodes of  $\Delta$ MS associated with CHO intake; AG metabolic acidosis with elevated D-lactate; spontaneous resolution if NPO

**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 Rx with acetaminophen (also described with flucloxacillin)
- 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 27<sup>th</sup> 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, 11<sup>th</sup> Edition, 2020: 496-536, Elsevier, Philadelphia PA