

Bradley M. Denker, MD.

Clinical Chief

**Renal Division, Department of Medicine
Beth Israel Deaconess Medical Center and
Atrius Health**

**Associate Professor of Medicine
Harvard Medical School**

Bradley M. Denker, MD



- State University of New York at Syracuse Medical School
- Medicine Residency at Johns Hopkins Hospital
- Nephrology Fellowship at BWH
- Associate Professor of Medicine@ HMS
- Clinical Chief Nephrology at BIDMC and Atrius Health
 - Clinical focus: General Nephrology, fluids and electrolytes

Financial disclosures

Bradley M. Denker, MD

No conflict of interest to disclose.

Objectives

1. Use physiologic approach to identify dysregulated physiology of:
 1. Acidemia
 2. Alkalemia
 2. Identify appropriate treatment for disorder based on physiology
-

Acid-Base Disorders

- General approach

- Acidosis-

 - Respiratory

 - Metabolic

- Alkalosis

 - Respiratory

 - Metabolic

General approach

Approach

1. Is there acidemia or alkalemia?
 2. What is the *primary* process (acidosis or alkalosis?); usually driven by the pH. Is it metabolic or respiratory?
 3. Is there an appropriate compensatory response?
-

1. Is there acidemia or alkalemia?

Acidemia $\text{pH} < 7.35$

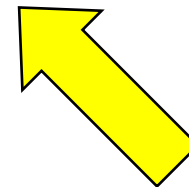
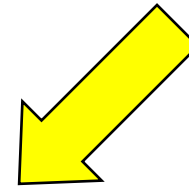
Alkalemia $\text{pH} > 7.45$

2. What is the primary process?

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.03 \times \text{PCO}_2}$$



Metabolic
processes



Respiratory
processes

pH	HCO_3^- ; PCO_2	Primary disorder
Acidemia	☐ HCO_3^-	Metabolic acidosis
	☐ PCO_2	Respiratory acidosis
Alkalemia	☐ HCO_3^-	Metabolic alkalosis
	☐ PCO_2	Respiratory alkalosis

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.03 \times \text{PCO}_2}$$

3. Is there an appropriate compensatory response?

Metabolic processes

Metabolic
acidosis

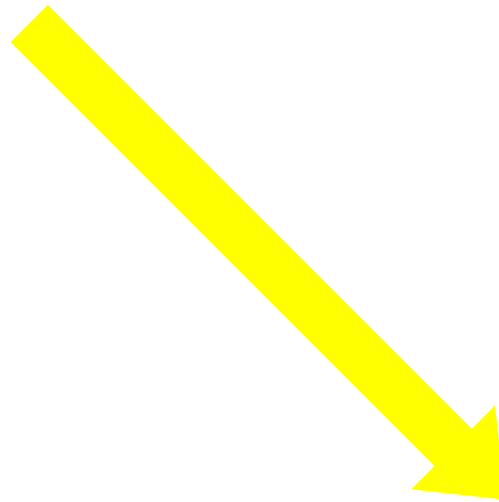
↓ HCO_3^-

Respiratory processes

“Respiratory
alkalosis”

↓ PCO_2

$1.5 \times [\text{HCO}_3] + 8 \pm 2$



3. Is there an appropriate compensatory response?

Metabolic processes

“Metabolic
acidosis”

↓ HCO_3^-

Acute:

2mEq/10mmHg

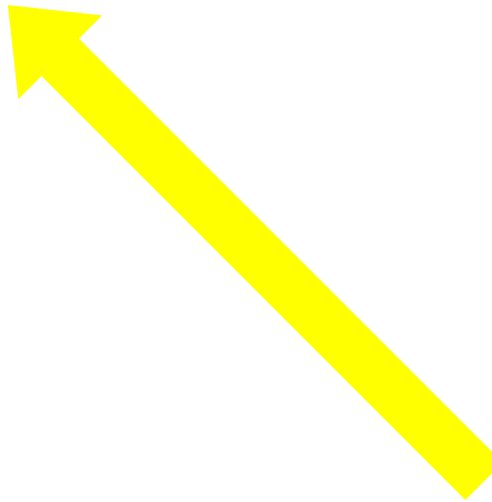
Chronic:

4mEq/10mmHg

Respiratory processes

Respiratory
alkalosis

↓ PCO_2

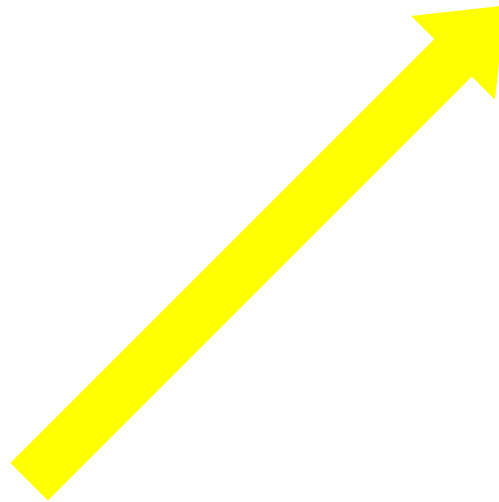


3. Is there an appropriate compensatory response?

Metabolic processes

Respiratory processes

Metabolic
alkalosis
 $\uparrow \text{HCO}_3^-$



“Respiratory
acidosis”

$\uparrow \text{PCO}_2$

0.6-0.7mmHg/1mEq

3. Is there an appropriate compensatory response?

Metabolic processes

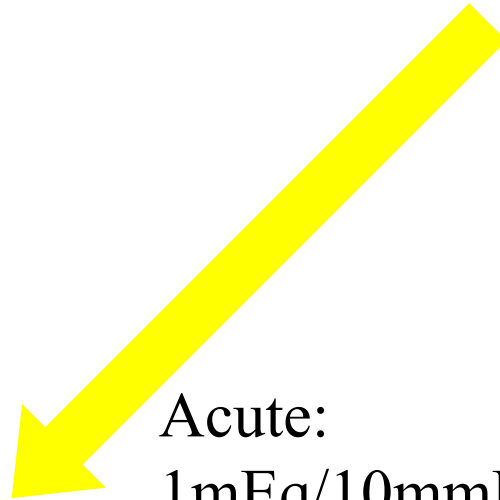
Respiratory processes

“Metabolic
alkalosis”

↑ HCO_3^-

Respiratory
acidosis

↑ PCO_2



Acute:

1mEq/10mmHg

Chronic:

3.5mEq/10mmHg

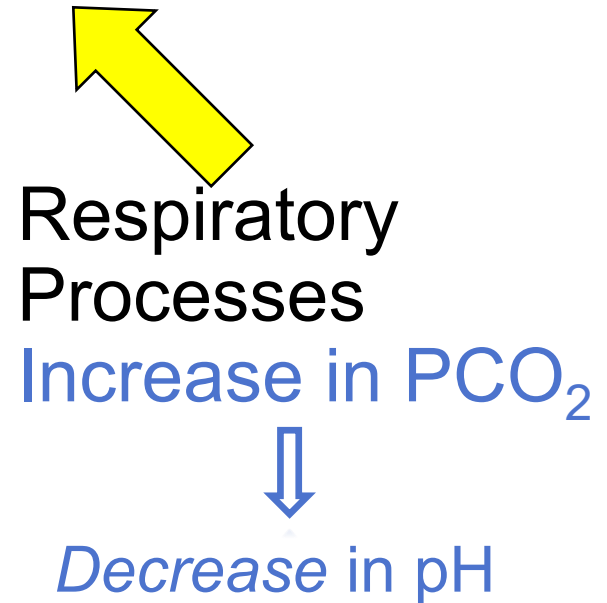
Compensatory mechanisms

- Remember the *direction* of compensation
 - Remember that compensation is *almost* never complete
 - Look for another *primary* process when:
 - Compensation is not “predicted”
 - The blood pH is “normal”
 - Concept of delta/delta – $\Delta\text{AG} / \Delta\text{Bicarb}$
-

Respiratory acidosis

Respiratory Acidosis (*Hypoventilation*)

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.03 \times \text{PCO}_2}$$

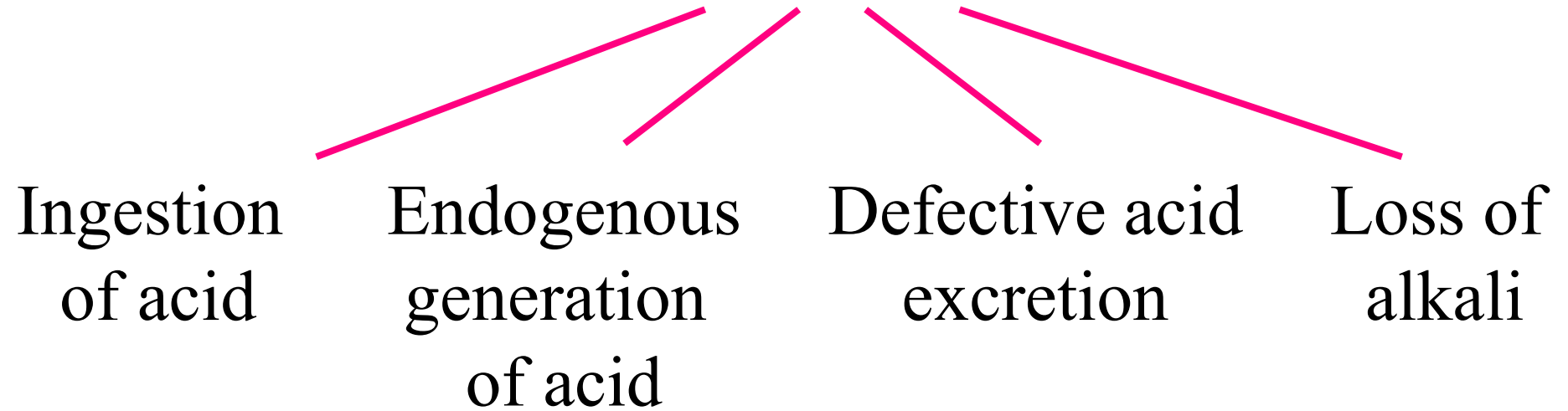


Respiratory Pathways for Eliminating CO_2

Central Nervous System ↓	<i>"Won't breathe"</i>
Peripheral Nervous System ↓	<i>"Can't breathe"</i>
Respiratory muscles ↓	
Chest wall and pleura ↓	
Upper airway ↓	
Lungs	Abnormal gas exchange: <i>"Can't breathe enough"</i>

Metabolic acidosis

Metabolic acidosis



Metabolic acidosis

```
graph TD; A[Metabolic acidosis] --> B[Ingestion of acid]; A --> C[Endogenous generation of acid]; A --> D[Defective acid excretion]; A --> E[Loss of alkali]; B --> B1[Ethylene glycol]; B --> B2[Methanol]; B --> B3[Toluene]; B --> B4[Salicylic acid]; B1 --> B1a[Oxalic acid/glycolic acid]; B2 --> B2a[Formic acid]; B3 --> B3a[Hippuric acid];
```

Ingestion
of acid

Endogenous
generation
of acid

Defective acid
excretion

Loss of
alkali

Ethylene glycol → Oxalic acid/glycolic acid

Methanol → Formic acid

Toluene → Hippuric acid

Salicylic acid

Metabolic acidosis

```
graph TD; MA[Metabolic acidosis] --- IA[Ingestion of acid]; MA --- EGA[Endogenous generation of acid]; MA --- DAE[Defective acid excretion]; MA --- LOA[Loss of alkali]; EGA --- LA[Lactic acidosis]; EGA --- KA[Ketoacidosis]; EGA --- RM[Rhabdomyolysis]; LA --- DM[Diabetes mellitus]; KA --- DM; RM --- DM; LA --- AL[Alcohol]; KA --- AL; RM --- AL;
```

Ingestion
of acid

Endogenous
generation
of acid

Defective acid
excretion

Loss of
alkali

Lactic acidosis

Ketoacidosis

Rhabdomyolysis

Diabetes mellitus

Alcohol

Metabolic acidosis

```
graph TD; A[Metabolic acidosis] --> B[Ingestion of acid]; A --> C[Endogenous generation of acid]; A --> D[Defective acid excretion]; A --> E[Loss of alkali]; D --> F[Renal failure]; D --> G[Distal renal tubular acidosis];
```

Ingestion
of acid

Endogenous
generation
of acid

Defective acid
excretion

Loss of
alkali

Renal failure

Distal renal tubular acidosis

Metabolic acidosis

```
graph TD; A[Metabolic acidosis] --> B[Ingestion of acid]; A --> C[Endogenous generation of acid]; A --> D[Defective acid excretion]; A --> E[Loss of alkali]; E --> F[Diarrhea]; E --> G[Proximal RTA];
```

Ingestion
of acid

Endogenous
generation
of acid

Defective acid
excretion

Loss of
alkali

Diarrhea
Proximal RTA

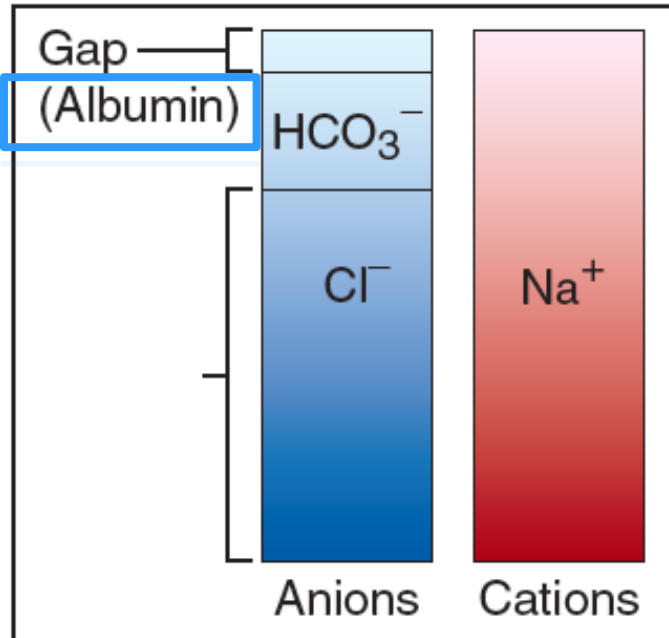
Serum anion gap

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

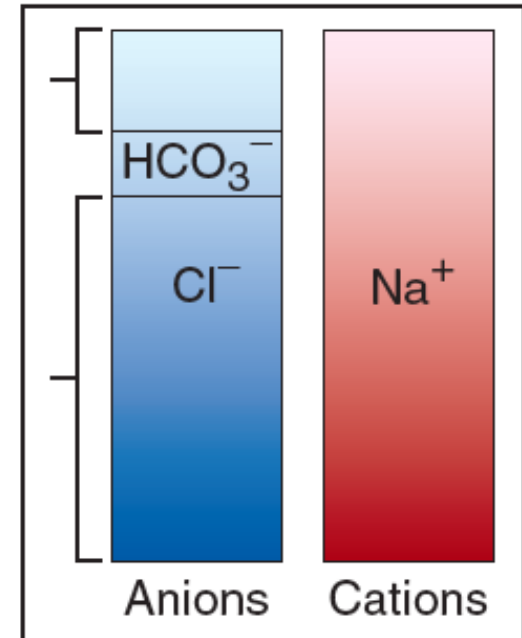
= Unmeasured anions - Unmeasured cations

(Normal range: 8 - 12)

Normal



Add H^+A^-



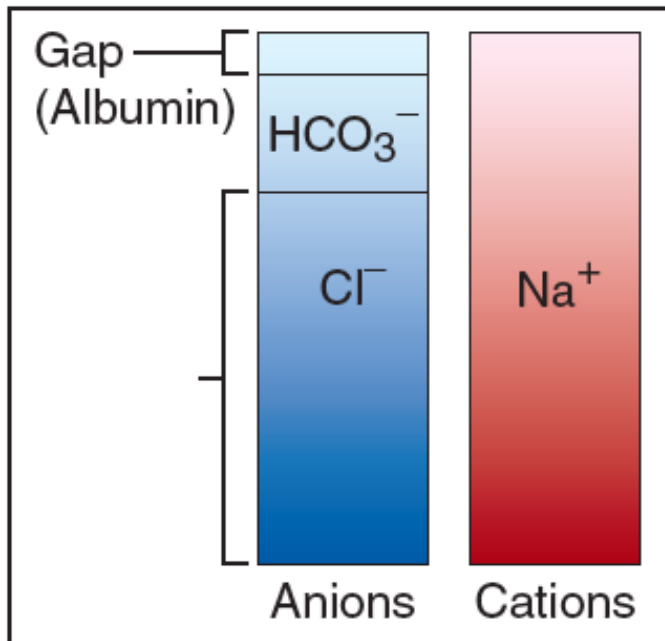
Serum anion gap

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

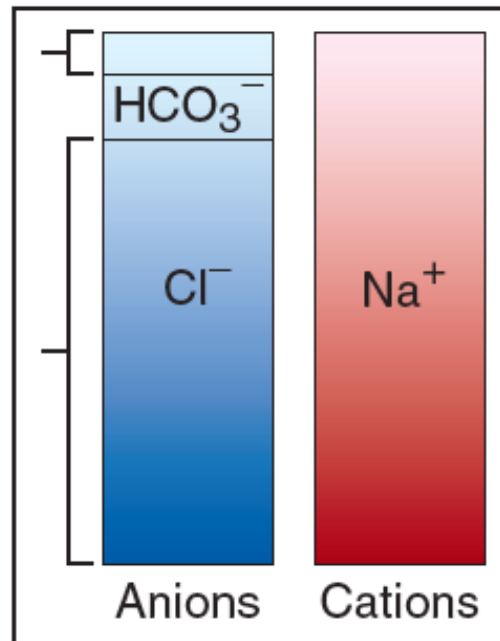
= Unmeasured anions - Unmeasured cations

(Normal range: 8 - 12)

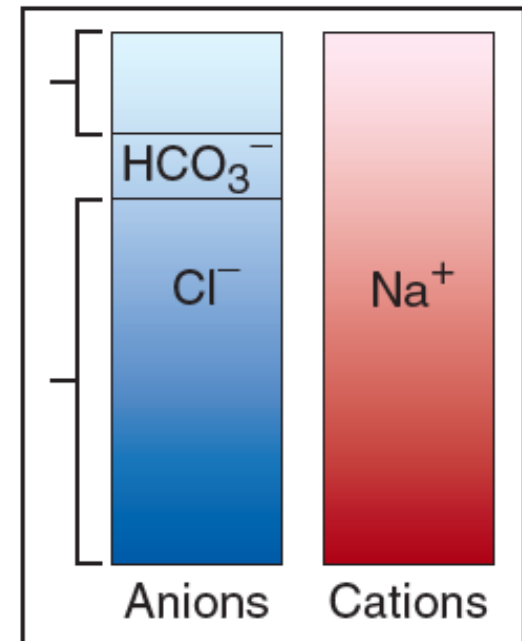
Normal



Add HCl
Lose HCO_3^-



Add $\text{H}^+ \text{A}^-$



High anion gap metabolic acidosis

Glycols (ethylene, propylene (lorazepam))

Oxypoline – paracetamol/women

L-Lactate

D-Lactate – short bowel syndrome

Methanol

Aspirin

Mehta et.al,
The Lancet, Volume 372, Issue 9642,
Page 892, 13 September 2008

Renal Failure

Ketosis – starvation, alcohol, diabetic

Anion and osmolal gap in diagnosis of intoxications

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

Serum osmolal gap

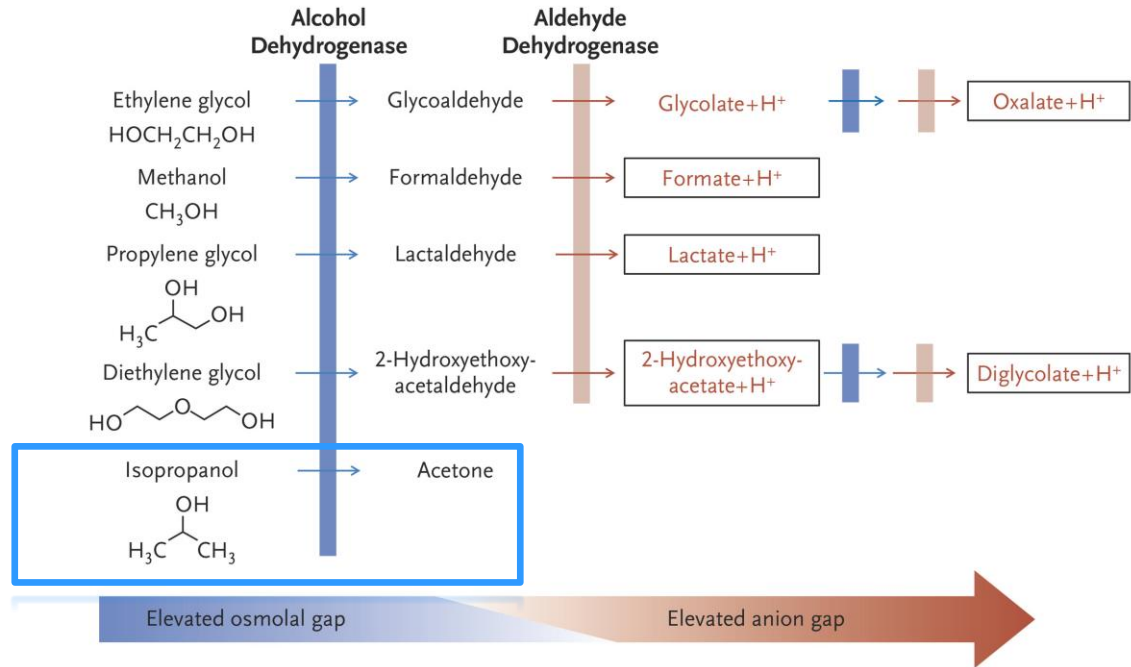
$$\text{Osmolal gap} = \text{Measured } S_{\text{osm}} - \text{Calc } S_{\text{osm}}$$

Calculated S_{osm} :

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

Metabolism of toxic alcohols

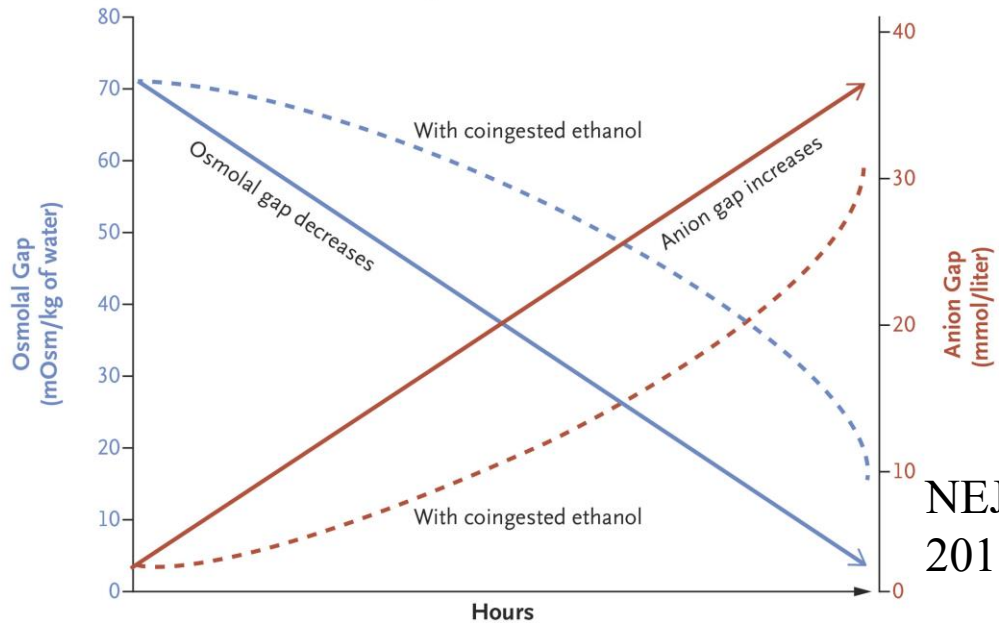
A Metabolic Pathways of Toxic Alcohols



Early Time Points:
Osm gap > Anion Gap

Later Time Points:
AG Increases
Osm gap decreases

B Time Course of Changes in the Osmolal and Anion Gaps



NEJM
2018

Clues to high anion gap acidosis syndromes

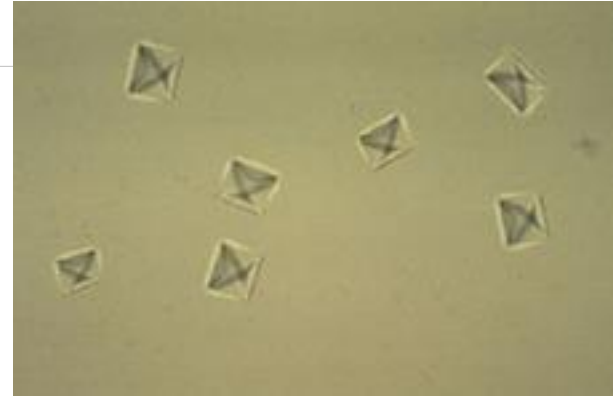
- Alcoholic fetor
- Papilledema
- Osmolar gap
- Undetectable serum ethanol

Methanol intoxication



Clues to high anion gap acidosis syndromes

- No fetor
- Osmolar gap
- Calcium oxalate dihydrate (envelope-shaped) crystalluria
- Urine fluoresces under Wood's (UV) lamp



Ethylene glycol intoxication

Clues to high anion gap acidosis syndromes

- Tinnitus/deafness
- Fever, tachycardia, hyperventilation
- Associated respiratory alkalosis and metabolic acidosis

Salicylate intoxication

Clues to high anion gap acidosis syndromes

- Normal glucose
- Serum Acetest/acetoacetate negative or borderline
- Serum β -hydroxybutyrate positive
- Serum ethanol may or may not be present

Alcoholic ketoacidosis

Clues to high anion gap acidosis syndromes

- Metformin, NRTIs, Linezolid, Propofol
- Lactic acid elevated

Type B lactic acidosis 2° Medications

Clues to high anion gap acidosis syndromes

- Short bowel syndrome
- Episodes of Δ MS associated with AG metabolic acidosis, after CHO intake
- Spontaneous resolution if NPO
- Serum lactic acid level negative

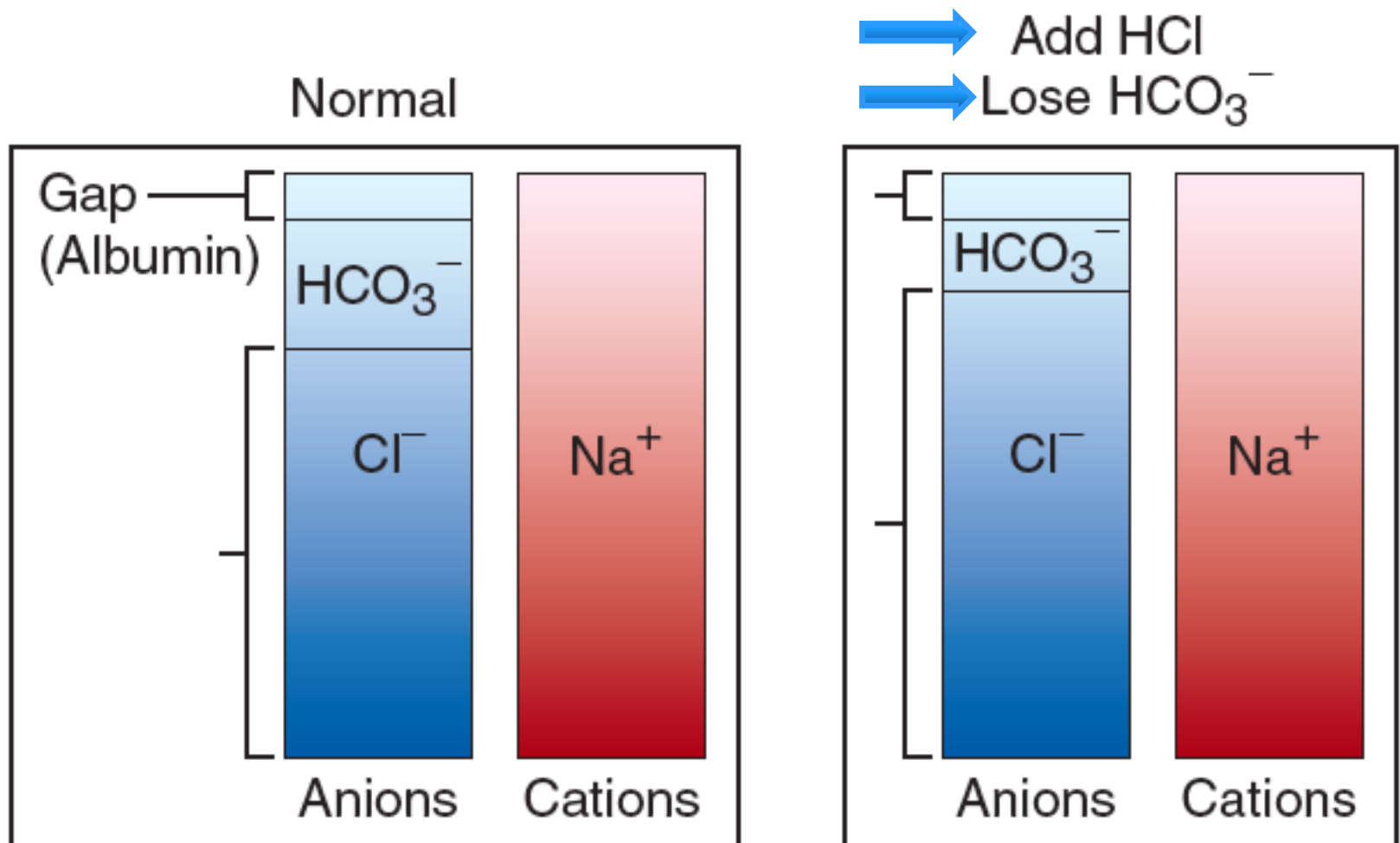
D-lactic acidosis

Clues to high anion gap acidosis syndromes

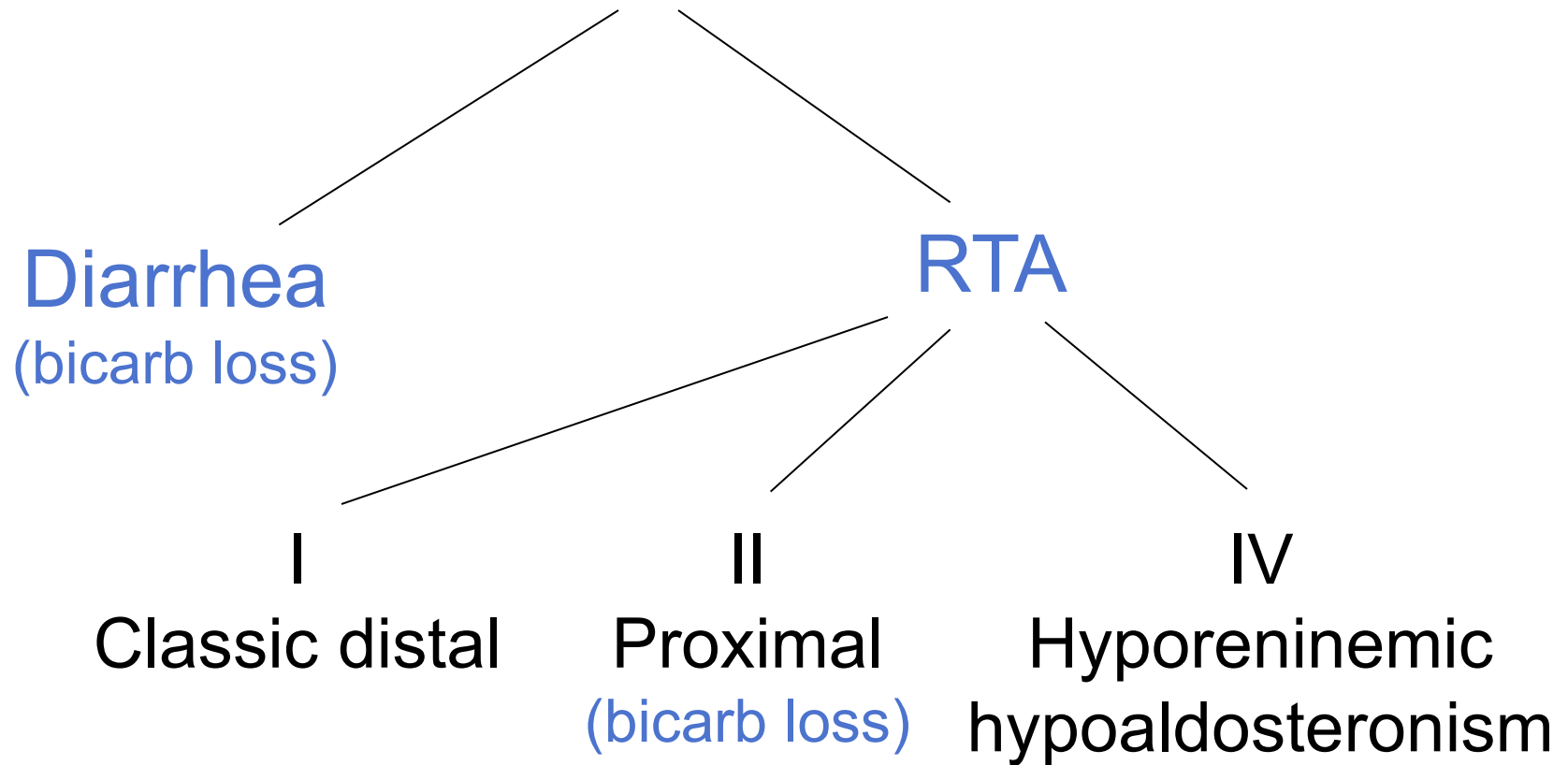
- ICU patient sedated with high dose intravenous infusion of lorazepam
- Osmolar gap
- Elevated serum lactic acid level

Propylene glycol intoxication

DDx of a non-gap metabolic acidosis



DDx of a non-gap metabolic acidosis



Impaired H^+ Excretion = retained HCl

DDx of RTA

	Proximal	Classic distal	Hyporenin hypoaldo
Serum K	Low	Low	High
Urine pH	Variable	> 5.5	< 5.5
Other features	Fanconi (low PO ₄ , glycosuria)	Nephrocalcinosis ± CaPO ₄ stones	

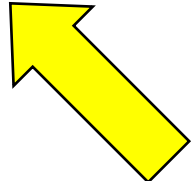
Causes and Rx of RTA

	Proximal	Classic distal	Hyporenin hypoaldo
Common causes	Ifosfamide NRTI (tenofovir, adefovir, cidofovir) Myeloma	Sjogren's SLE Amphotericin	CKD plus: DbM Obstruction Sick cell dz SLE NSAIDs
Rx	Bicarbonate (lots)	Bicarbonate (1 mEq/kg/day)	K ⁺ lowering Rx: Diuretics Kayexalate Low K diet Mineralocorticoid

Respiratory Alkalosis

Respiratory Alkalosis (*Hyperventilation*)

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.03 \times \text{PCO}_2}$$


Respiratory
Processes
Decrease in PCO_2

Increase in pH

Hyperventilation

Pulmonary disorders

- Pneumothorax
- Pulmonary embolism
- Pneumonia
- Exacerbation of asthma/COPD
- Upper airway obstruction
- Intrapulmonary shunt

- Interstitial lung disease
- High altitude sickness
- Asthma
- COPD
- Paradoxical vocal fold motion
- Upper airway obstruction

Cardiovascular disorders

- Acute coronary syndrome
- Heart failure
- Dysrhythmias
- Shock

- Angina
- Heart failure
- Dysrhythmias

Metabolic disorders

- Anion gap acidosis (eg, ketoacidosis, lactic acidosis, salicylate poisoning, non-ethanol alcohol toxicity, carbon monoxide poisoning)
- Nonanion gap acidosis (eg, renal failure)

- Hypocalcemia
- Hypoglycemia
- Diabetic ketoacidosis

Endocrine disorders

- Hyperthyroidism
- Pheochromocytoma

- Hyperthyroidism
- Pheochromocytoma

Neurologic and psychological disorders

- Central nervous system tumor
- Certain stroke syndromes (eg, hemispheric)
- Anxiety, panic
- Pain

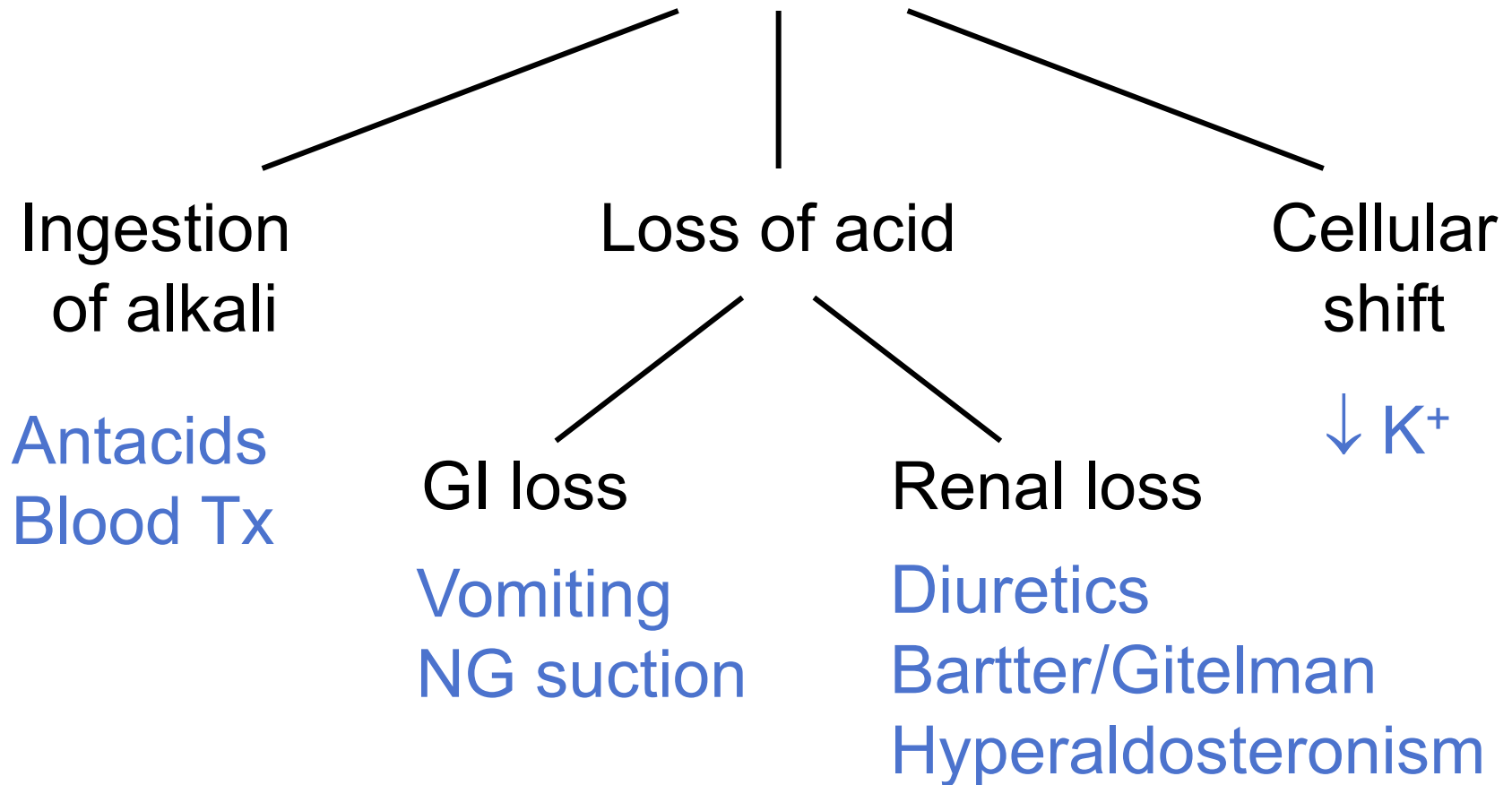
- Anxiety, panic
- Pain
- Hyperventilation syndrome

Miscellaneous

- Pregnancy
- Hepatic failure
- Sepsis

Metabolic alkalosis

Induction of metabolic alkalosis



Maintenance of alkalosis

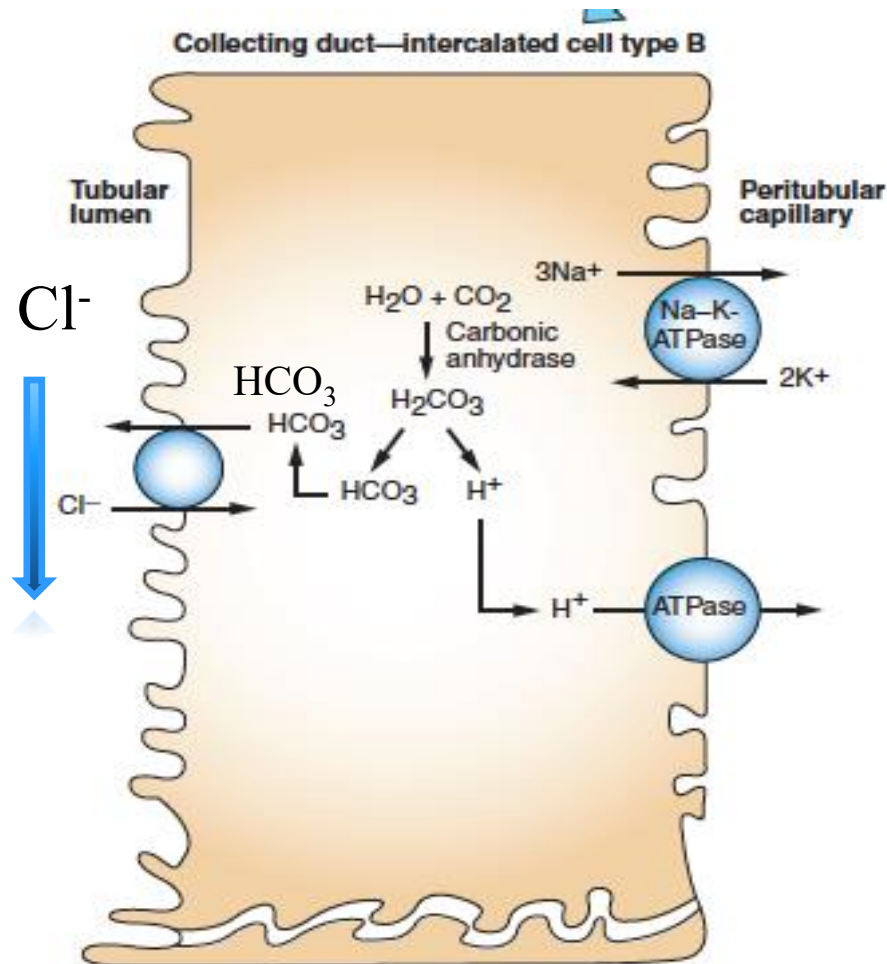
Requires impairment of renal excretion of excess bicarbonate:

- Volume contraction (e.g. vomiting, diuretics)
 - Hypokalemia
 - Renal failure
 - Hyperaldosteronism
-

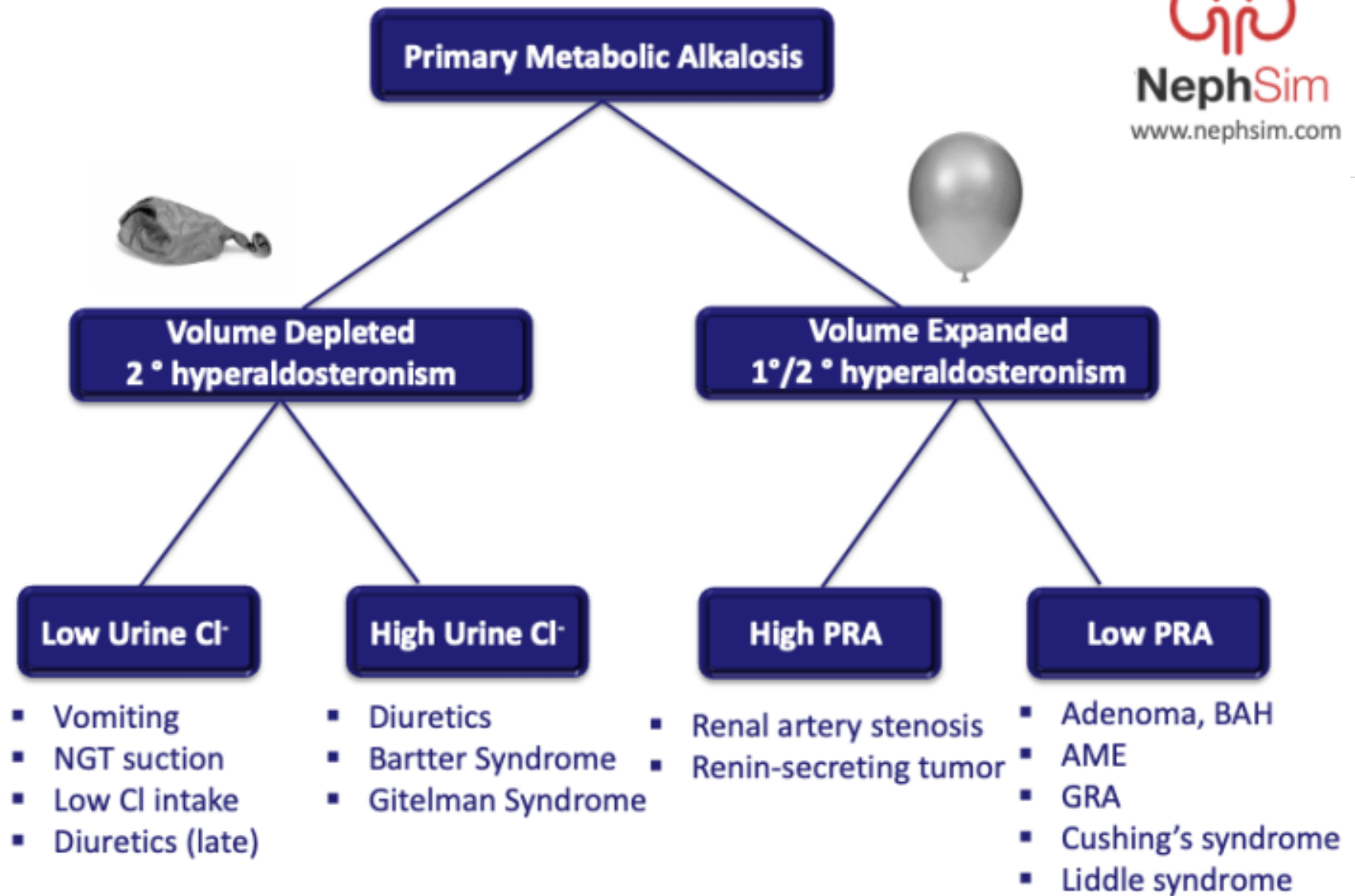
Urine Changes with Metabolic Alkalosis

	UNa ⁺	UK ⁺	UCl ⁻	pH (bicarb)
Day 1-3				
>3 days				

Correction of Alkalosis *Requires* Cl^- to Allow HCO_3^- Excretion



Collecting duct: Intercalated Cell



PRA: plasma renin activity; AME: apparent mineralocorticoid excess; GRA: glucocorticoid remediable aldosteronism

Cryptogenic hypokalemic metabolic alkalosis

	Volume status/BP	Urine Cl ⁻	Urine diuretics
Hyperaldosteronism	↑	> 40 mEq/L	-
Surreptitious vomiting	NI or ↓	< 25 mEq/L	-
Diuretic abuse	NI or ↓	> 40 mEq/L	+
Bartter/Gitelman syndrome	NI or ↓	> 40 mEq/L	-

Lets Practice

An 18 year-old female is brought in with change in mental status and suspected toxic ingestion. Her blood pressure is 100/73 mm Hg, pulse rate 89, respiratory rate 40, temperature 100.5° C. She vomited once in the emergency room and is poorly responsive.

Laboratory studies:

Serum sodium	142 mEq/L
Serum potassium	3.6 mEq/L
Serum chloride	102 mEq/L
Serum bicarbonate	16 mEq/L
Blood urea nitrogen	21 mg/dL
Serum creatinine	1.8 mg/dL
Serum glucose	62 mg/dL

[Next page →](#)

Acetest	Negative
Serum lactate	1.8 mmol/L
Serum osmolality	295 mOsm/kg

Arterial blood studies on room air:

pH	7.39
PCO ₂	25 mm Hg

Which of the following treatments would be most likely to be effective in the management of this patient?

- (A) Breathe into a bag
- (B) Insulin drip
- ☒ (C) Forced alkaline diuresis
- (D) 5% dextrose
- (E) Fomepizole

pH 7.39, PCO_2 25 mm Hg, HCO_3 16 mEq/L

Primary metabolic acidosis, & probably respiratory alkalosis

Predicted PCO_2 from Winter's formula = $(1.5 \times 16) + 8 = 32$

Concomitant respiratory alkalosis

Na 142 mEq/L, Cl 102 mEq/L

Anion gap = $142 - 102 - 16 = 24$ (normal 8-12)

Anion gap metabolic acidosis

$$\Delta\text{AG} = 24 - 10 = 14$$

$$\Delta\text{HCO}_3 = 24 - 16 = 8$$

$$\Delta/\Delta = 14/8 = 1.8$$

$\Delta/\Delta > 1.8$ Suggests vomiting induced metabolic alkalosis

Bicarb higher than expected for degree of elevation of AG

Serum osmolal gap=0

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

Calculated S_{osm} :

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

$$(2 \times 142) + (62/18) + (21/2.8) = 295$$

$$\text{Osmolal gap} = 295 - 295 = 0$$

Anion and osmolar gap in diagnosis of intoxications

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

Take Away Messages

- **Assess pH (emia), PCO_2 (Resp) and HCO_3^- (metabolic)**
- Compensation is opposite process and direction *but not to normal pH.*
- Respiratory Acidosis=Hypoventilation
- Respiratory Alkalosis=Hyperventilation
- Metabolic Acidosis
 - Elevated AG; addition of H^+ with *non- Cl^-* anion
 - Normal AG; addition of H^+Cl^- OR Bicarb loss (GI or Renal)
 - Use $\Delta\text{AG}/\Delta\text{bicarb}$ to Assess for Another Metabolic process
- Metabolic Alkalosis- loss of HCl ; vomiting and diuretics

Suggested reading

- Rennke, H.G., Denker, B.M., **Renal Pathophysiology – The Essentials**, 5th Edition, Lippincott Williams & Wilkins, 2025
 - Mount, D.B., **Fluid and Electrolyte Disturbances**. In Harrison's Principles of Internal Medicine, 21st Edition, Eds. Loscalzo, Joseph; Fauci, Anthony S.; Kasper, Dennis L.; Hauser, Stephen; Longo, Dan; Jameson, J. Larry. Chapter 53
 - DuBose, T.D., Jr. **Acidosis and Alkalosis**. In Harrison's Principles of Internal Medicine, 21st Edition, Eds. Loscalzo, Joseph; Fauci, Anthony S.; Kasper, Dennis L.; Hauser, Stephen; Longo, Dan; Jameson, J. Larry. Chapter 55
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