ΜΕΤΑΒΟΛΙΚΗ ΟΞΕΩΣΗ ΚΑΙ ΜΕΙΚΤΕΣ ΔΙΑΤΑΡΑΧΕΣ

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417 ΝΙΜΤΣ

Evaluation of acid-base disorders

1. History and physical exam

- Gastrointestinal
- Renal
- Respiratory
- Neurologic
- Drugs and toxins
- Volume status and respiratory rate

Evaluation of acid-base disorders
2. Arterial pH

- pH < 7.37 Acidemia
- pH > 7.43 Alkalemia

Evaluation of acid-base disorders

3. 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

4. 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 ↓ HCO_3^- → 1.2 mm Hg ↓ P_{CO_2}
Metabolic alkalosis	Each 1 mEq/L ↑ HCO_3^- → 0.7 mm Hg ↑ P_{CO_2}
Respiratory acidosis	
Acute	Each 1 mm Hg ↑ P_{CO_2} → 0.1 mEq/L ↑ HCO_3^-
Chronic	Each 1 mm Hg ↑ P_{CO_2} → 0.3 mEq/L ↑ HCO_3^-
Respiratory alkalosis	
Acute	Each 1 mm Hg ↓ P_{CO_2} → 0.2 mEq/L ↓ HCO_3^-
Chronic	Each 1 mm Hg ↓ P_{CO_2} → 0.4 mEq/L ↓ 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 pCO_2 is:

  $$(1.5 \times HCO_3^-) + 8 \pm 2$$

Example 3

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

What is the acid-base disturbance?
What do you suspect?

Combined metabolic acidosis and respiratory alkalosis: salicylate poisoning?

Metabolic acidosis

Serum anion gap

$[Na^+] - ([Cl^-] + [HCO_3^-])$

= Unmeasured anions - Unmeasured cations

(Normal range: 8 - 12)

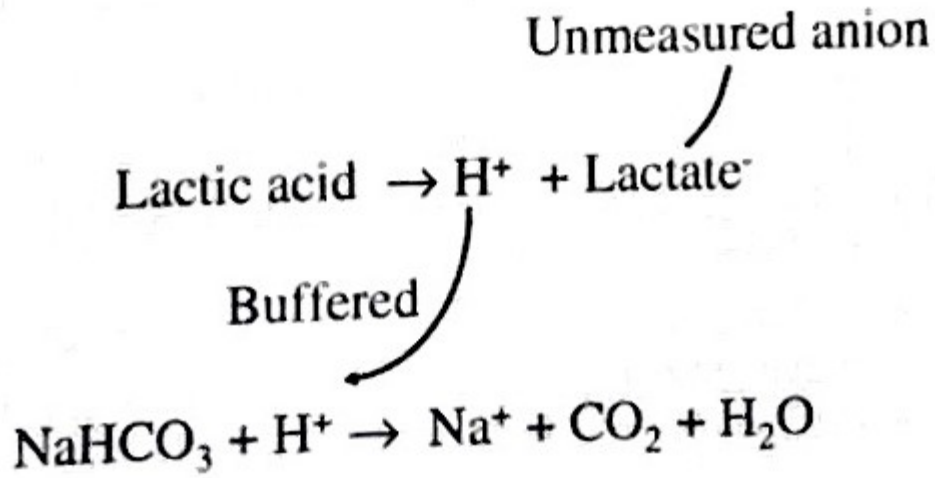
Serum anion gap

Unmeasured anions	Unmeasured cations
Albumin	K
PO_4	Ca
SO_4	Mg
Lactate	Immunoglobulins
Pyruvate	

Correction of the anion gap

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

Cause of anion-gap acidosis



High anion gap metabolic acidosis

Methanol	Rhabdomyolysis
Uremia	Toluene abuse
Diabetic ketoacidosis	
Paraldehyde	Type B lactic acidosis (metformin, NNRTI)
Ischemia	D-lactic acidosis
Lactic acidosis	
Ethylene glycol & ethanol	Propylene glycol
Salicylates	5-oxoprolinuria

What is the unmeasured anion?

Methanol	Formate
Ethylene glycol	Oxalate
Propylene glycol	Lactate
Toluene	Hippurate
Ketoacidosis	Acetoacetate
	β-hydroxybutyrate
Uremia	Sulfate
	Phosphate
	Urate

Type B lactic acidosis 2° to nucleoside reverse transcriptase inhibitors (NRTI)

- Inhibition of mitochondrial DNA polymeraso-γ
- DDI and stavudine most common cause
- 2 mth - 2 yr after start of Rx
- Risk factors: Female gender, low GFR, low CD4
- N/V, abdo pain, fatigue, wt loss
- Can be induced by drug interaction (tenofovir increases AUC of DDI by 50%)
- 30-60% mortality

D-lactic acidosis

Pathogenesis

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

Clinical features

Short bowel syndrome with malabsorption

Episodes of ΔMS associated with CHO intake

AG metabolic acidosis with elevated D-lactate

Spontaneous resolution if NPO

Commonly used intravenous drugs containing propylene glycol

Drug	% by volume
Lorazepam, 2 mg/mL	80
Phenobarbital, 30-130 mg/mL	70
Diazepam, 5 mg/mL	40
Pentobarbital, 50 mg/mL	20-40
Phenytoin, 50 mg/mL	40
Trimethoprim-sulfamethoxazole, 16:80 mg/mL	40
Etomidate, 2 mg/mL	35
Nitroglycerin, 5 mg/mL	30
Esmolol, 250 mg/mL	25

Arroliga 2004 Crit Care Med, 32(8):1709

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 Δ anion gap/Δ HCO_3^- should 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

Example 4

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?

Primary anion-gap metabolic acidosis
Primary respiratory acidosis

Example 4

Na 136, K 3.5, Cl 90, HCO_3 18

pH 7.20, PCO_2 45 mm Hg

Anion gap = 136-90-18=28

ΔAnion gap = 28-10 = 18 mM

ΔHCO_3^- = 24-18 = 6 mM

$\Delta AG/\Delta HCO_3^-$ = 18/6 = 3

Alternatively:

Adding the ΔAG of 18 to the HCO_3^- of 18 corrects it to 36 mM.

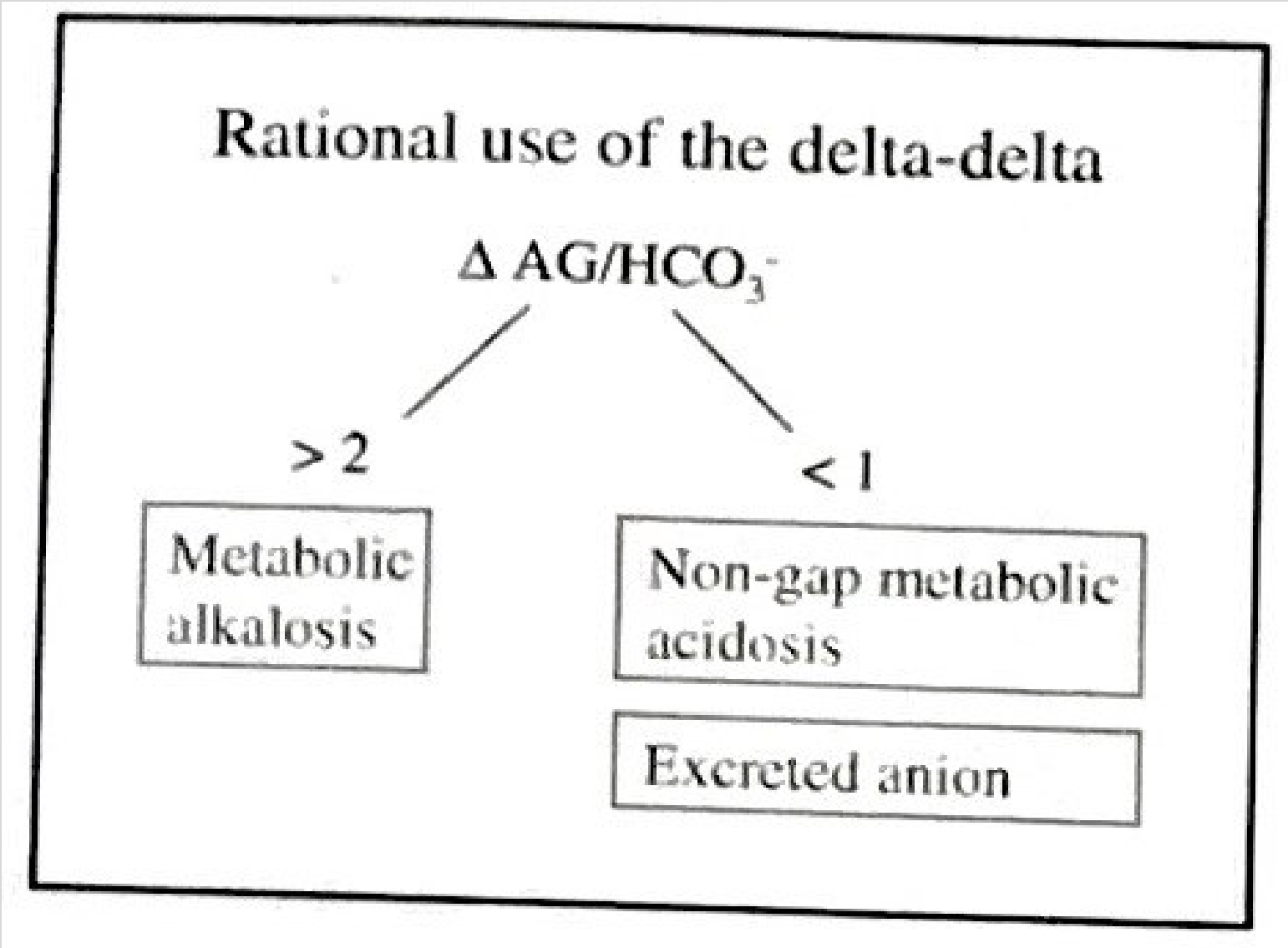
Pitfalls in interpretation of the Δ/Δ

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)

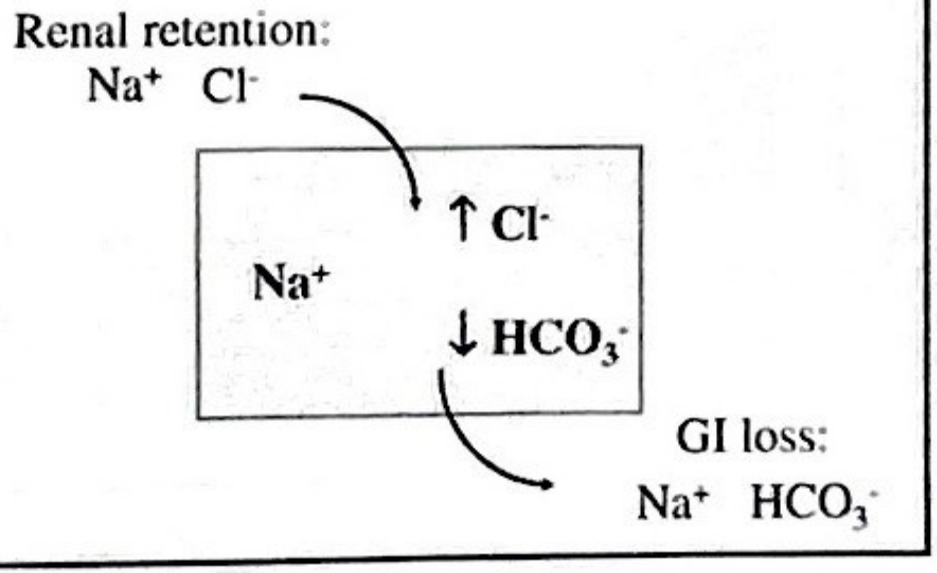
Many unmeasured acid anions are rapidly renally excreted

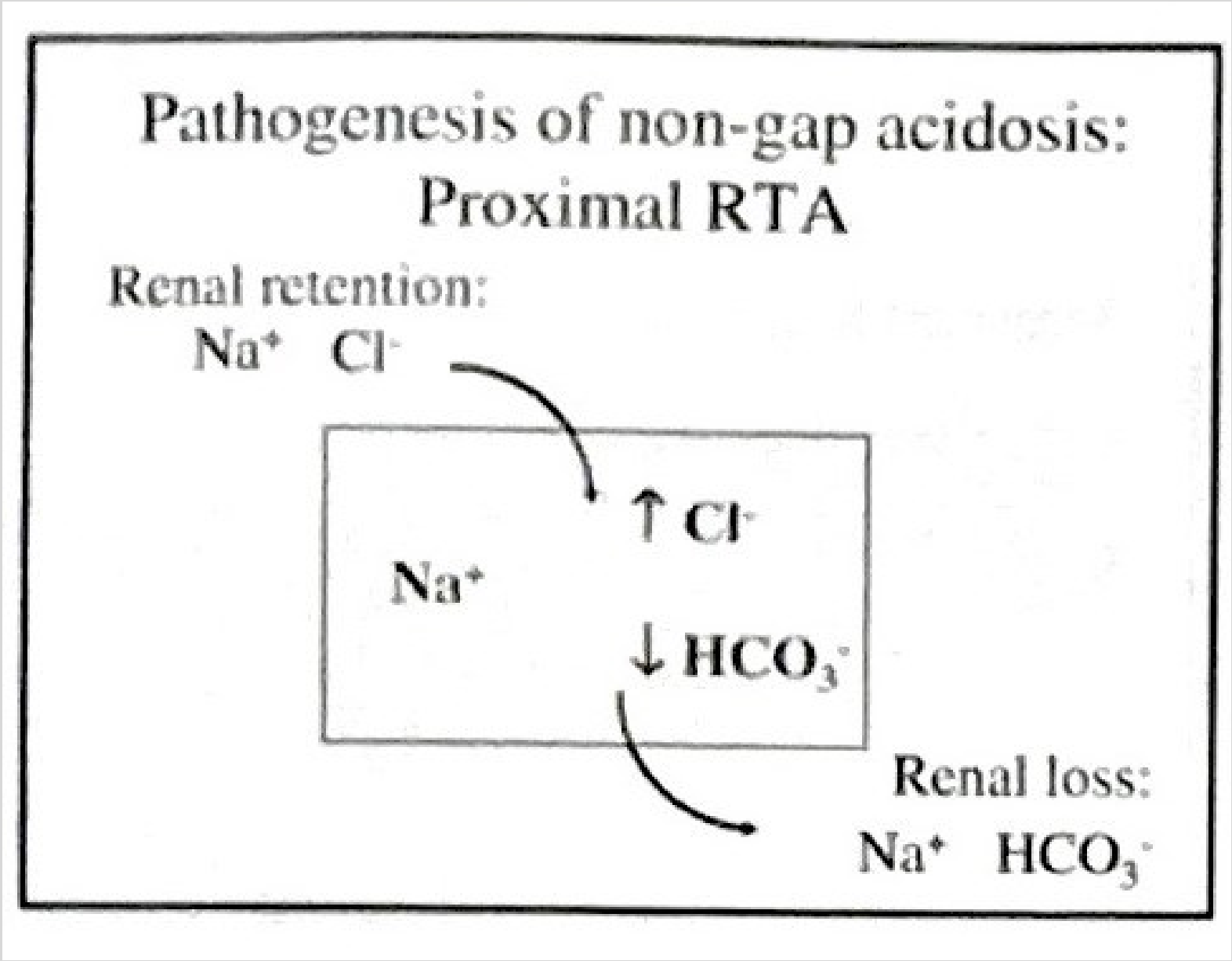

Rational use of the delta-delta
Δ AG/HCO3-
> 2
< 1
Metabolic alkalosis
Non-gap metabolic acidosis
Excreted anion

Non-gap (hyperchloremic) metabolic acidosis

- Lower GI bicarbonate loss
- Renal tubular acidosis
- Dilutional acidosis

Pathogenesis of non-gap acidosis: Diarrhea

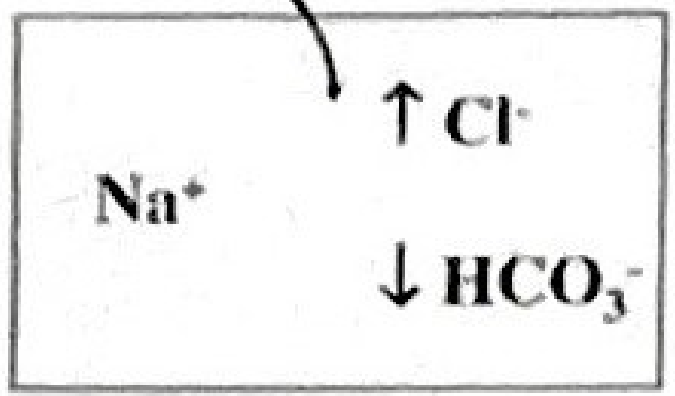



Pathogenesis of non-gap acidosis:
Proximal RTA
Renal retention:
Na+ Cl-
↑ Cl-
Na+
↓ HCO3-
Renal loss:
Na+ HCO3-

Pathogenesis of non-gap acidosis: Distal RTA

Renal retention:

H^+ Cl^-



Diagnosis of RTA

Determination of the urine anion gap

Urine anion gap = $[Na^+] + [K^+] - [Cl^-]$

Normal < 0

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

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

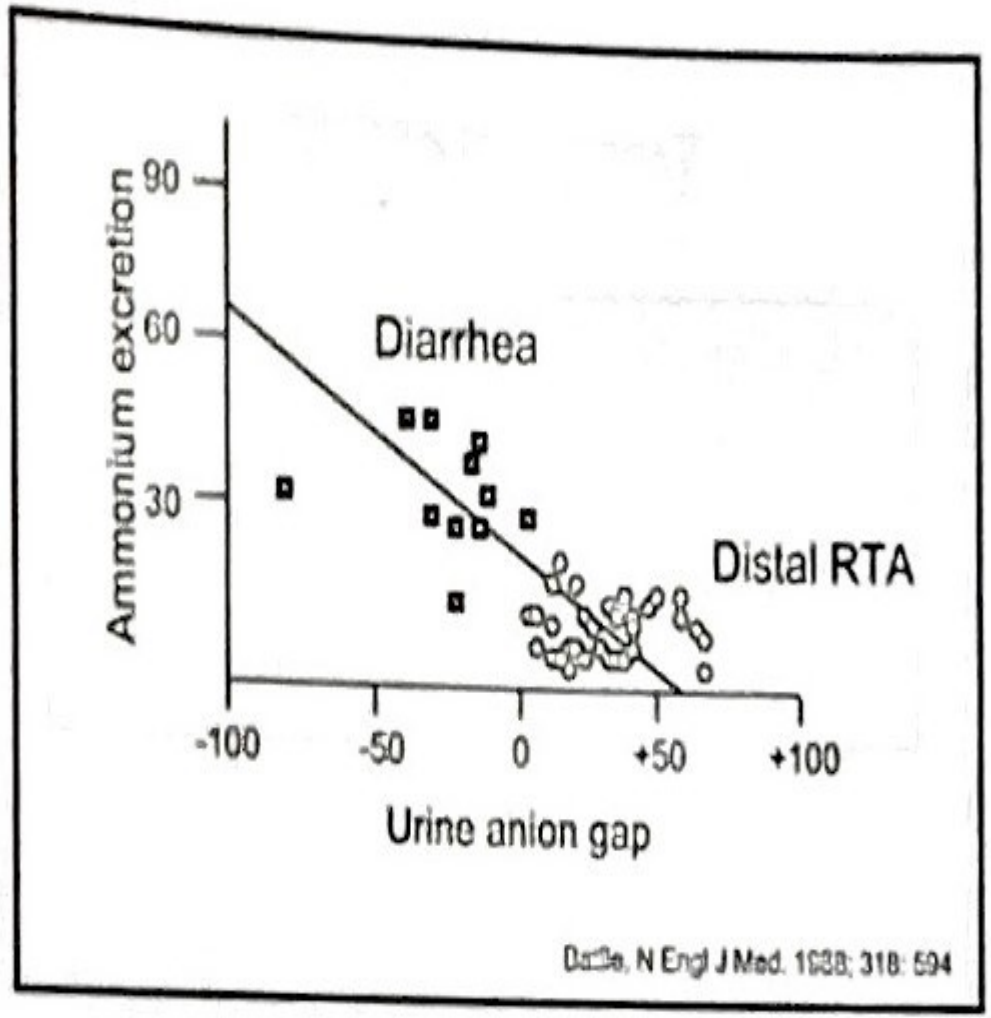
= Unmeasured anions - unmeasured cations

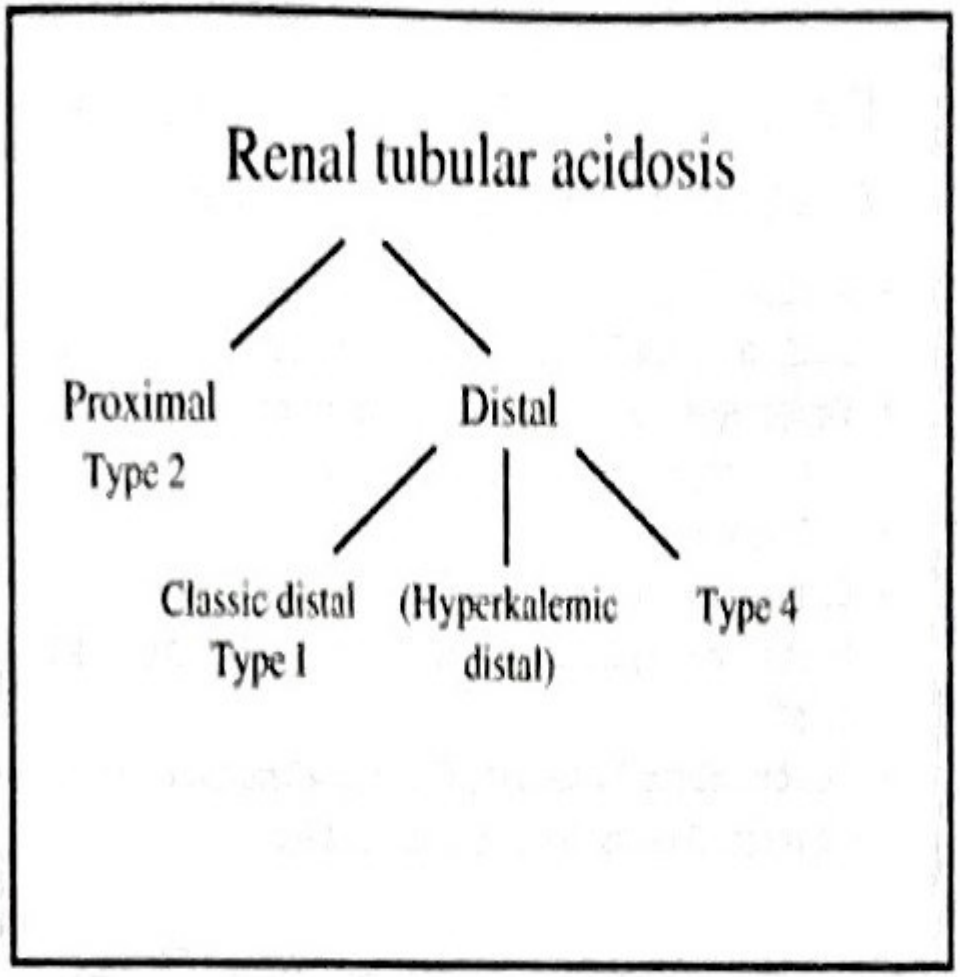
Sulfate	Calcium
Phosphate	Magnesium
Bicarbonate	NH_4^+
Organic anions	

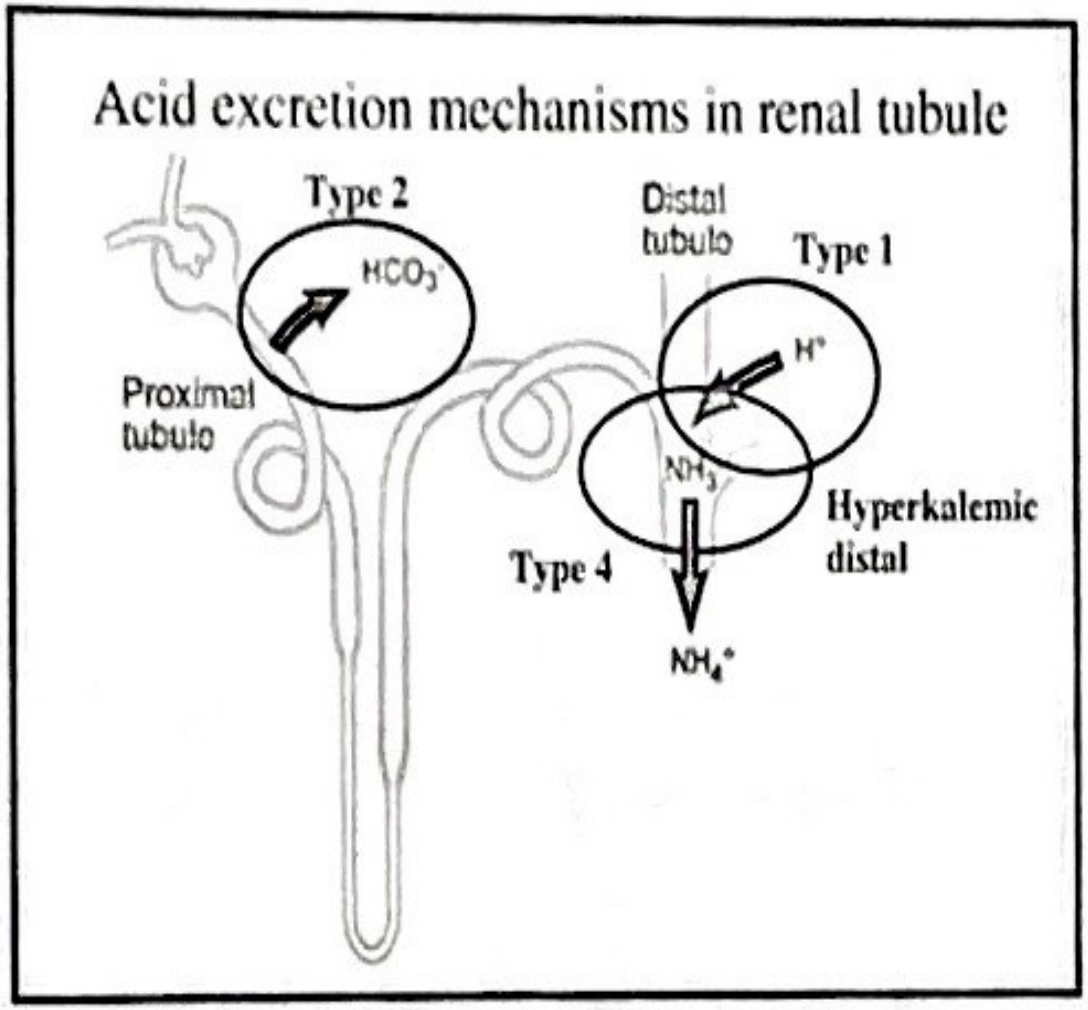
Urine anion gap

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

=> Urine AG should be LOW


Ammonium excretion
90
60
30
Diarrhea
Distal RTA
-100
-50
0
+50
+100
Urine anion gap


Renal tubular acidosis
Proximal
Type 2
Distal
Classic distal
Type I
(Hyperkalemic
distal)
Type 4



Clinical features of RTA

	Diarrhea	Proximal RTA	Distal RTA		
			Type I	Type 4	Hyperkalemic distal
Serum K^+		⇩		⇧	
Urine AG	Negative	Variable		Positive	
Urine pH	Variable		>5.5	<5.5	>5.5
Other		Fanconi syndrome	Nephro-calcinosis		

Fanconi syndrome

- Hypokalemia, non-gap metabolic acidosis

plus

- Glycosuria despite normoglycemia
- Generalized amino-aciduria
- Hypophosphatemia and urinary phosphate wasting ($F_EPO_4 > 5\%$)
- Hypouricemia

Causes of RTA

Proximal RTA	Distal RTA		
	Type I	Type 4	Hyperkalemic distal
Cystinosis	Hereditary		
	Medullary sponge kidney		
Myeloma	Sjogren's	Hyporeninemic hypoaldosteronism (CRF + DbN)	
LCDD	SLE		
Ifosfamide	Cirrhosis		
NNRTI	Amphotericin	Sickle cell	Sickle cell
		SLE	SLE
		Obstruction	Obstruction
		HIV	HIV

Treatment of RTA

Proximal RTA	Distal RTA		
	Type I	Type 4	Hyperkalemic distal
Na & K bicarbonate 2-4 mEq/kg/d	K bicarbonate or citrate 1-3 mEq/kg/d	Control of hyperkalemia (diuretics, polystyrene sulfate)	

EVALUATION OF PATIENT WITH ACID-BASE DISTURBANCE

The initial step in evaluation of any patient is the history, focusing on the gastrointestinal, renal, respiratory and neurologic systems, and medication list, and the physical exam, focusing on respiratory rate and volume status. Next the arterial pH is measured to determine whether there is acidemia or alkalemia. The direction of changes in serum bicarbonate and PCO_2 are used to discern the presence of underlying metabolic or respiratory disorders, respectively. The direction and degree of any compensatory responses are next assessed. Inadequate or excessive compensation generally points to a mixed acid-base disorder.

Metabolic acidosis

The serum anion gap is the most useful test for distinguishing disorders with a high anion gap (the commonest are lactic acidosis, ketoacidosis, intoxication with ethylene glycol, methanol, salicylates, and renal failure) from those with a normal gap (diarrhea, renal tubular acidosis and dilutional acidosis). In anion gap acidoses, comparison of the magnitude of the increased gap to the severity of the acidosis (the "delta-delta") may suggest the presence of a mixed disorder due to superimposed metabolic alkalosis (delta-delta > 1) or non-gap acidosis (delta-delta < 1). In the presence of potential intoxication, measurement of the serum osmolality and calculation of the osmolar gap may indicate the presence of additional osmotically active solutes such as ethanol, methanol, ethylene glycol, or isopropanol. Newer causes of gap acidosis that the clinician should be aware of include D-lactic acidosis, 5-oxoprolinuria, and propylene glycol intoxication. In the non-gap acidoses, the urine anion gap should be measured. An elevated urine anion gap suggests either inadequate urine ammonium, or (rarely) the presence of urine bicarbonate, and point to renal tubular acidosis, while a negative gap is consistent with diarrhea. The various forms of renal tubular acidoses can usually be distinguished by the serum K, urine pH, and the presence of any associated abnormalities such as nephrocalcinosis or Fanconi syndrome. Proximal renal tubular acidoses generally require considerably more alkali to correct than distal renal tubular acidoses. Type IV renal tubular acidoses are usually treated by lowering the serum potassium with diuretics or ion exchange resins.