

Acid-Base Disorders II: Non-gap acidosis and metabolic alkalosis

Alan S. L. Yu, M.B., B.Chir.

Director, Division of Nephrology & Hypertension

Jared Grantham Kidney Institute

University of Kansas Medical Center

Alan S. L. Yu, MB, BChir



- University of Cambridge Medical School
- Medicine Residency @BWH
- Nephrology Fellowship @BWH
- Professor of Medicine @University of Kansas
 - Clinical focus: Nephrology
 - Research focus: Kidney physiology, PKD

Disclosures

- I have no financial disclosures

Objectives

- Review the diagnostic approach and management of non-anion gap metabolic acidosis
- Review the diagnostic approach and management of metabolic alkalosis

Non-gap (hyperchloremic) metabolic acidosis

1. Lower GI bicarbonate loss*
2. Renal tubular acidosis (RTA)*
3. Dilutional acidosis
4. Urinary diversion
5. (Compensation for respiratory alkalosis)

*Common

Diagnosis of RTA

Determination of the urine anion gap

$$\text{Urine anion gap} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$$

Normal range: depends on diet

Why does the UAG work?

Total anions = Total cations

Measured anions + unmeasured anions =
measured cations + unmeasured cations

Measured cations - Measured anions =
Unmeasured anions - unmeasured cations

Urine anion gap

= Measured cations - Measured anions

= $(\text{Na}^+ + \text{K}^+) - \text{Cl}^-$

= Unmeasured anions - unmeasured cations

Sulfate

Phosphate

Bicarbonate

Organic anions

Calcium

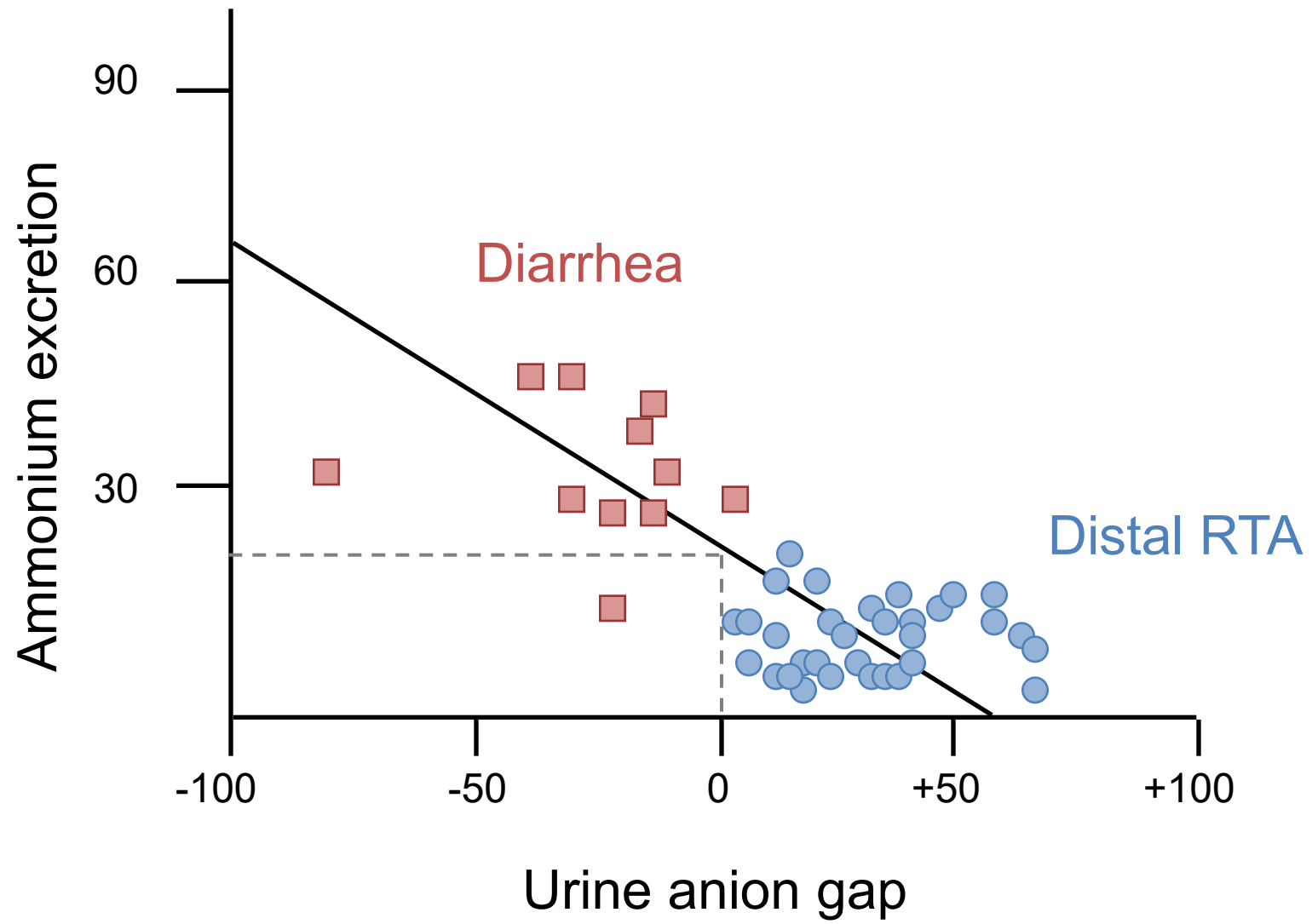
Magnesium

NH_4^+

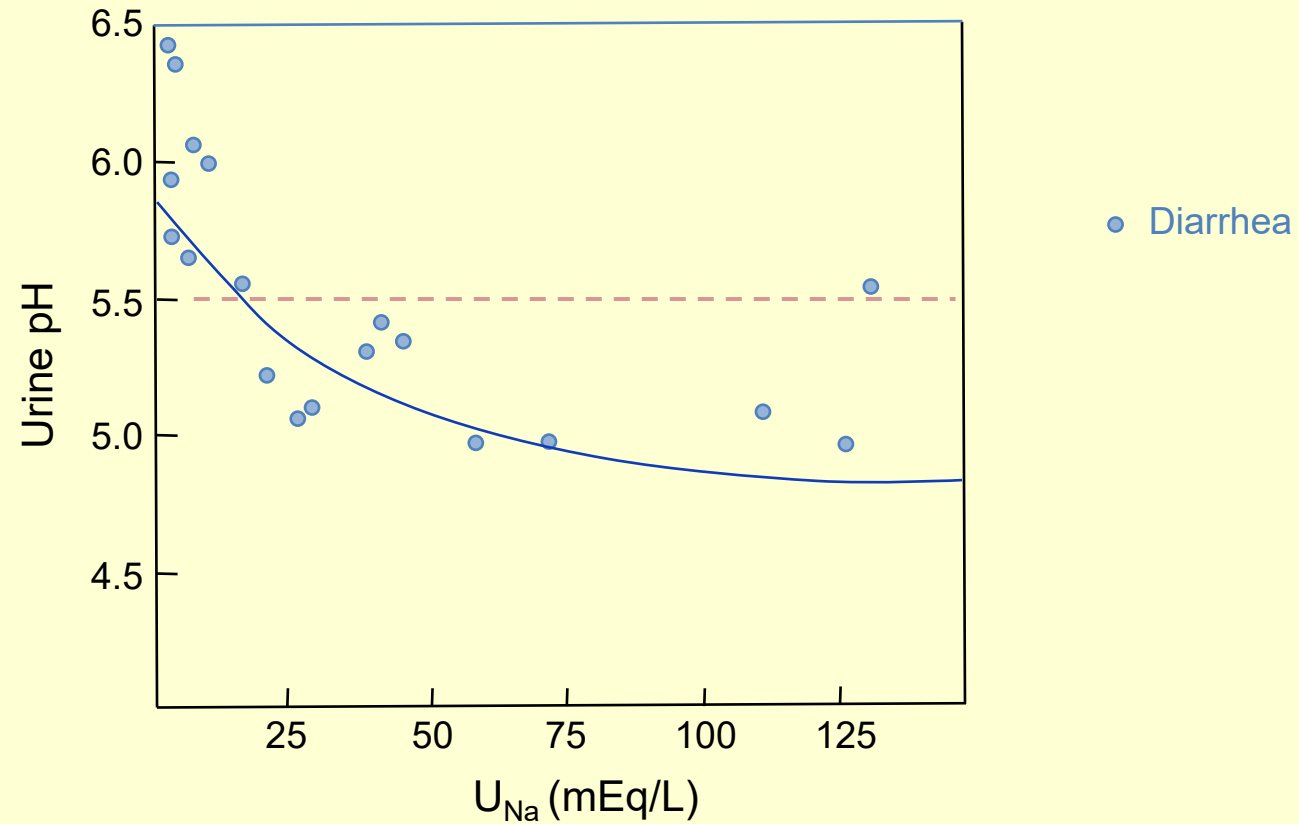
Urine anion gap

In the setting of acidemia, urine HCO_3^- should be negligible, and urine NH_4^+ should be HIGH

→ Urine AG should be *LOW*



Why urine pH is not used to distinguish diarrhea from RTA



Non-gap metabolic
acidosis



Urine anion gap



Negative
Diarrhea

Positive
RTA

Non-gap metabolic
acidosis



Urine anion gap

Negative

Diarrhea

Proximal RTA

Positive

RTA

Excreted anions

Polling question 1

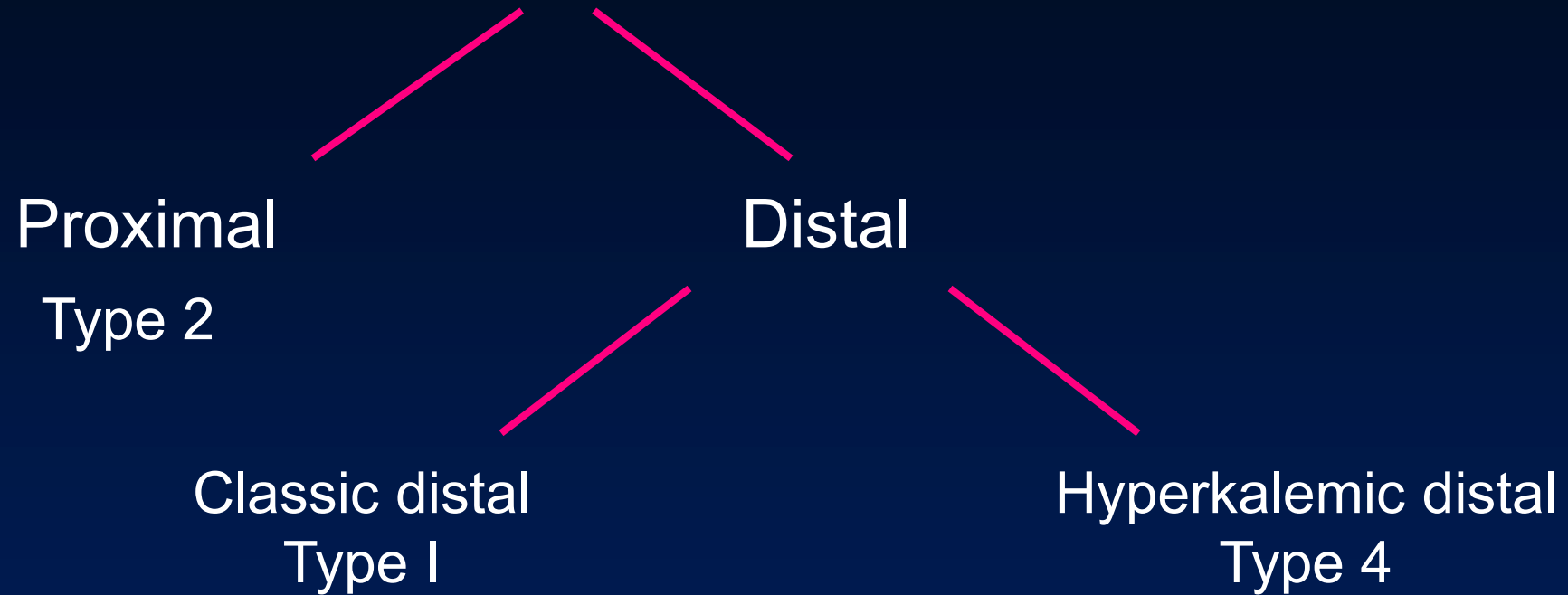
The following labs are consistent with which of the following diagnoses?

Na 140, K 3.3, Cl 116, CO₂ 16, venous pH 7.28

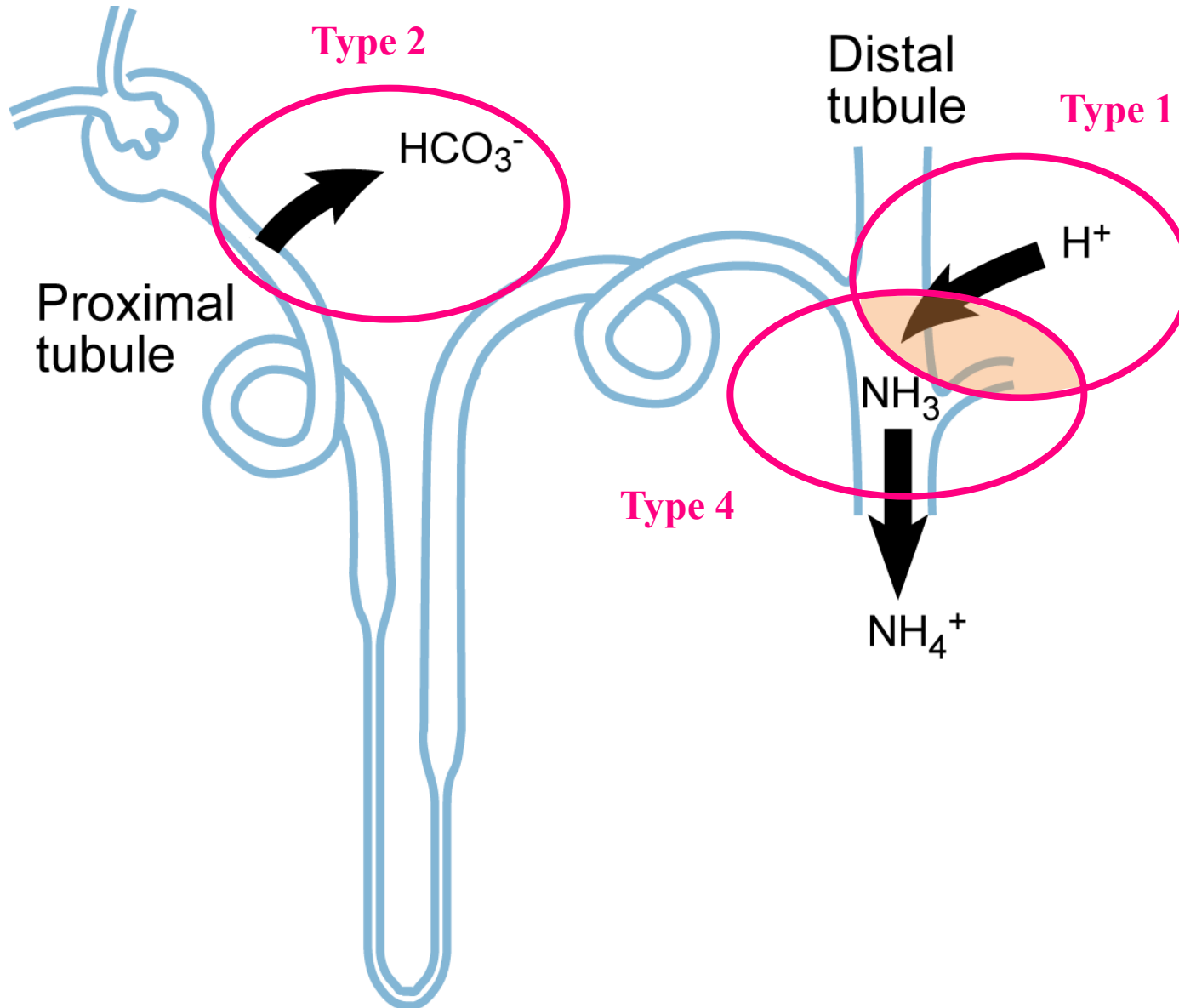
Urine pH 6, Na 45, K 53, Cl 60

- A. Distal renal tubular acidosis
- B. Diarrhea
- C. Hyperventilation syndrome
- D. Adrenal insufficiency
- E. Seizure

Renal tubular acidosis



Acid excretion mechanisms in renal tubule



Clinical features of RTA

	Diarrhea	Proximal RTA	Distal RTA	
			Type I	Type 4
Serum K ⁺	↓			↑
Urine AG	Negative	Variable	Positive	
Urine pH	Variable	Variable	> 5.5	< 5.5
Other		Fanconi syndrome	Nephro-calcinosis	

Fanconi syndrome

- Hypokalemia, non-gap metabolic acidosis
- +
- Glycosuria despite normoglycemia
- Generalized amino-aciduria
- Hypophosphatemia and urinary phosphate wasting
($F_E\text{PO}_4 > 5\%$)
- Hypouricemia

Causes of RTA

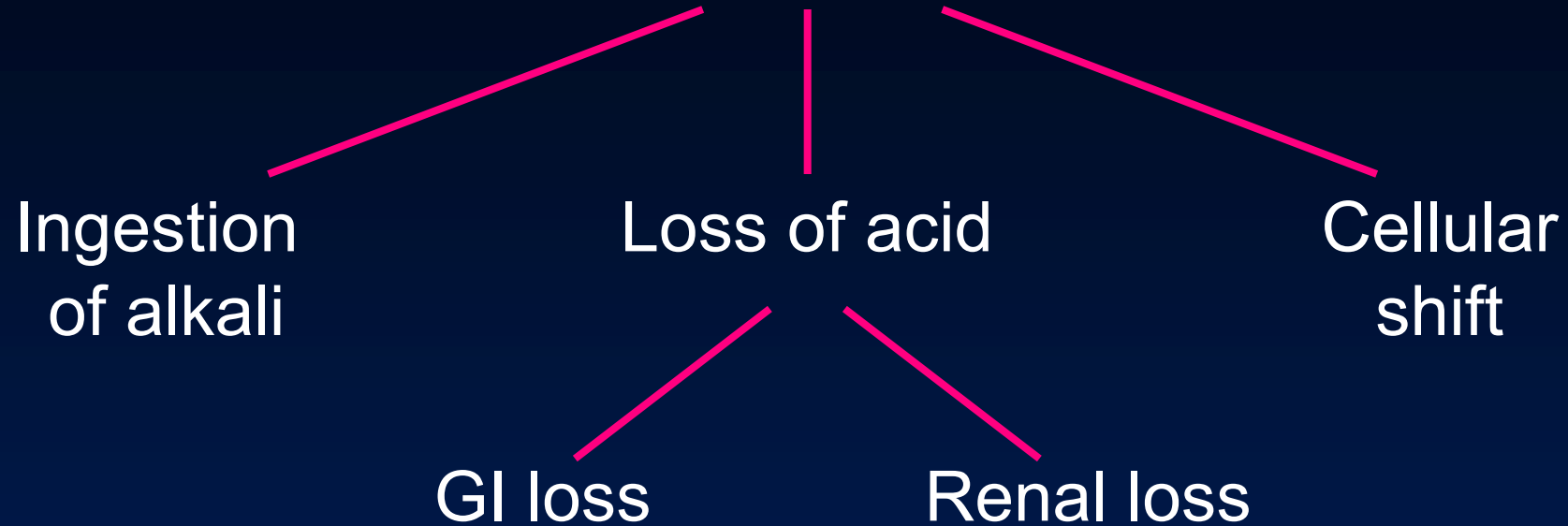
Proximal RTA	Distal RTA	
	Type I	Type 4
1. Plasma cell dyscrasia (myeloma, amyloid, LCDD) 2. Ifosfamide 3. NRTI Heavy metals Cystinosis Wilson's	1. Sjogren's/SLE 2. Cirrhosis 3. Amphotericin 4. Medullary sponge kidney	1. Hyporeninemic hypoaldosteronism (DM) 2. Tubulointerstitial disease (sickle cell, SLE, obstruction, HIV) 3. Drugs (ACEI/ARB, NSAIDs, CNI, heparin)

Treatment of RTA

Proximal RTA	Distal RTA	
	Type I	Type 4
Na & K bicarbonate $\geq$ 4 mEq/kg/day	K bicarbonate or citrate 1-3 mEq/kg/day	Control of hyperkalemia (diuretics, K-binding resins)

Metabolic alkalosis

Induction of metabolic alkalosis



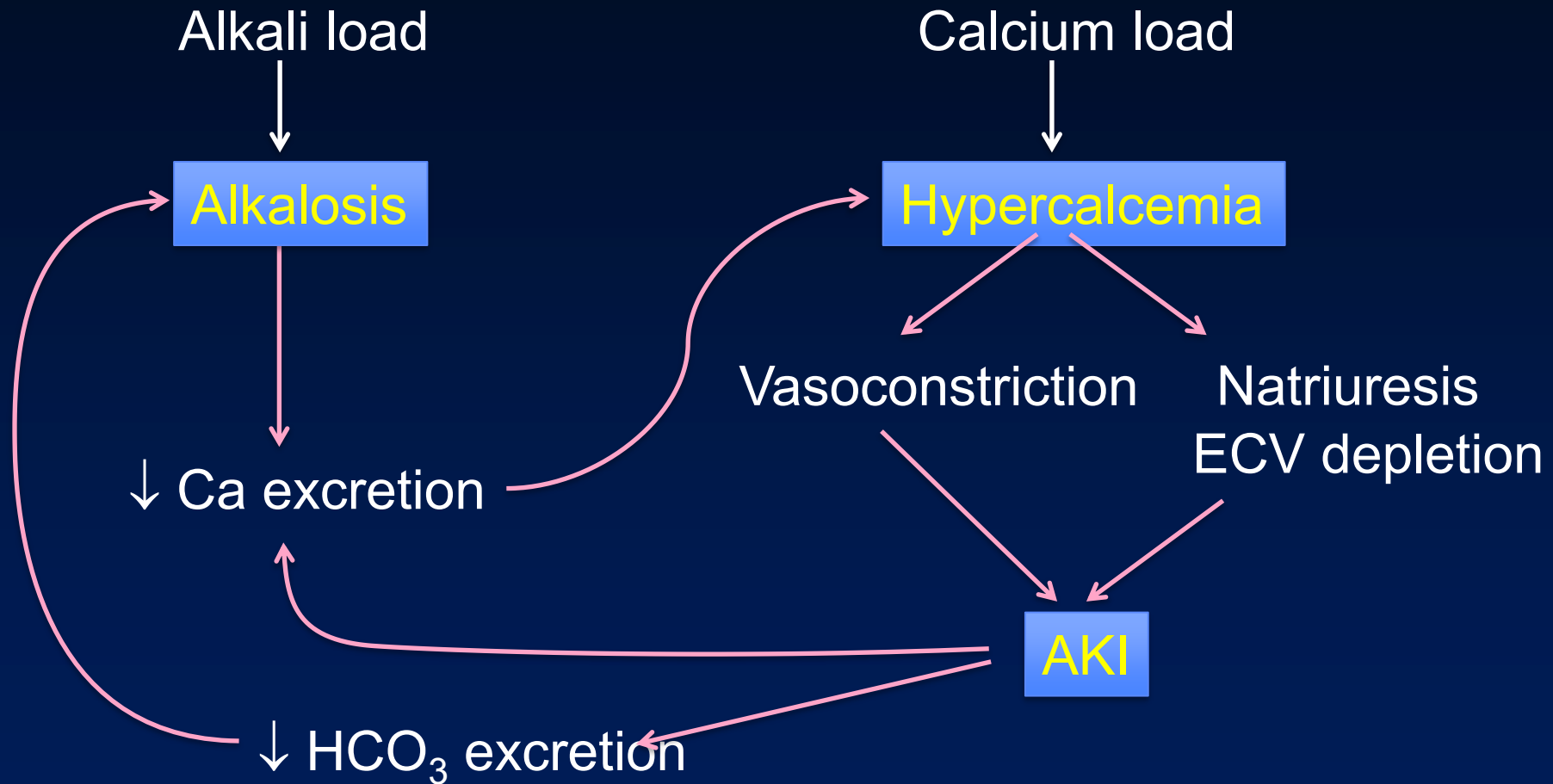
Induction of metabolic alkalosis



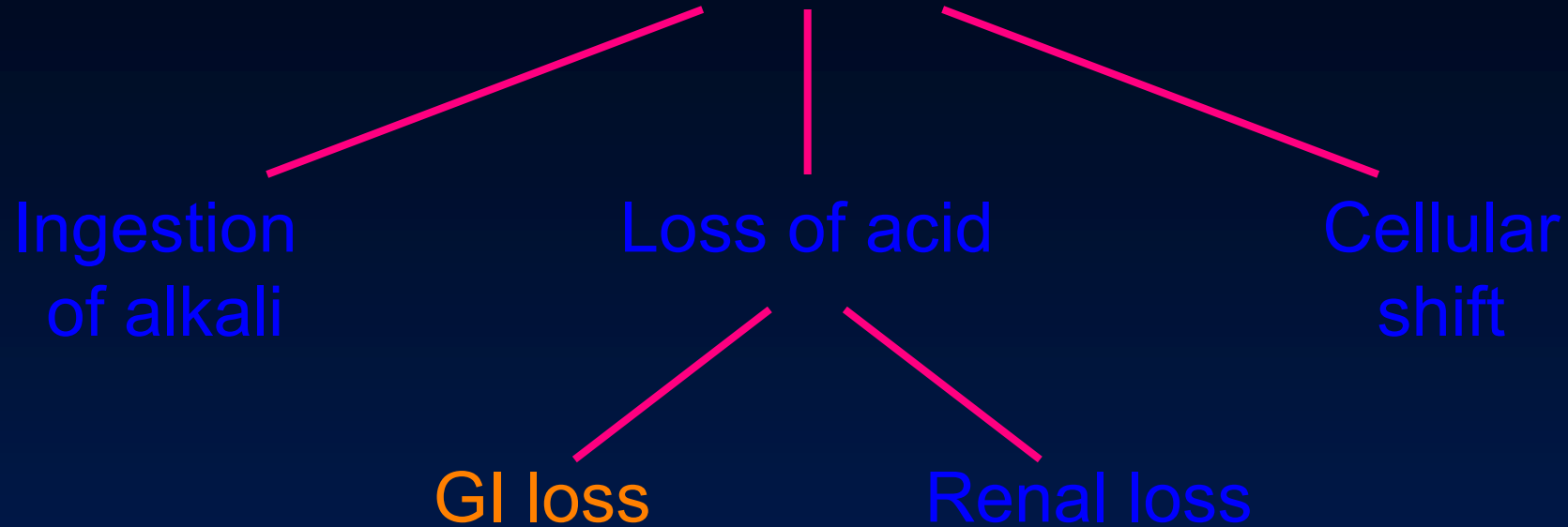
Milk-alkali syndrome (calcium-alkali syndrome)

- Metabolic alkalosis + hypercalcemia + AKI
- Now 8-12% of hospitalized pts with hypercalcemia
- Most commonly due to CaCO_3 ingestion

Pathogenesis of milk-alkali syndrome



Metabolic alkalosis

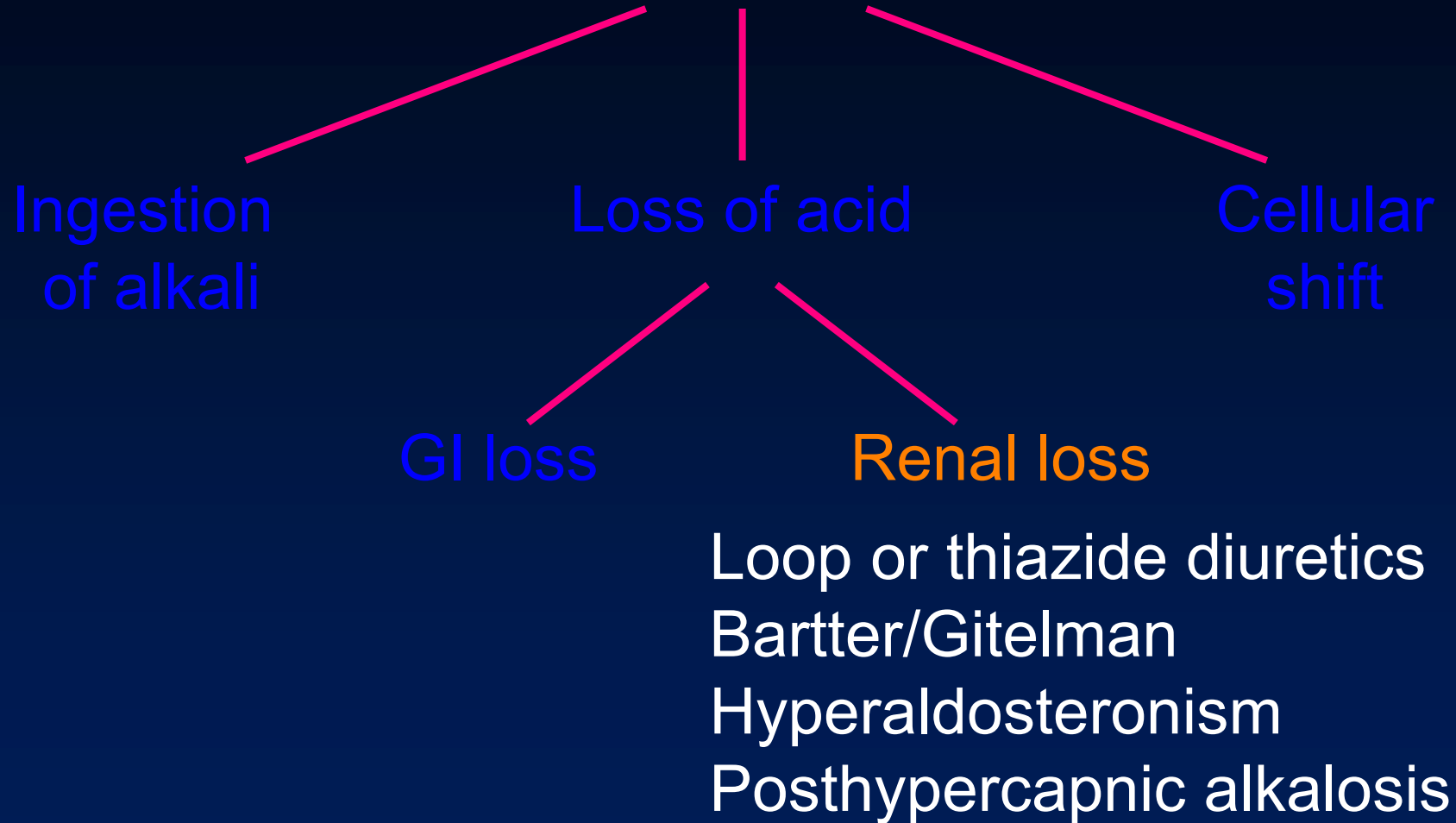


Vomiting

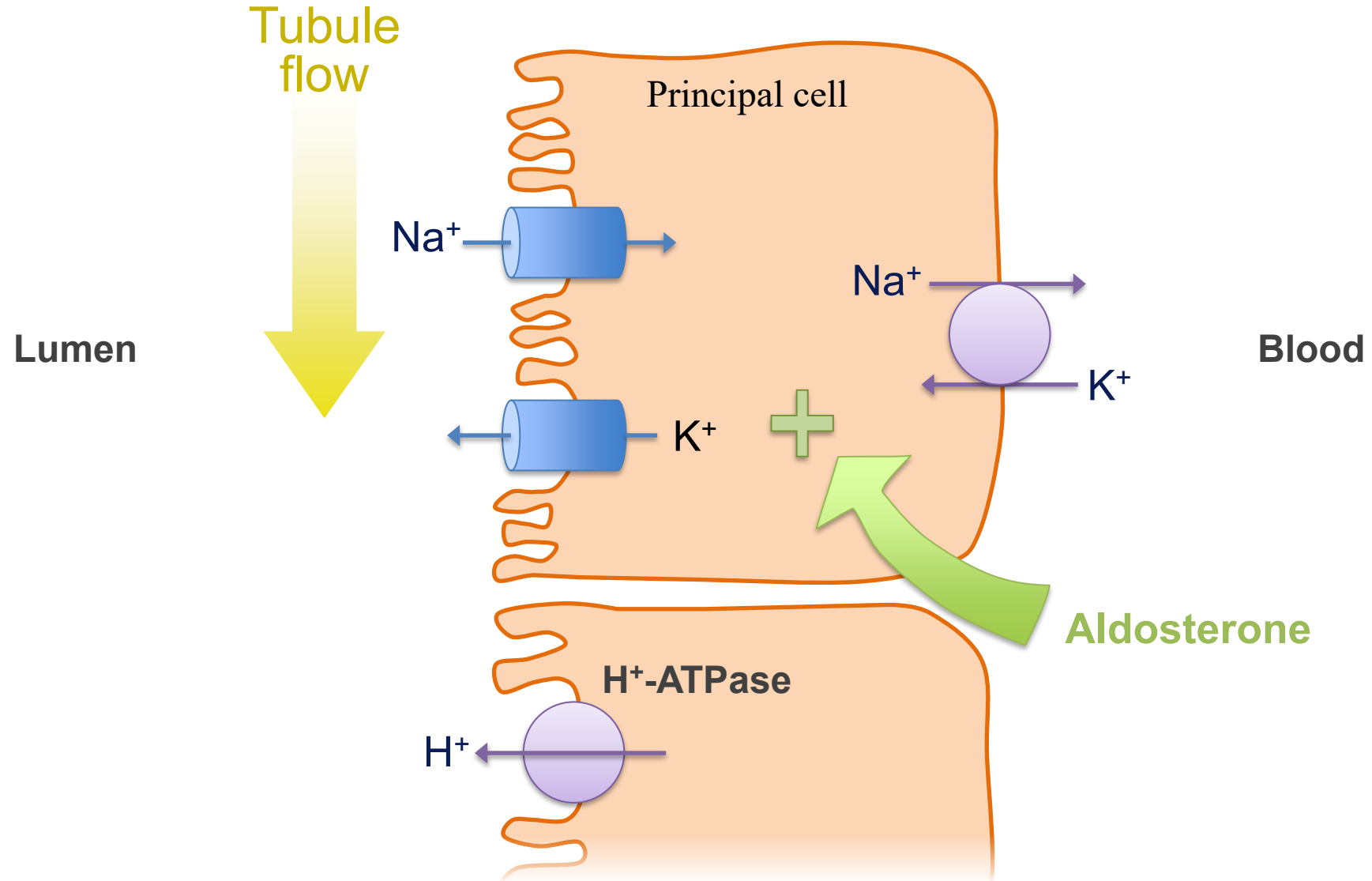
Nasogastric suction

(Chloridorrhea from villous adenoma, laxatives)

Metabolic alkalosis

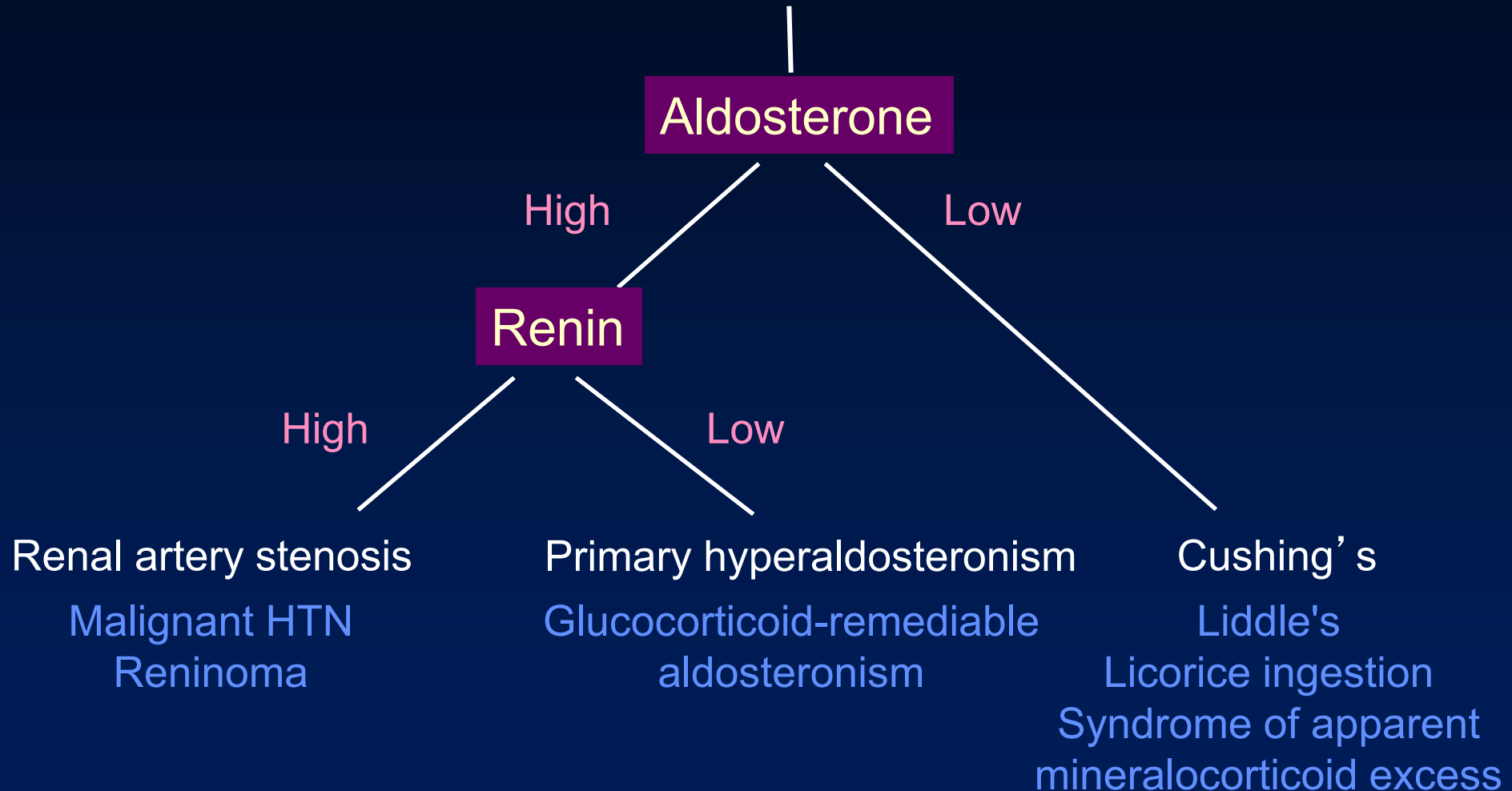


Collecting duct H^+ secretion



HYPERALDOSTERONISM:

Hypokalemia metabolic alkalosis + hypertension



Post-hypercapnic alkalosis

Chronic CO₂ retention



Compensatory renal HCO₃⁻ retention

Mechanical ventilation



Normalization of PCO₂

Transient inappropriately high serum HCO₃ and pH



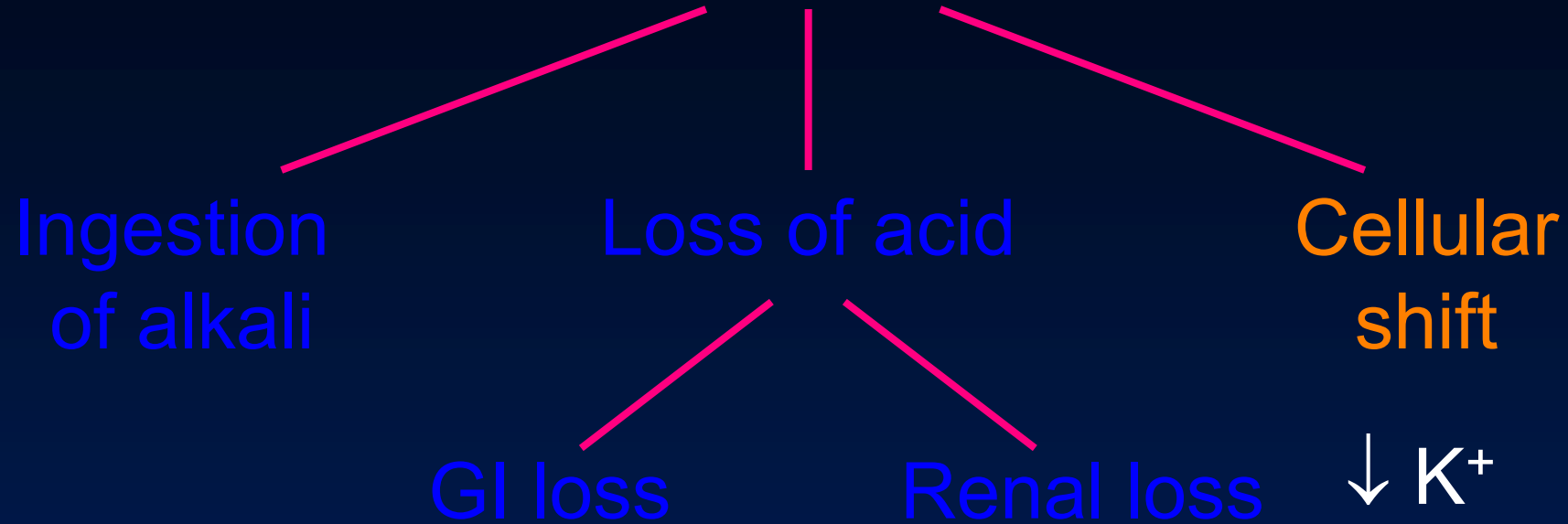
Excretion of excess HCO₃⁻ if.....

Sufficient time

Adequate renal function

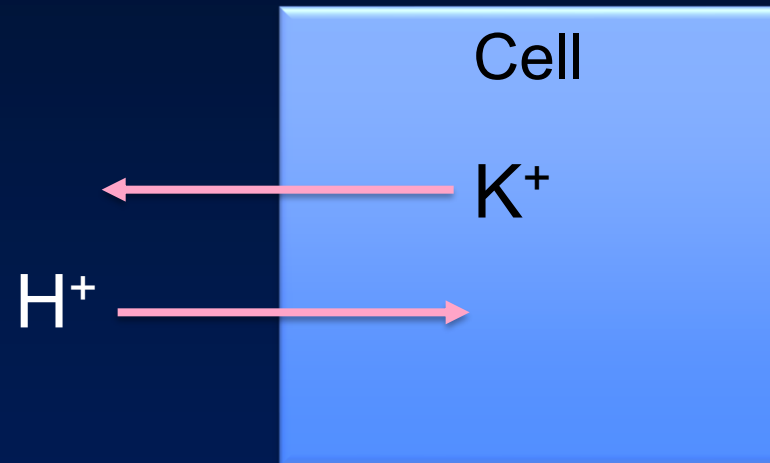
Euvoemia

Metabolic alkalosis



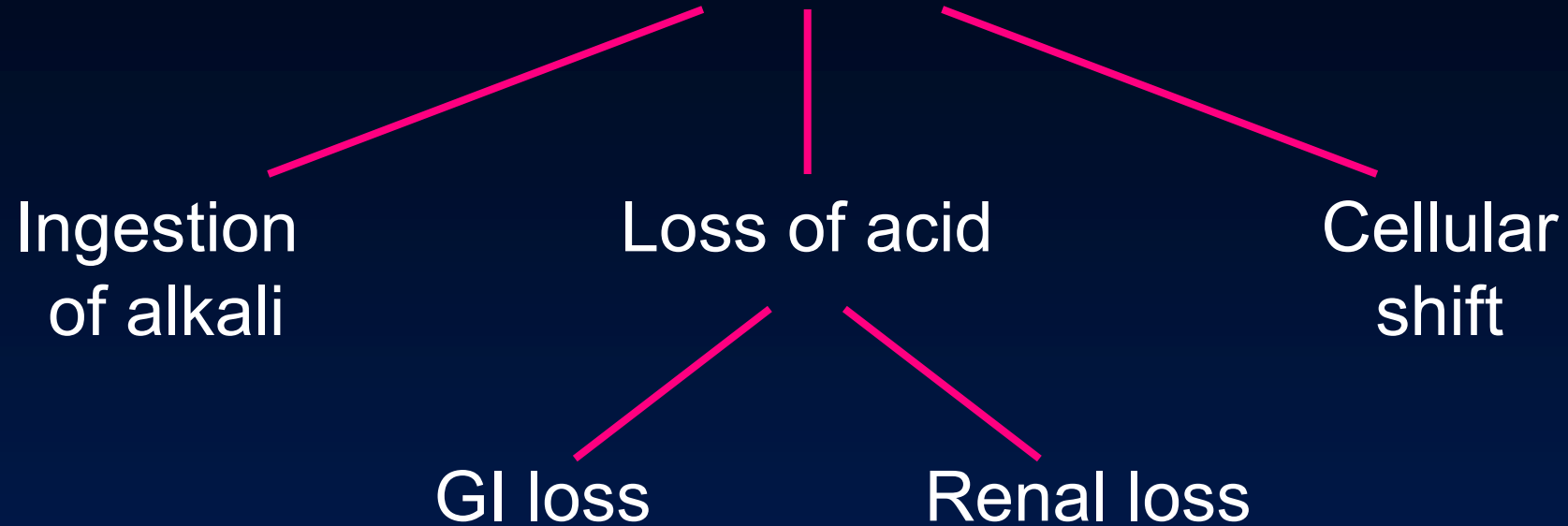
Mechanism for hypokalemia-induced metabolic alkalosis

1. Reciprocal cellular shift of H^+ and K^+



2. $\uparrow$ H-K-ATPase in the medullary CD

Induction of metabolic alkalosis



+

Contraction alkalosis

Pathogenesis of contraction alkalosis (Cl-depletion alkalosis)

Loss of Cl^- and water in excess of HCO_3^-

Failure of renal HCO_3^- excretion

↑ Proximal tubule Na^+
reabsorption with HCO_3^-

↓ CCD Cl^- delivery →
↓ β -intercalated cell
 Cl^- - HCO_3^- exchange

2° hyperaldosteronism → ↑ CCD
 Na^+ reabsorption with H^+ secretion

Maintenance of alkalosis

Requires impairment of renal excretion of excess bicarbonate:

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

Time-dependent change in urine lytes in vomiting

	Na^+	K^+	Cl^-	HCO_3^-	pH
Early	↑	↑	↓	↑	> 6.5

Appropriate attempt to get rid of
excess alkali as NaHCO_3 in urine

Time-dependent change in urine lytes in vomiting

	Na^+	K^+	Cl^-	HCO_3^-	pH
Early	↑	↑	↓	↑	> 6.5
Late	↓	↓	↓	↓	< 5.5

Conservation of Na in the face of severe volume contraction leads to paradoxical aciduria

Time-dependent change in urine lytes in vomiting

	Na^+	K^+	Cl^-	HCO_3^-	pH
Early	↑	↑	↓	↑	> 6.5
Late	↓	↓	↓	↓	< 5.5

Urine chloride remains low throughout,
hence best diagnostic indicator of volume
depletion

Cryptogenic metabolic alkalosis

	Volume status	Urine Cl ⁻	Urine diuretics
Hyperaldosteronism	↑	> 40 mEq/L	-
Surreptitious vomiting (or other extrarenal Cl loss)	NI or ↓	< 25 mEq/L	-
Diuretic abuse	NI or ↓	> 40 mEq/L*	+
Bartter/Gitelman syndrome	NI or ↓	> 40 mEq/L	-

*Can be low after post-diuretic effect

Polling question 2

A young woman is referred with chronic hypokalemia and alkalosis. BP is 95/44. Labs are as follows:

Na 136, K 2.9, Cl 90, CO₂ 38

Urine pH 6.5, Na 37, K 44, Cl <5

What is the most likely diagnosis?

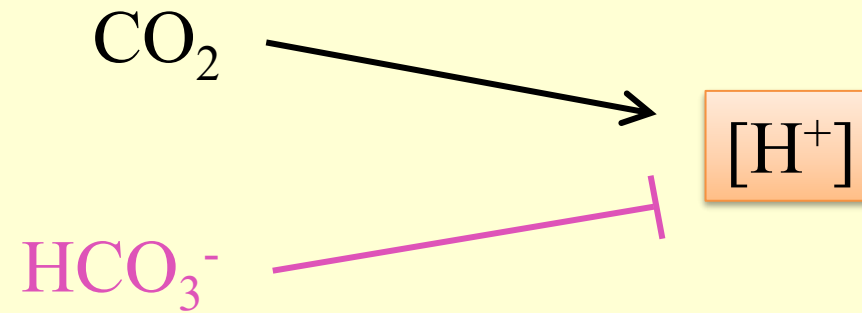
- A. Gitelman syndrome
- B. Diuretic abuse
- C. Surreptitious vomiting
- D. Primary hyperaldosteronism
- E. Laxative abuse

Treatment of metabolic alkalosis

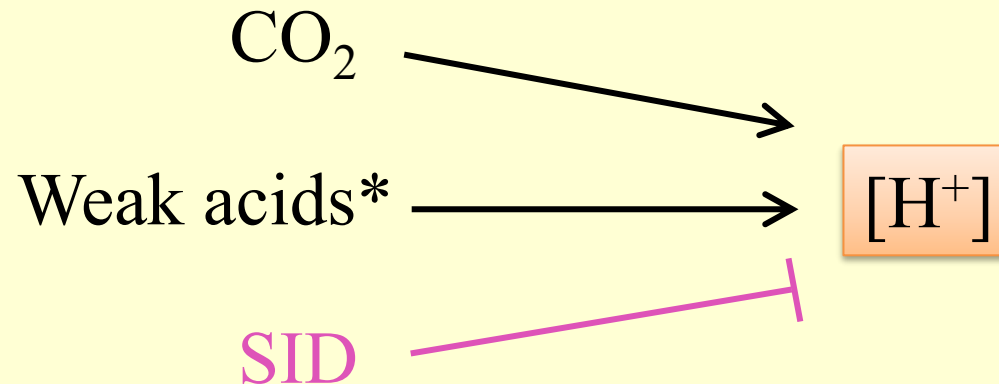
- Treat underlying cause
- Correct ECV depletion
- Correct Cl and K depletion
- Acetazolamide (in edematous states)
- Dialysis/HCl

Strong ion difference: an alternative approach?

Henderson-Hasselbalch

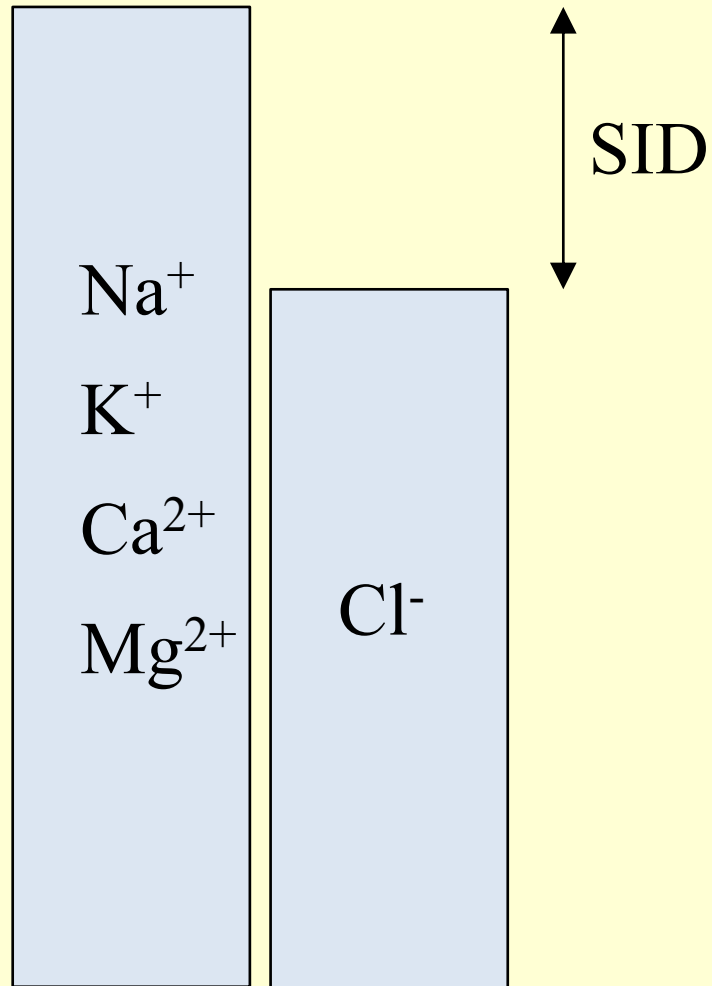


Stewart

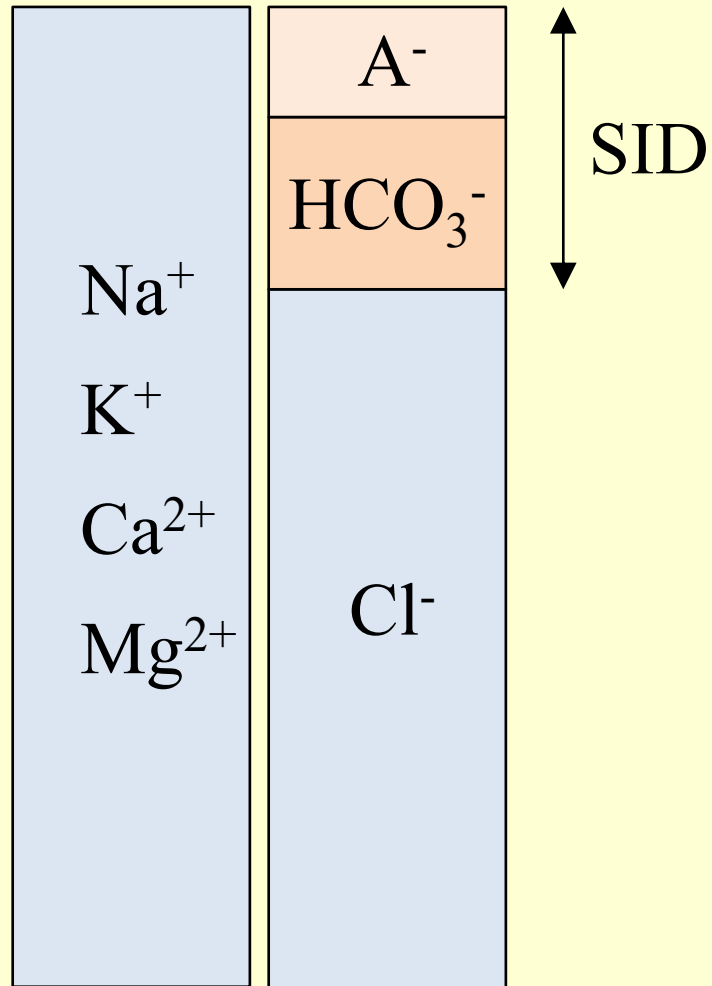


*Phosphate, albumin

Strong ion difference: an alternative approach?



Strong ion difference: an alternative approach?



Strong ion difference: an alternative approach?

“Contraction” alkalosis

Cl⁻ depletion → SID↑ → **Alkalosis**

Dilutional acidosis

Cl⁻-rich fluid → SID↓ → **Acidosis**

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