Acid base balance

Normal serum electrolyte and arterial blood gas values (ABG values)

- pH 7.35-7.45
- HCO_3^- 22-26mmol/L (Av. 24 mmol/L)
- Cl^- 96-106 mmol/L
- K^+ 3.5-5 mmol/L
- Na^+ 135-145 mmol/L
- pO_2 80-100mmHg
- pCO_2 35-45 mmHg (Av.40 mmHg)

MECHANISM OF REGULATION OF PH

- First line of defence: Buffers
  (instantaneous)

- Second line of defence: Respiratory regulation
  (6-24hr)

- Third line of defence: Renal regulation
  (24h-5days)

Renal regulation is supplemented by: Liver

Bicarbonate Buffer System

- **Most important buffer of ECF.**
- **$CO_2 + H_2O$------H_2CO_3**

Phosphate Buffer

’

- Mainly intracellular, effective at a wide pH range
- Most important buffer in the urine (K_2HPO_4 / KH_2PO_4)
- Even in mild acidosis, bone phosphate is released into plasma to maintain the ratio
- In chronic acidosis, bone could be decalcified

Protein Buffers

Buffering capacity depends on the amino acids in the protein (ionizable side-chains)

ROLE OF LUNGS IN ACID BASE BALANCE

- The lungs prevent an increase in the Pco2 in the blood by excreting the CO2 that the body produces the rapid pulmonary response (usually within 6 to 24 hours) to changes in the CO2 concentration occurs via central sensing of the Pco2 and a subsequent increase or decrease in ventilation to maintain a normal Pco2 (35-45 mm Hg).

- An increase in ventilation decreases the Pco2, and a decrease in ventilation increases the Pco2.

ROLE OF KIDNEY IN ACID BASE BALANCE

Kidney regulates acid base homeostasis by 3 mechanisms:

Proton secretion

Bicarbonate reabsorption

Bicarbonate generation

- Acidosis ® H+ secreted ® acidic urine
- Alkalosis ® HCO3- excreted ® alkaline urine

SECRETION OF PROTONS

- Protons from fixed acids are constantly secreted by proximal tubular cells, distal tubular cells and collecting duct cells in to the lumen

- Predominantly Na+- dependent in proximal tubules

- Relatively Na+- independent in distal tubules and collecting ducts, either ATP driven proton pump or H + -K+ ATPase

BICARBONATE REABSORBTION

- Occurs mainly in proximal tubules
- Na+-K+ ATPase on basolateral membrane moves Na+ from tubular cell to interstitium
- The low intracellular Na+ drives the entry of Na+ from tubular lumen to cell, helps in easy secretion of H+
- No net gain of bicarbonate
- No net loss of hydrogen ions
- Maintains steady state but cannot correct an acidosis

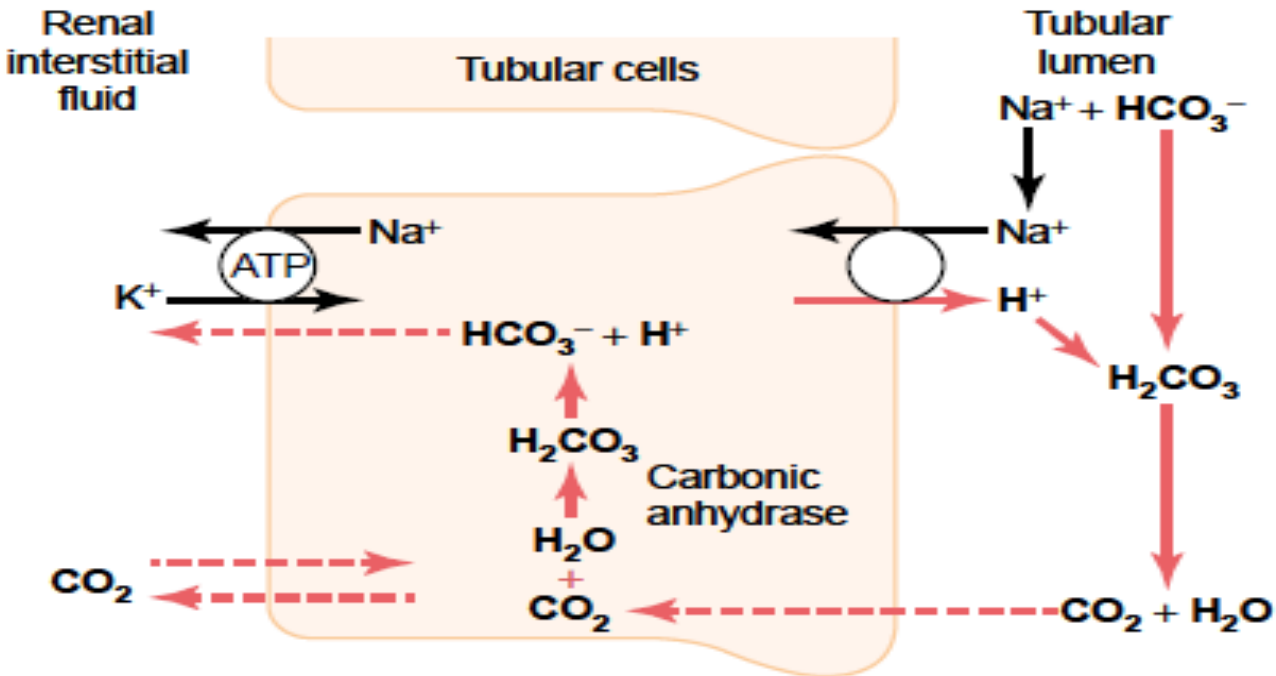


Figure 30–5

Cellular mechanisms for (1) active secretion of hydrogen ions into the renal tubule; (2) tubular reabsorption of bicarbonate ions by combination with hydrogen ions to form carbonic acid, which dissociates to form carbon dioxide and water; and (3) sodium ion reabsorption in exchange for hydrogen ions secreted. This pattern of hydrogen ion secretion occurs in the proximal tubule, the thick ascending segment of the loop of Henle, and the early distal tubule.

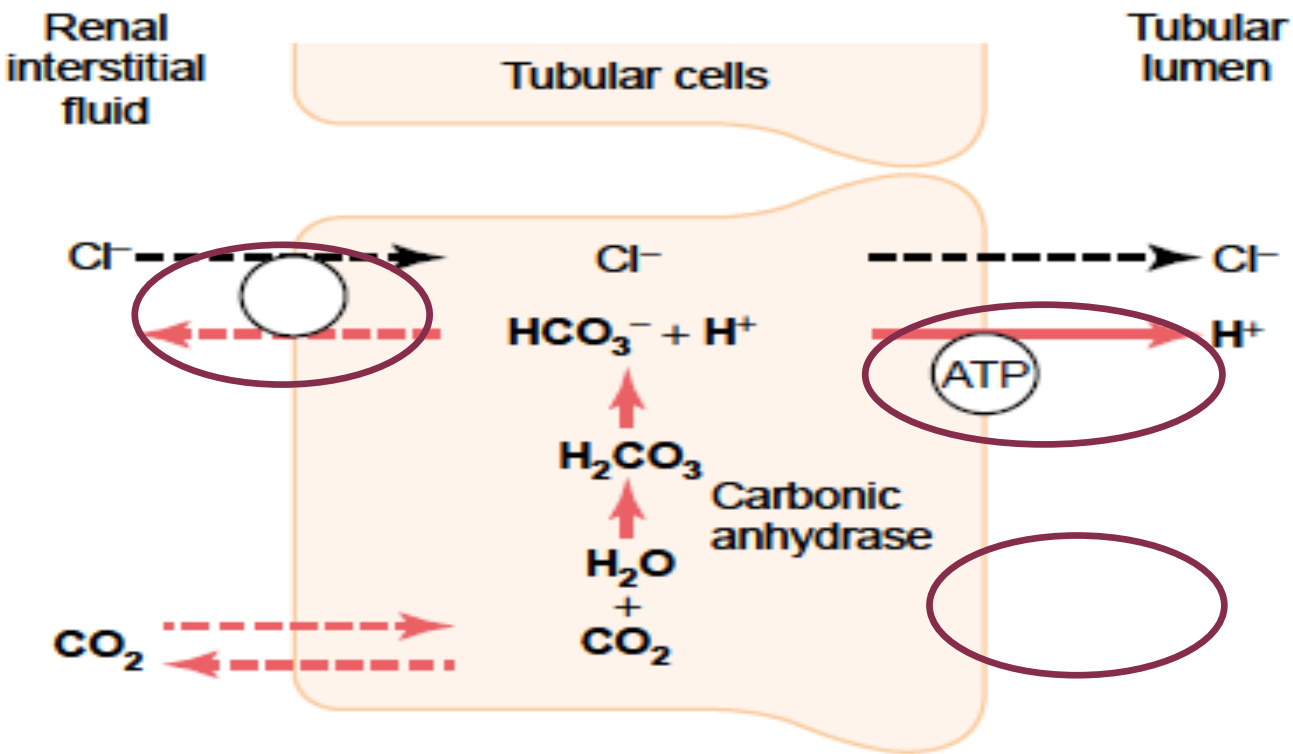


Figure 30–6

Primary active secretion of hydrogen ions through the luminal membrane of the intercalated epithelial cells of the late distal and collecting tubules. Note that one bicarbonate ion is absorbed for each hydrogen ion secreted, and a chloride ion is passively secreted along with the hydrogen ion.

BICARBONATE GENERATION

- Production of new bicarbonate to add to alkali reserve

- Net loss of protons from the body
- Net gain of bicarbonate

- Can correct an acidosis

- Depends on the presence of other buffer bases Eg. Phosphate, ammonia
- Phosphate buffer functions mainly in distal tubules and collecting ducts
- Ammonia buffer functions mainly in proximal tubules and collecting ducts

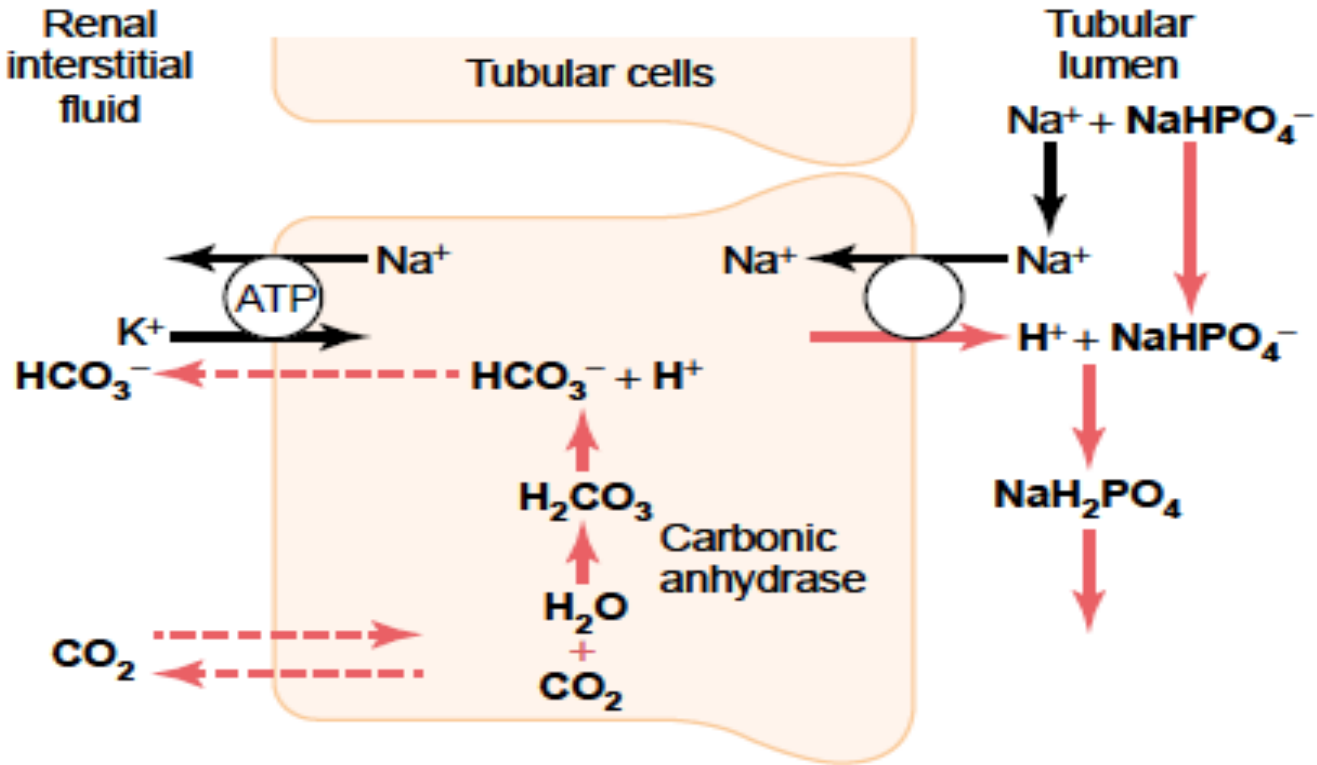


Figure 30–7

Buffering of secreted hydrogen ions by filtered phosphate ($NaHPO_4^-$). Note that a new bicarbonate ion is returned to the blood for each $NaHPO_4^-$ that reacts with a secreted hydrogen ion.

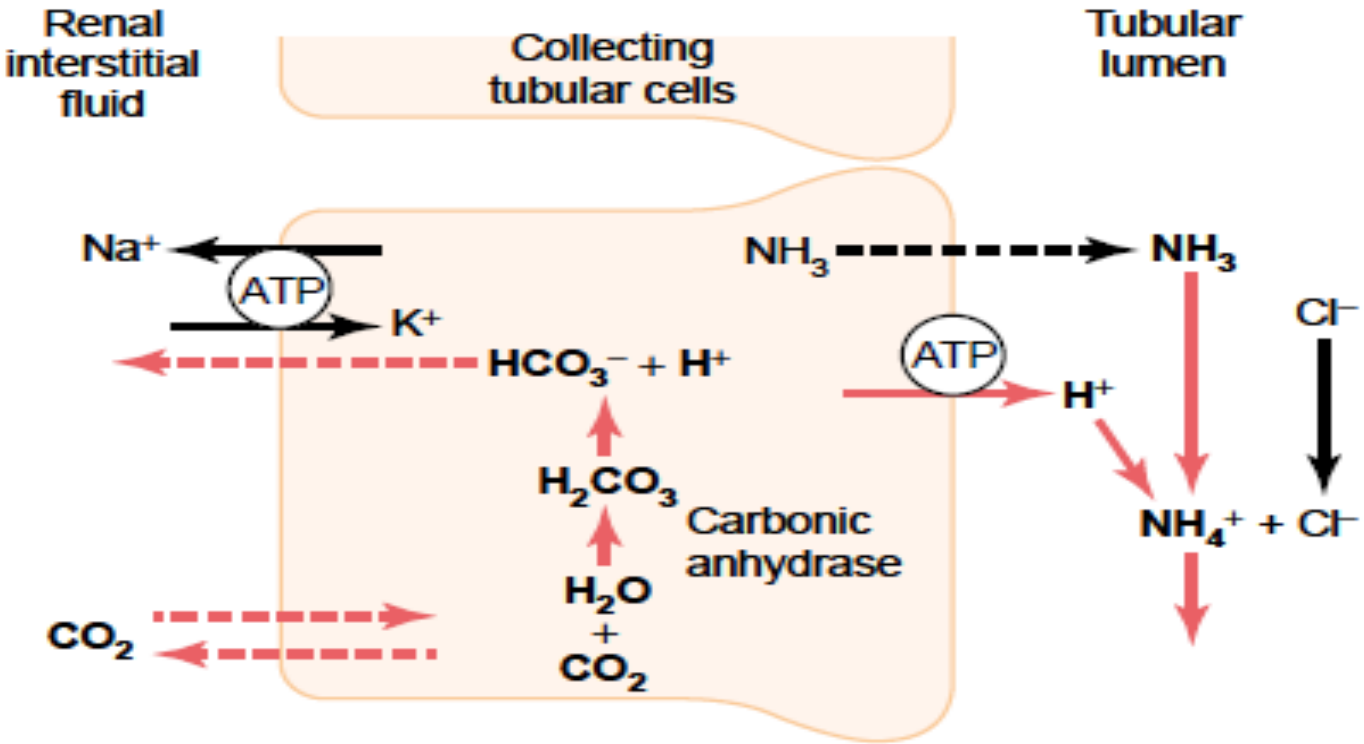


Figure 30–9

Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules. Ammonia diffuses into the tubular lumen, where it reacts with secreted hydrogen ions to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

ROLE OF AMMONIA BUFFER IN BICARBONATE GENERATION

- Functions when all other buffers have been depleted
- Very important in severe or chronic acidosis

ACIDOSIS

- **Acidemia: Decrease in blood pH (below 7.38)**
- **Acidosis: Any process that can lead to acidemia.**
- **Acidosis can be respiratory (due to change in pCO2) or metabolic (due to change in [HCO3-])**

COMPENSATORY RESPONSE

- Body tries to correct the disorder by an adaptive response
- Adaptive (compensatory) response is in the direction of the primary disturbance (in simple disturbances)
- Compensatory response tries to restore the pH to normal

ANION GAP

- Normally, [cations] = [anions] for electrical neutrality
- Plasma cations measured in lab are Na+ & K+ (contributes to 95% of total cations)
- Plasma anions measured in the lab are HCO3- & Cl- (contributes to 80% of total anions)
- Anion gap = difference between the conc.of measured cations and measured anions
- Represents the unmeasured anions in plasma

ANION GAP

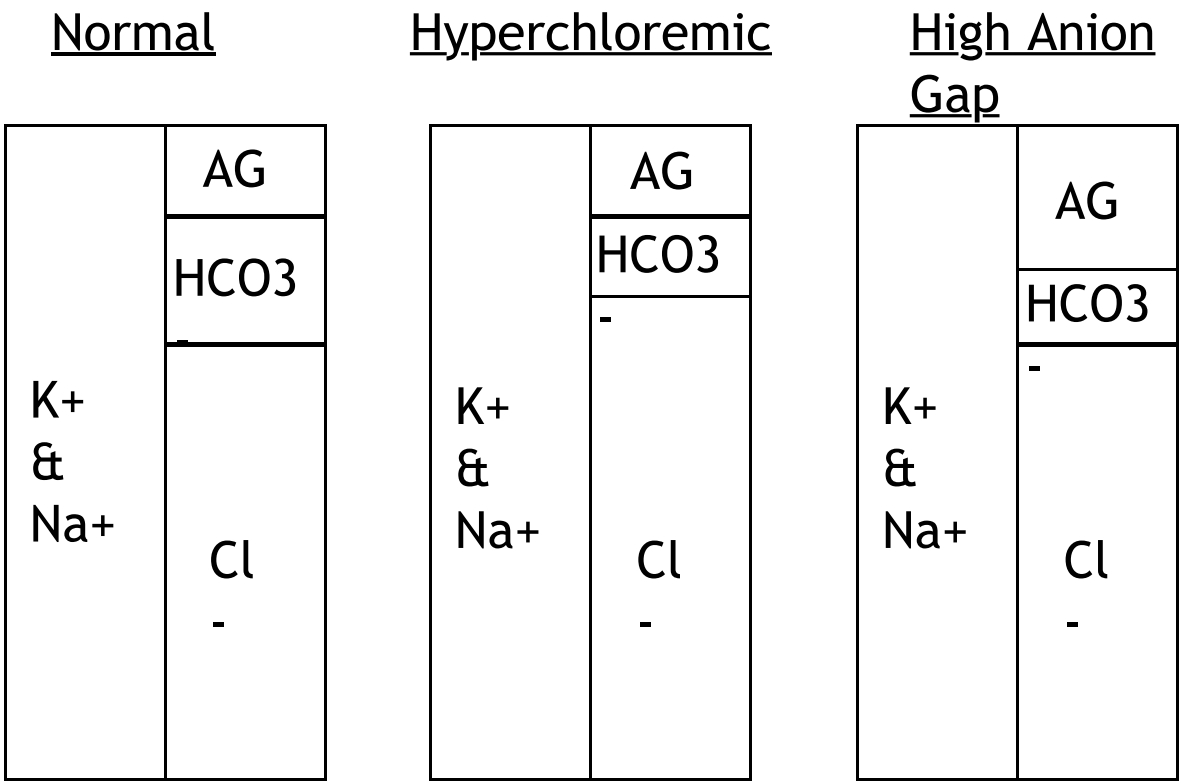
- Unmeasured anions include protein , phosphate, sulfate, urate & organic acids

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

Normal anion gap is 12-14 mEq/L

ANION GAP

METABOLIC ACIDOSIS



METABOLIC ACIDOSIS

- **Primary change: ↓ [HCO3-]**
- **Compensatory change: Hyperventilation (to↓pCO2)**
- **Causes:**

Normal anion gap (hyperchloremic)	High anion gap (normochloremic)
Renal tubular acidosis	Ketoacidosis
Diarrhea	Lactic acidosis
Carbonic anhydrase inhibitors	Renal failure
Hypoaldosteronism	Toxins

PH AND PLASMA POTASSIUM

- During acidemia, there may be exchange of H+ in blood with K+ in ICF to maintain pH of blood
- Therefore, acute acidosis → hyperkalemia

  acute alkalosis → hypokalemia
- When you try to correct acidosis, K+ may suddenly go back to cells→ hypokalemia
- Hence, important to maintain potassium balance during correction of acidosis

- Hypoalbuminemia can mask an increased concentration of gap ions and lowering the value of AG
- Adjusted AG = AG +2.5 x (normal albumin – actual albumin)

Example: Pt. albumin 2.0g/dL and AG 15

15 + 2.5 x (4 – 2) = 15 + 5
Adjusted AG = 20

- Ex :

Na+ = 138

HCO3- = 14

Cl- = 108

K+ = 4

Anion Gap = (138+4) – (108+14)

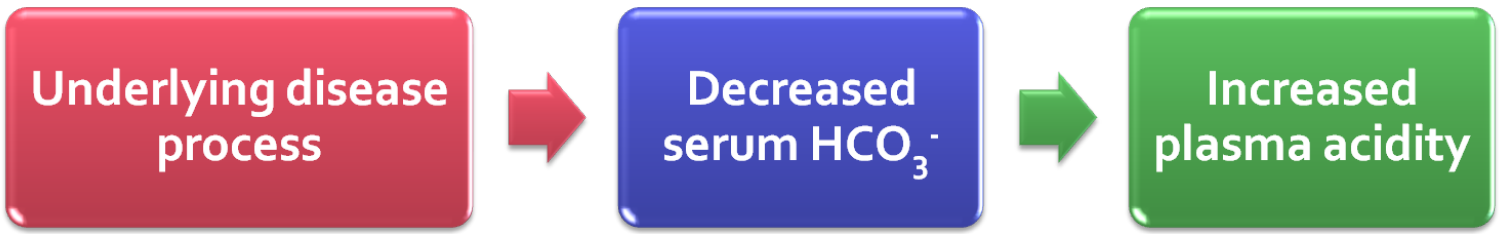
= 20 □ wide anion Gap

THANK YOU

Metabolic Acidosis

Diagnosis and Treatment

Metabolic Acidosis



Clinical Manifestations

- The clinical manifestations are related to the degree of acidemia!

- The underlying disorder usually produces most of signs and symptoms with mild to moderate metabolic acidosis.

- Compensation and less severe acidemia.. have fewer manifestations

- At a serum pH less than **7.20**, there is impaired **cardiac contractility** and an increased risk of **arrhythmias**, especially if underlying heart disease or other predisposing electrolyte disorders are present.

- With acidemia there'll be a **decrease in the CV response to catecholamine**, potentially exacerbating hypotension in children with volume depletion or shock.

- Acidemia causes **vasoconstriction** of the pulmonary vasculature.

- Chronic metabolic acidosis causes **failure to thrive**.

Clinical Manifestations

- Respiratory compensation(Hyperventilation) in patients with metabolic acidosis:
- The body compensates for metabolic acidosis by creating hyperventilation which create respiratory alkalosis.
- This mechanism may subtle with mild metabolic acidosis but can cause increased respiratory effort with worsening acidosis.

Clinical Manifestations

- The acute metabolic effects of acidemia include:

- **Insulin resistance**
- **Increased protein degradation**
- **Reduced ATP synthesis**

Clinical Manifestations

- The acidemia causes the potassium to shift from intracellular to extracellular space thereby there will be **Hyperkalemia**.

- Severe acidemia will impair brain metabolism and eventually may result in lethargy and coma.

Metabolic acidosis

- The primary defect is decreased serum HCO3.
- Calculation of the anion gap is used to help narrow differential diagnosis.
- **AG = Na – (Cl + HCO3)**
- Normal **AG = 12 +/- 2** and is made of phosphate, sulfates, organic acids and negatively charged proteins.

Classification of Metabolic Acidosis by Anion Gap:

- Metabolic Acidosis with Increased AG *(Also called high anion gap metabolic acidosis - HAGMA)*
- Metabolic Acidosis with Normal AG *(Also called Non-AG metabolic acidosis or hyperchloremic metabolic acidosis - NAGMA)*
- Metabolic Acidosis with Decreased AG

Metabolic Acidosis with:

Decreased Anion Gap

- Are less commonly seen.
- May be caused by:

- Hypoalbuminemia
- multiple myeloma
- ingestion of bromide and lithium.

Metabolic acidosis with:

Increased AG

- The differential of the most common causes of an anion gap acidosis is remembered by the mnemonic **MUDPILES**.
- Besides history and physical examination, evaluation of serum ketones, serum lactate, toxicology screen, and salicylate level should be considered.

Differential Diagnosis of Metabolic Acidosis with Increased AG

M: Methanol
U: Uremia
D: DKA or Alcoholic ketoacidosis, Drugs.
P: Paraldehyde
I : Ischemia , Isoniazide or Iron toxicity
L : Lactate [Lactic acidosis]
E : Ethylene glycol (antifreeze)
S : Starvation or Salicylates.

Metabolic acidosis:

1. Ketosis:
   1. DKA
   2. Starvation
   3. Alcohol ketoacidosis
2. Poisoning:
   1. Ethylene glycol (Antifreeze)
   2. Paraldehyde
   3. Methanol

Metabolic Acidosis with: Normal AG

- Also referred to as a non-anion gap acidosis, although anion gap is present but normal.
- In this group, the increased anion is chloride, and anion gap does not change.
- Therefore, is sometimes referred to as **hyperchloremic acidosis**.
- The mnemonic for the most common causes of a non-AG acidosis is **DURHAM**.

Differential Diagnosis of metabolic acidosis with normal AG

- **D** : Diarrhea
- **U** : Ureteral diversion
- **R** : Renal tubular acidosis
- **H** : Hyperalimentation: Administration or consumption of nutrients beyond minimum normal requirements, in an attempt to replace nutritional deficiencies.
  A : Acetazolamide or Ammonium chloride
- **M** : Miscellaneous (amphotericin B, toluene*, others)

Urine anion gap

- May be helpful in the evaluation of patients with non-AG metabolic acidosis; to differentiate RTA from other causes(GI).

UAG = NA + K – CL

- Positive UAG means Renal cause.
- Negative UAG means GI and other causes.

Diagnosis and Approach

- *The etiology of a metabolic acidosis is often apparent from the history and examination.*
- ***Acutely, diarrhea*** *and hypoperfusion are common causes of a metabolic acidosis. Hypoperfusion, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, shock, or heart*
- *disease.*
- ***Failure to thrive*** *suggests a chronic metabolic acidosis, as happens with renal insufficiency or RTA.*
- ***New onset of polyuria*** *occurs in children with undiagnosed* ***diabetes mellitus and DKA.***
- ***Metabolic acidosis with seizures and/or a depressed sensorium****, especially in an infant, warrants consideration of an inborn error of metabolism.*
- ***meningitis and sepsis with lactic acidosis*** *are a more common explanation for metabolic acidosis with neurologic signs and symptoms.*
- ***Identification of toxic ingestions****, such as ethylene glycol or methanol, is especially important because of the potential excellent response to specific therapy. they may be*
- *prescribed or accidentally ingested.*
- ***Hepatomegaly and metabolic acidosis*** *may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.*

Investigations

- Basic laboratory tests in a child with a metabolic acidosis should include measurments of BUN , Creatinine , Glucose , Urinalysis and serum Electrolyte, ketones.

- ***Metabolic acidosis***, *hyperglycemia, glycosuria, and* ***ketonuria*** *support a diagnosis of diabetic ketoacidosis.*
- *Less commonly, secondary to an inborn error of metabolism.*
- ***Starvation causes ketosis***, *but the metabolic acidosis, if present, is mild (HCO3- > 18).*
- ***metabolic acidosis with ketosis*** *occurs in* ***inborn errors of metabolism***; *these patients may have hyperglycemia, normoglycemia, or hypoglycemia.*
- ***Adrenal insufficiency*** *may cause metabolic acidosis and hypoglycemia.* ***Metabolic acidosis*** *with hypoglycemia occurs with liver failure.*
- ***Metabolic acidosis***, *normoglycemia, and glycosuria occur in children when type II // Fanconi syndrome*

- ***The serum potassium level*** *is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the intracellular space to the extracellular space, many patients with a metabolic acidosis have a low serum potassium level due to excessive body losses of potassium.*
- ***With diarrhea, there are high stool losses of potassium*** *and often secondary renal losses of potassium, whereas in type I or type II RTA there are increased urinary losses of potassium*
- ***DKA****, urinary losses of potassium are high, but the shift of potassium out of cells due to lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum potassium can be low, normal, or high, even though total body potassium is almost always decreased.*
- ***The serum potassium*** *is usually* ***increased*** *in patients with acidosis due to renal insufficiency; urinary potassium excretion is impaired.*
- ***The combination of metabolic acidosis, hyperkalemia****, and* ***hyponatremia*** *occurs in patients with severe aldosterone deficiency or aldosterone resistance.*
- ***Patients with less severe type IV RTA often have only hyperkalemia and metabolic acidosis.***
- ***Very ill children with metabolic acidosis*** *may have an elevated serum potassium level as a result of a combination of renal insufficiency, tissue breakdown, and shift of potassium from the intracellular space to the extracellular space secondary to the metabolic acidosis.*

Problem #1

- 10 yr male presents to the ED. You have no history other than he has been breathing rapidly and is less responsive than usual.

- Na+ 123 Cl- 99 HCO3- 5
- pH 7.31 pCO2 10

Clinical presentation

- Respiratory compensation in patients with metabolic acidosis:

- Equation **only** valid when primary disorder is **metabolic acidosis**; do not use this equation when the primary disorder is not a metabolic acidosis..
- If the measured pCO_2 is not close to what we predict; a second disorder coexists..
  - pCO_2 < expected respiratory alkalosis
  - pCO_2 > expected respiratory acidosis

Na+ 123 Cl- 99 HCO3- 5 pH 7.31 pCO2 10

Steps for Acid-Base Analysis

Step 1. Is there an acidemia or alkalemia?

Acidemia (Blood pH < 7.35)

Na+ 123 Cl- 99 HCO3- 5 pH 7.31 pCO2 10

Steps for Acid-Base Analysis

Step 2. Is the primary process metabolic or respiratory?

pCO2 = 10 should drive pH ↑
HCO3- = 5 should drive pH ↓

Na+ 123 Cl- 99 HCO3- 5 pH 7.31 pCO2 10

Steps for Acid-Base Analysis

Step 3: Is the respiratory compensation adequate?

The body compensates for metabolic acidosis by creating respiratory alkalosis. pCO2 may be predicted by the following equation:

(Winter's formula)

[1.5 (HCO3) + 8] +/- 2 = expected pCO2

The expected pCO2 is :

[1.5 (5) +8] +/- 2 = [13.5 – 17.5]

So this patient has extra CO2 washing ,,, tachypnic

Na+ 123 Cl- 99 HCO3- 5 pH 7.31 pCO2 10

Steps for Acid-Base Analysis

Step 4: Is there an anion gap?

Na+ - Cl- - HCO3- > 12?

123 - 99 - 5 = 19

Anion Gap Metabolic Acidosis

Na+ 123 Cl- 99 HCO3- 5 pH 7.31 pCO2 10

Steps for Acid-Base Analysis

Step 5: Are there any other metabolic disturbances?
the so-called Delta-Delta
delta AG – delta HCO3 = 0±5

Delta anion gap = (19-14) = 5
Delta HCO3 = (24-10) = 14
delta AG – delta HCO3 = 0±5
5-14 = - 9
So there are extra HCO3 losses either form the kidneys
?? RTA or severe diarrhea

Treatment :

The most effective therapeutic approach>>> underlying disorder.

Insulin in diabetic ketoacidosis or restoration of adequate perfusion in lactic acidosis .

The use of bicarbonate therapy… irreparable; examples include RTA and chronic renal failure.

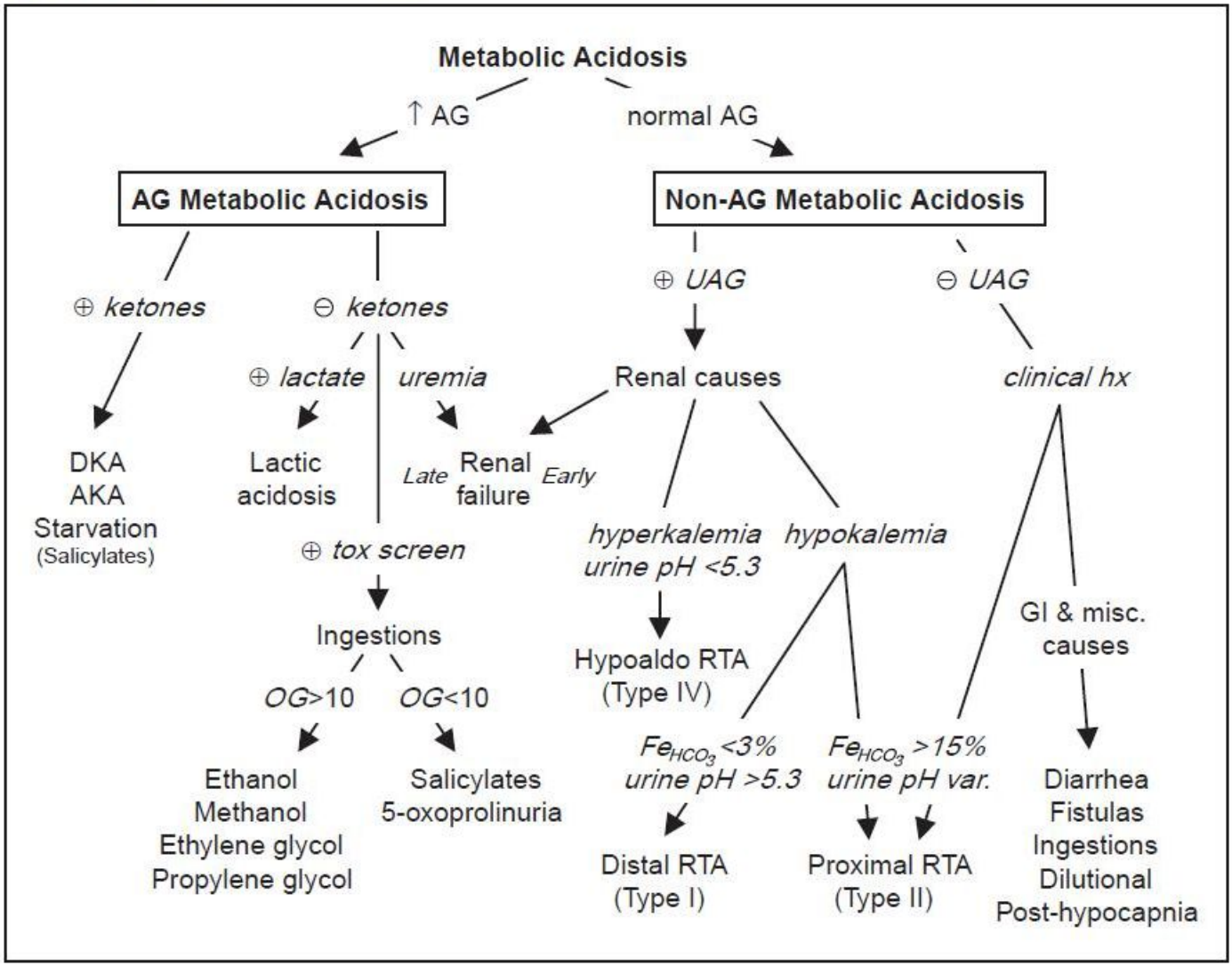
In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings and inborn errors of metabolism(e.g., ethylene glycol or methanol) and inborn errors of metabolism (e.g., pyruvate carboxylase deficiency or propionic acidemia). Some inborn errors of metabolism require chronic base therapy.

- Prevent the hypokalemia during treatment?

- Because hypokalemia can cause life-threatening cardiac arrhythmias.

-Hemodialysis is an appropriate choice in Pt with renal insufficiency especially if significant uremia or Hyperkalemia is also present.

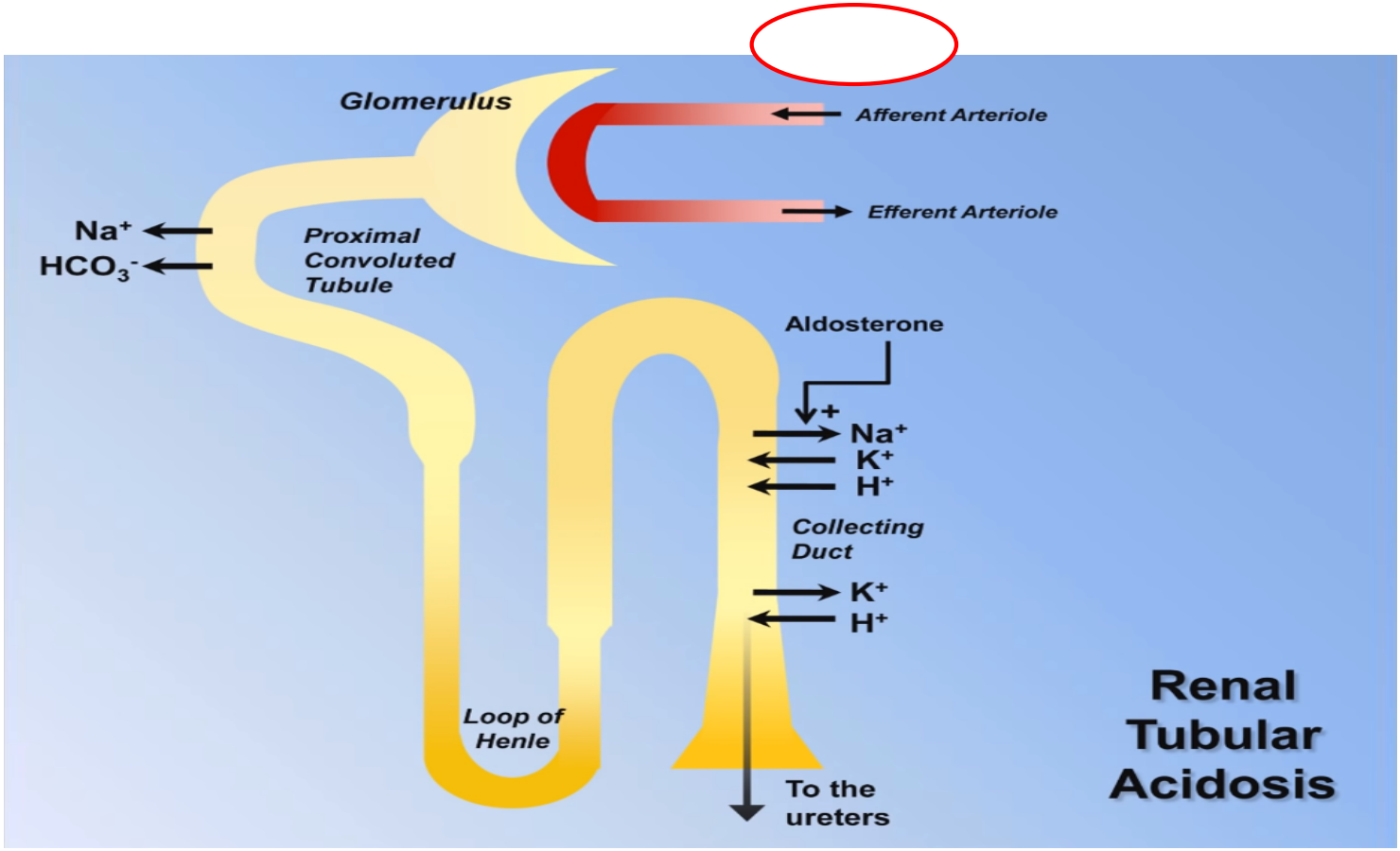
Figure 4-2 Approach to metabolic acidosis



Thank you

Renal Tubular Acidosis

- A group of transport defects characterized by
- a normal anion gap (hyperchloremic) metabolic acidosis in the setting of normal or near-normal glomerular filtration rate.
- may be inherited and persistent from birth or acquired, as is seen more commonly in clinical practice.


Glomerulus
Afferent Arteriole
Efferent Arteriole
Na+
HCO3-
Proximal Convoluted Tubule
Aldosterone
+
Na+
K+
H+
Collecting Duct
K+
H+
Loop of Henle
To the ureters
Renal Tubular Acidosis

Renal Tubular Acidosis

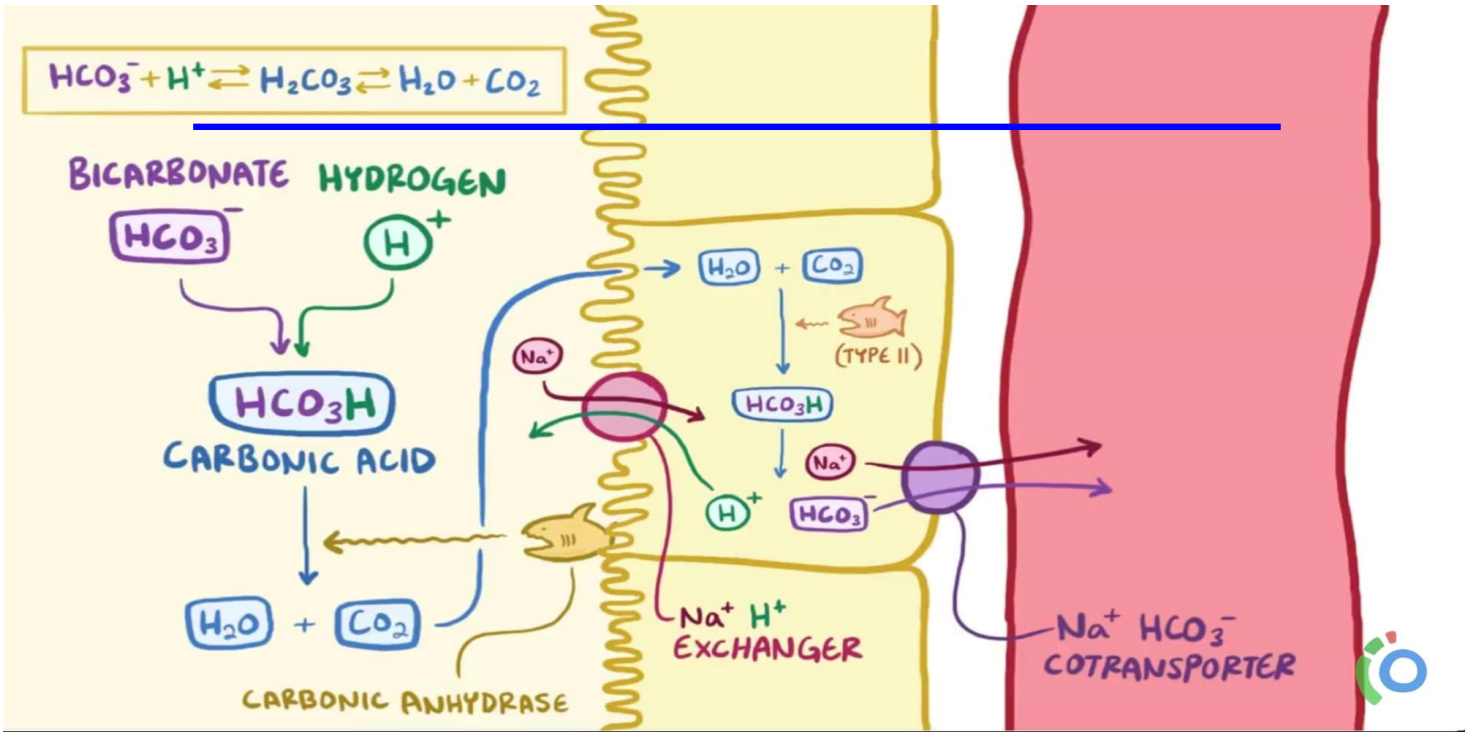
- **Proximal RTA (type 2)**
- **Classical distal RTA (type 1)**
- **Hyperkalaemic distal RTA (type 4)**

- **what about type 3 RTA (Mixed type) ?**

- Term inconsistently applied to a rare congintal deficiency of **carboic anhydrase II**, which result in features of both type 1 and type 2 RTA

Proximal RTA (type 2)

- **Proximal (type II) RTA is characterized by impairment of PCT reabsorption of bicarbonate**
- **Distal acidification mechanisms are intact.**
- The distal intercalated cells function normally, so the acidemia is less severe than dRTA and the alpha intercalated cells can produce H+ to acidify the **urine to a pH of less than 5.5**
- **In proximal RTA, the serum potassium concentration tends to be low.**
- Potassium wasting is a result of increased sodium delivery to the distal tubule promoting potassium excretion and causing secondary hyperaldosteronism.


$HCO_3^- + H^+ \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2$
BICARBONATE
HYDROGEN
HCO_3^-
H^+
HCO_3H
CARBONIC ACID
H_2O + CO_2
CARBONIC ANHYDRASE
Na^+
H_2O + CO_2
(TYPE II)
HCO_3H
Na^+
H^+
HCO_3^-
Na^+ H^+
EXCHANGER
Na^+ HCO_3^-
COTRANSPORTER

Proximal RTA (type 2)

- **Primary isolated proximal RTA** secondary to defective HCO3 reabsorption is rare,may occur as sporadic or inherited (AR).
- In children proximal RTA is usually part of **global proximal tubular dysfunction** or **Fanconi syndrome**, which is characterized by low-molecular-weight proteinuria, glycosuria, phosphaturia, aminoaciduria, and proximal RTA.
- Among inherited conditions **cystinosis** is commonly identified

Causes of Proximal RTA

- Primary
- Sporadic
- Inherited
- Inherited renal disease (idiopathic Fanconi)
  - Sporadic (most common)
  - Autosomal recessive
  - Autosomal dominant
  - X-linked (Dent disease)
- Inherited syndromes
  - Cystinosis
  - Oculocerebral dystrophy (Lowe syndrome)
  - Tyrosinemia type 1
  - Galactosemia
  - Wilson disease
- Hereditary fructose intolerance

- Secondary
- **Intrinsic renal disease**
  - Autoimmune diseases (Sjögren syndrome)
  - Hypokalemic nephropathy
  - Renal transplant rejection
- **Hematologic disease**
  - Myeloma
- **Drugs**
  - carbonic anhydrase inhibitors
  - Amphotericin-B
  - outdated tetracycline
  - Gentamicin
  - Sodium valproate
  - Ifosfamide
- **Heavy metals**
  - Lead / Cadmium/ Mercury
- **Organic compounds:** Toluene
- **Nutritional:** Kwashiorkor
- **Hormonal:** Primary hyperparathyroidism

Clinical manifestations of Proximal RTA

- Patients with isolated, sporadic, or inherited pRTA present with **failure to thrive** in the 1st yr of life.
- Additional symptoms can include **polyuria**, **dehydration** (from sodium loss), **anorexia**, **vomiting, constipation, and hypotonia.**
- Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as **rickets**.
- Those with systemic diseases present with additional signs and symptoms specific to their underlying disease.

Fanconi syndrome

- Fanconi's syndrome is a syndrome of inadequate reabsorption in the proximal renal tubules of the kidney. The syndrome can be caused by various underlying congenital or acquired diseases

- It is associated with glucosuria , phosphaturia,, proteinuria ,polyuria, dehydration,, and hypokalemia
- (leads to skeletal problems: rickets / impaired growth in children/ osteomalacia/ osteoporosis/ and pathological fractures in adults).

Aquired Causes include:

- ingesting expired tetracyclines, and as a side effect of tenofovir in cases of pre-existing renal impairment
- Multiple myeloma or monoclonal gammopathy of undetermined significance can also cause the condition

Inherited Causes include:

- Inherited Cystinosis is the most common cause of Fanconi syndrome in children.
- Other recognised causes are Wilson's disease, Lowe syndrome, tyrosinemia (type I) galactosemia, glycogen storage diseases, and hereditary fructose intolerance.

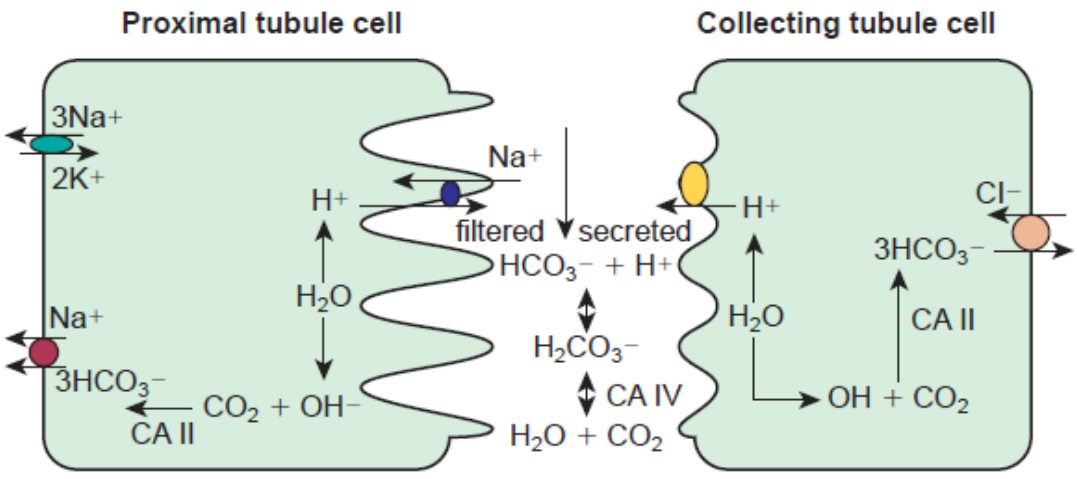
Treatment :

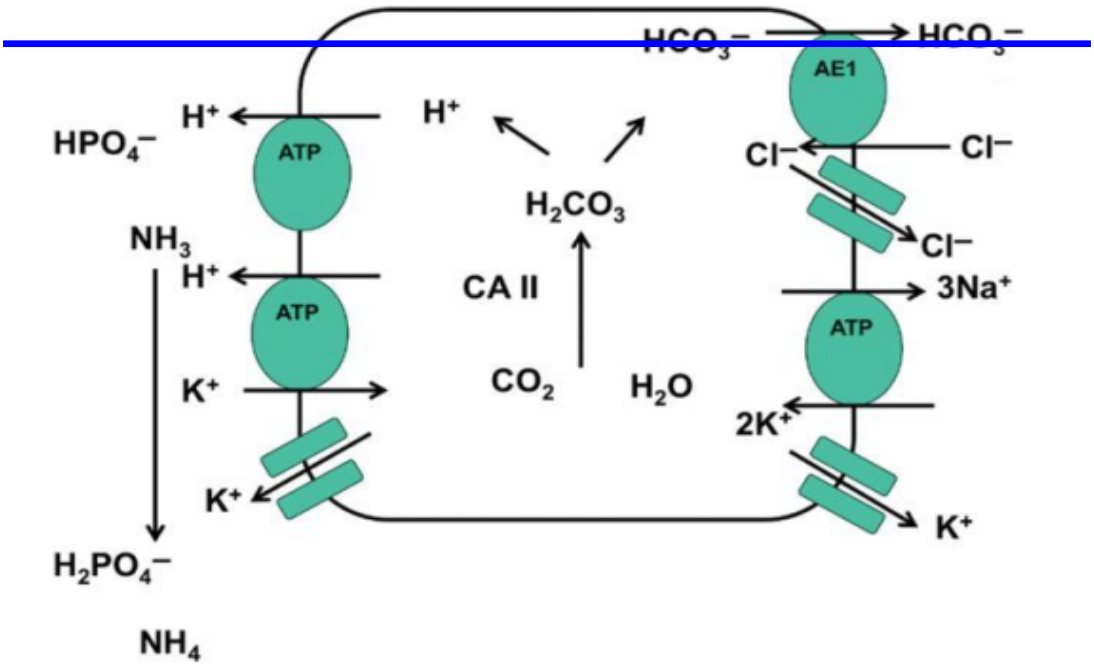
- Treat with
- phosphate ,
- potassium,
- alkali ,
- and salt supplementation
- as well as adequate hydration .

Distal (Type I) Renal Tubular Acidosis

PATHOGENESIS

- The distal nephron is responsible for secreting the acid generated from metabolism
- In distal RTA , this function is defective (defective proton secretion)




HCO_3^-
HCO_3^-
AE1
H^+
HPO_4^-
ATP
H^+
H_2CO_3
Cl^-
Cl^-
Cl^-
NH_3
H^+
ATP
CA II
$3Na^+$
ATP
K^+
CO_2
H_2O
$2K^+$
K^+
K^+
$H_2PO_4^-$
NH_4

- Distal RTA *can* be *sporadic or inherited*. It can also *occur* as a *complication* of *inherited or acquired diseases* of the *distal* tubules.
- *Primary or secondary* causes of distal RTA *can result* in *damaged or impaired functioning of one or more transporters or proteins involved in* the *acidification* process, *including* the *H+/ATPase* the *HCO3−/Cl− anion exchangers, or* the *components* of the *aldosterone pathway*.
- Distal RTA can be secondary to collagen vascular diseases such as Sjögren syndrome or drugs such as amphotericin B .

DISTAL RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Inherited

- Inherited renal diseases
  - Autosomal dominant
  - Autosomal recessive
  - Autosomal recessive with early-onset hearing loss
  - Autosomal recessive with later-onset hearing loss
- Inherited syndromes associated with type I renal tubular acidosis
  - Marfan syndrome
  - Wilson syndrome
  - Ehlers-Danlos syndrome
- Familial hypercalciuria

Secondary

Intrinsic renal

- Interstitial nephritis
- Pyelonephritis
- Transplant rejection
- Sickle cell nephropathy
- Lupus nephritis
- Nephrocalcinosis
- Medullary sponge kidney

Urologic

- Obstructive uropathy
- Vesicoureteral reflux
- Hepatic
- Cirrhosis

Toxins or medications

- Amphotericin B
- Lithium
- Toluene
- Cisplatin

Clinical features

- Because of *impaired hydrogen ion excretion*, *urine pH cannot be reduced* to *<5.5*, *despite* the *presence* of *severe metabolic acidosis*.

- *Loss* of *sodium bicarbonate distally*, *due* to *lack of H+ to bind* to *in* the *tubular lumen* , *results in increased chloride absorption* and *hyperchloremia .. So Hyperchloremic metabolic acidosis .*

- *Inability* to *secrete H+* is *compensated by increased K+ secretion distally*, leading to *hypokalemia*.
- The hypokalemia can be severe enough to cause muscle weakness,

Clinical features

- The chronic metabolic acidosis results in bone demineralization and hypercalciuria.
- Bone demineralization in distal RTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA so *Bone disease* is *common*.
- Citrate is an important factor increasing the solubility of urinary calcium. The increased calcium excretion along with hypocitraturia, the result of increased citrate absorption by the proximal tubule due to acidosis and hypokalemia, leads to nephrocalcinosis.
- It has long been known that acidosis decreases renal citrate excretion, whereas alkalosis increases it .

Clinical manifestations

- Distal RTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of distal RTA include nephrocalcinosis and hypercalciuria.

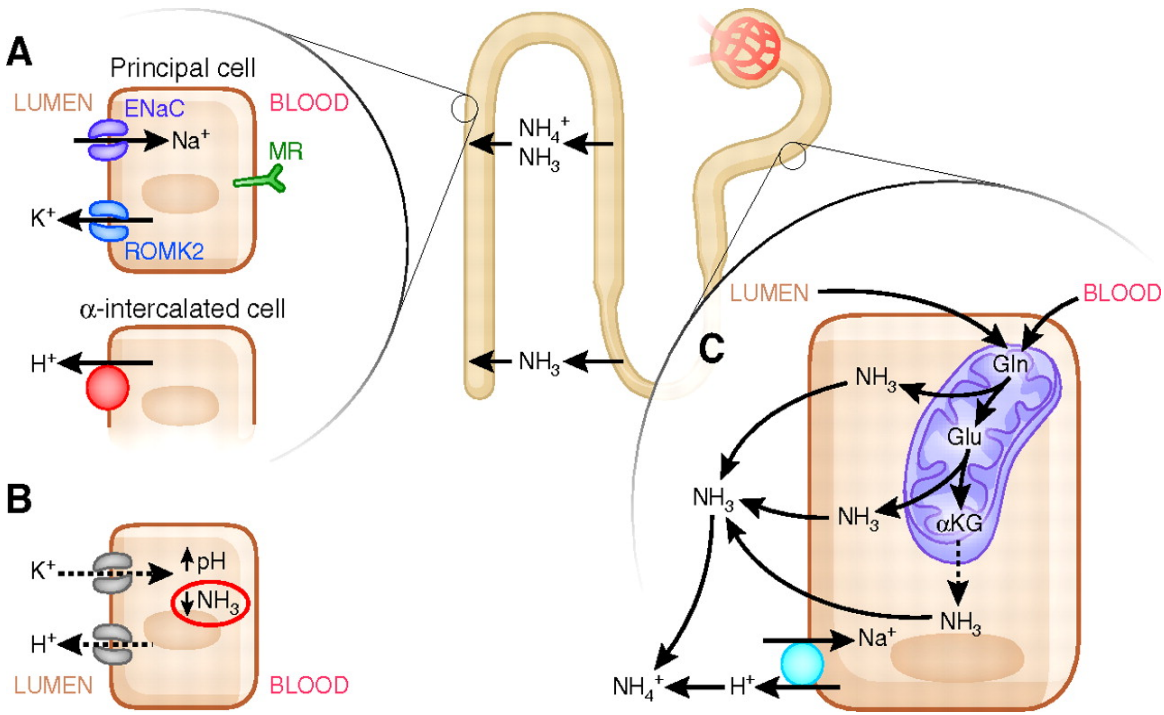
- The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent.
- H /ATPase deficincey autosomal recessive form is associated with sensorineural deafness.

Hyperkalemic (Type IV) Renal Tubular Acidosis
PATHOGENESIS

1-occurs as the result of *impaired aldosterone production* (*hypoaldosteronism*) or

2- impaired renal responsiveness to aldosterone (*pseudohypoaldosteronism*).

- *Acidosis* results *because aldosterone* has a *direct effect* on the *H+/ATPase* responsible *for hydrogen secretion*.
- In addition, *aldosterone* is a *potent stimulant* for *potassium secretion* in the *collecting tubule*; consequently, *lack* of *aldosterone results* in *hyperkalemia*. This further *affects acid–base* status *by inhibiting ammoniagenesis and*, thus, *H+ excretion*.


A
Principal cell
LUMEN
ENaC
BLOOD
Na+
MR
K+
ROMK2
α-intercalated cell
H+
B
K+
pH
NH3
H+
LUMEN
BLOOD
NH4+
NH3
NH3
C
LUMEN
BLOOD
NH3
Gln
Glu
NH3
αKG
NH3
NH3
Na+
NH4+
H+

Causes of type 4 RTA

- Aldosterone deficiency typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia.
- In children, aldosterone unresponsiveness is a more common cause of type IV RTA.
- This can occur transiently, during an episode of acute pyelonephritis or acute urinary obstruction,
- or chronically, particularly in infants and children with a history of obstructive uropathy.
- Angiotensin-converting enzyme inhibitors and chronic heparin administration can result in hypoaldosteronism.

HYPERKALEMIC RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Genetic

- Hypoaldosteronism
- Addison disease
- Congenital adrenal hyperplasia
- Pseudohypoaldosteronism (type I or II)

Secondary

Urologic

- Obstructive uropathy

Intrinsic renal

- Pyelonephritis
- Interstitial nephritis

Systemic

- Diabetes mellitus
- Sickle cell nephropathy

Drugs

- Trimethoprim/sulfamethoxazole
- Angiotensin-converting enzyme inhibitors
- Cyclosporine
- Prolonged heparinization

Addison disease

CLINICAL MANIFESTATIONS

- Patients with type IV RTA can present with growth failure in the first few years of life. Polyuria and dehydration (from salt wasting) are common.
- Rarely, patients (especially those with pseudohypoaldosteronism type 1) present with life-threatening hyperkalemia.
- Patients with obstructive uropathies can present acutely with signs and symptoms of pyelonephritis, such as fever, vomiting, and foul-smelling urine.
- Laboratory tests reveal a hyperkalemic non–anion gap metabolic acidosis , Urine may be alkaline or acidic .
- Elevated urinary sodium levels with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

TABLE 13-7. CLINICAL AND LABORATORY MANIFESTATIONS OF VARIOUS RENAL TUBULAR ACIDOSES

	Type 1 (Classic, Distal)	Type 2 (Proximal)	Type 4 (Aldosterone Deficiency)
Growth failure	+++	++	+++
Serum potassium	Normal or low	Normal or low	High
Nephrocalcinosis	Frequent	Rare	Rare
Low citrate excretion	+++	±	±
Fractional excretion of filtered HCO_3 at normal serum HCO_3 levels	<5%	5%-10%	<10%
Daily alkali treatment (mEq/kg)	1-3	5-20	1-3
Daily potassium requirement	Decreases with correction	Increases with correction	
Urine pH	>5.5	<5.5	<5.5
Presence of other tubular defects	Rare	Common	Rare

DIAGNOSTIC APPROACH TO RTA
summary

- The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis,
- identify electrolyte abnormalities,
- assess renal function, and rule out other causes of bicarbonate loss such as diarrhea .
- Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with correction of volume depletion.
- Patients with protracted diarrhea can deplete their total-body bicarbonate stores and can have persistent acidosis despite apparent restoration of volume status.

- In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores.
- If acidosis persists beyond a few days in this setting, additional studies are indicated.
- Serum electrolytes, blood urea nitrogen, calcium, phosphorus, creatinine, and pH should be obtained by venous puncture.

DIAGNOSTIC APPROACH TO RTA

- If tachypnea is noted, evaluation of an arterial blood gas might help to rule out the possibility of a mixed acid-base disorder primarily involving respiratory and metabolic components.
- A detailed history, with particular attention to growth and development, recent or recurrent diarrheal illnesses, and a family history of mental retardation, failure to thrive, end-stage renal disease, infant deaths, or miscarriages is essential.
- Physical examination should determine growth parameters and volume status as well as the presence of any dysmorphic features suggesting an underlying syndrome.

- Urine analyis

- Once the presence of a non–anion gap metabolic acidosis is confirmed, **urine pH** can help distinguish distal from proximal causes.
- A urine pH <5.5 in the presence of acidosis suggests pRTA,
- whereas patients with distal RTA 1 typically have a urine pH >6.0.
- **The urine anion gap** ([urine Na+ + urine K+] − urine Cl−) is sometimes calculated to confirm the diagnosis of distal RTA.
- A positive gap suggests a deficiency of ammoniagenesis and, thus, the possibility of a distal RTA.
- A negative gap is consistent with proximal tubule bicarbonate wasting or (gastrointestinal bicarbonate wasting).

- A urinalysis should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction.
- Random or 24 hr urine calcium and creatinine measurements will identify hypercalciuria. Renal ultrasonography should be performed to identify underlying structural abnormalities such as obstructive uropathies as well as to determine the presence of nephrocalcinosis

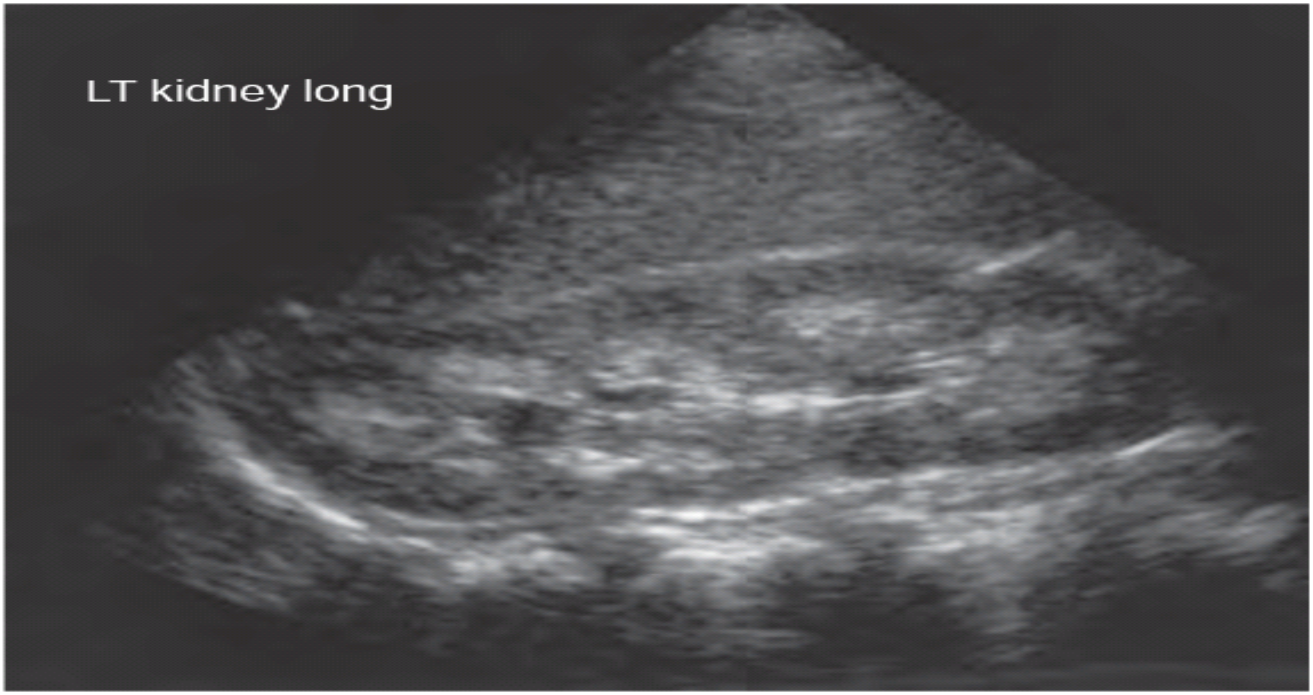


Figure 529-2 Ultrasound examination of a child with distal RTA demonstrating medullary nephrocalcinosis.

TREATMENT AND PROGNOSIS

- The mainstay of therapy in all forms of RTA is bicarbonate replacement.
- Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution (Bicitra or Shohl solution).
- The base requirement for distal RTAs is generally in the range of 2-4 mEq/kg/24 hr, although patients' requirements can vary.

- Patients with Fanconi syndrome usually require phosphate supplementation.
- Patients with distal RTA should be monitored for the development of hypercalciuria. Those with symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis can require thiazide diuretics to decrease urine calcium excretion.
- Patients with type IV RTA can require chronic treatment for hyperkalemia with sodium-potassium exchange resin (Kayexalate).

prognosis

- *Prognosis* of RTA depends to a large part on the nature of any existing *underlying disease*. Patients with *treated isolated proximal* or *distal RTA* generally *demonstrate improvement in growth*, provided serum bicarbonate levels can be maintained in the normal range.
- Patients *with systemic illness and Fanconi* syndrome can *have* ongoing *morbidity with growth failure*, *rickets*, and *signs* and *symptoms* related to their *underlying disease*.

Rickets Associated with Renal Tubular Acidosis

- Rickets may be present in primary RTA, particularly in type II RTA. Hypophosphatemia and phosphaturia are common in the renal tubular acidoses, which are also characterized by hyperchloremic metabolic acidosis, various degrees of bicarbonaturia, and, often, hypercalciuria and hyperkaluria.
- Bone demineralization without overt rickets usually is detected in type I) distal RTA.(

- This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures.

- the circulating levels of 1,25(OH)2D in patients with either type of RTA are generally normal unless patients with RTA have chronic renal insufficiency, serum 1,25(OH)2D levels are reduced in relation to the degree of renal impairment.
- In addition, "*double osteomalacia*" may be evident *when* patients with either type of RTA also *have vitamin D deficiency.*

Management of RTA assoiated rickets

- Bone demineralization in distal RTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA.
- Administration of sufficient bicarbonate to reverse acidosis reverses bone dissolution and the hypercalciuria that is common in distal RTA.
- Proximal RTA is treated with both bicarbonate and oral phosphate supplements to heal rickets.
- *Vitamin D* is required to *offset* the *secondary hyperparathyroidism* that *complicates oral phosphate* therapy.

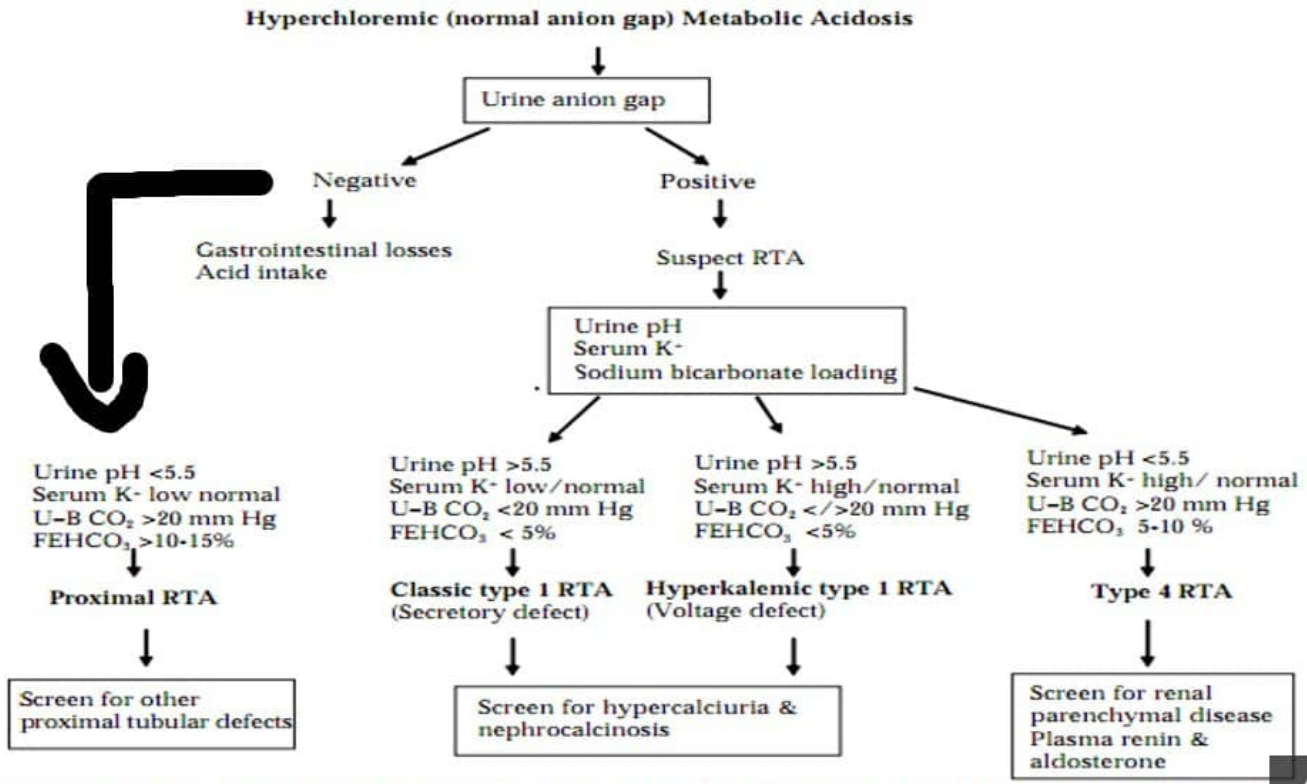
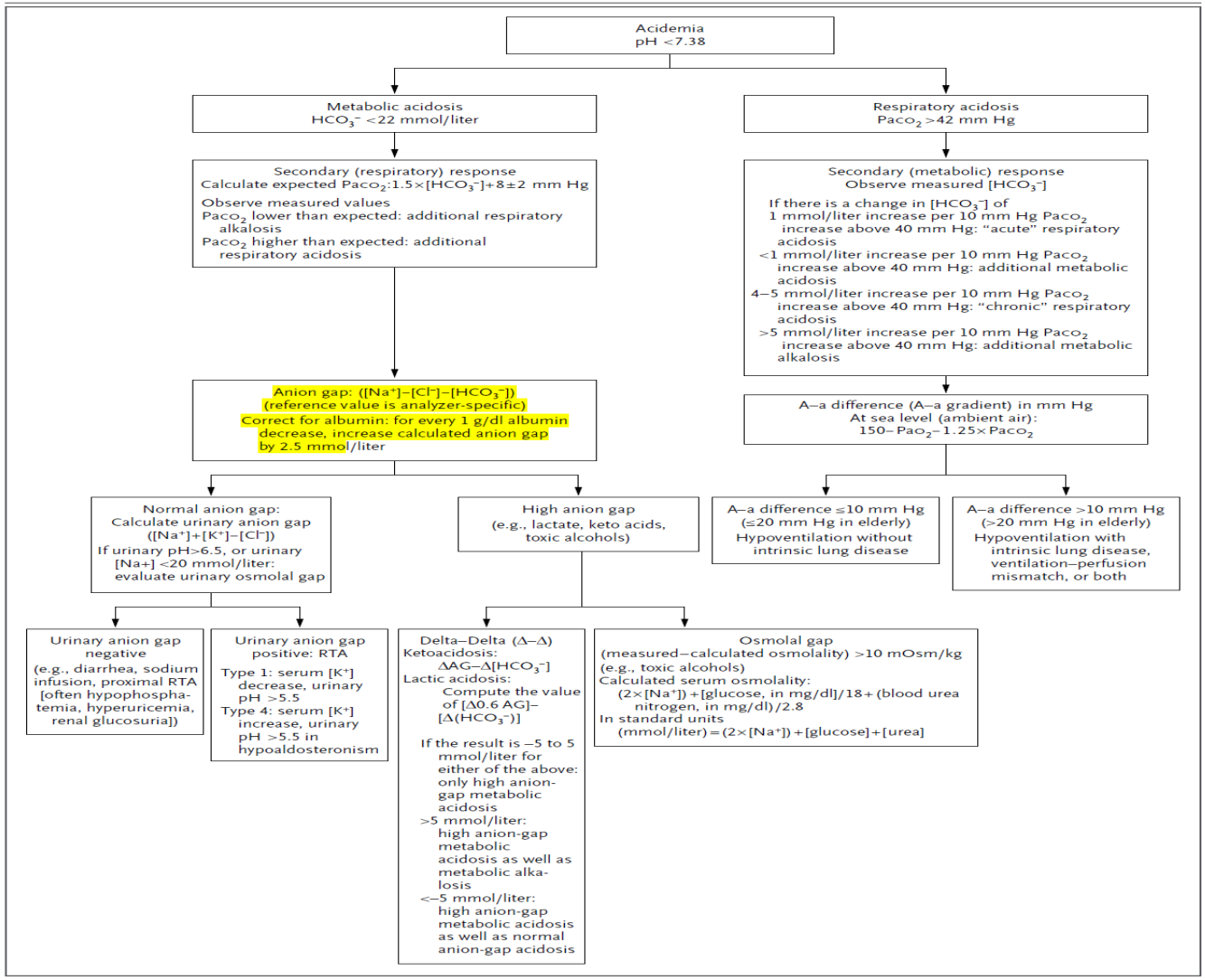


Fig. 6. Evaluation of a patient with renal tubular acidosis. GI: gastrointestinal, U-B CO_2: urine to blood PCO_2 gradient, $FEHCO_3$ fraction excretion of HCO_3^-


Acidemia
pH <7.38
Metabolic acidosis
HCO_3^- <22 mmol/liter
Respiratory acidosis
$Paco_2$ >42 mm Hg
Secondary (respiratory) response
Calculate expected $Paco_2$:1.5×[HCO_3^-]+8±2 mm Hg
Observe measured values
$Paco_2$ lower than expected: additional respiratory alkalosis
$Paco_2$ higher than expected: additional respiratory acidosis
Secondary (metabolic) response
Observe measured [HCO_3^-]
If there is a change in [HCO_3^-] of
1 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: "acute" respiratory acidosis
<1 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: additional metabolic acidosis
4–5 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: "chronic" respiratory acidosis
>5 mmol/liter increase per 10 mm Hg $Paco_2$ increase above 40 mm Hg: additional metabolic alkalosis
Anion gap: ([Na^+]–[Cl^-]–[HCO_3^-])
(reference value is analyzer-specific)
Correct for albumin: for every 1 g/dl albumin decrease, increase calculated anion gap by 2.5 mmol/liter
A–a difference (A–a gradient) in mm Hg
At sea level (ambient air):
150–Pao_2–1.25×$Paco_2$
Normal anion gap:
Calculate urinary anion gap
([Na^+]+[K^+]–[Cl^-])
If urinary pH>6.5, or urinary [Na+] <20 mmol/liter: evaluate urinary osmolal gap
High anion gap
(e.g., lactate, keto acids, toxic alcohols)
A–a difference ≤10 mm Hg
(≤20 mm Hg in elderly)
Hypoventilation without intrinsic lung disease
A–a difference >10 mm Hg
(>20 mm Hg in elderly)
Hypoventilation with intrinsic lung disease, ventilation–perfusion mismatch, or both
Urinary anion gap negative
(e.g., diarrhea, sodium infusion, proximal RTA [often hypophosphatemia, hyperuricemia, renal glucosuria])
Urinary anion gap positive: RTA
Type 1: serum [K^+] decrease, urinary pH >5.5
Type 4: serum [K^+] increase, urinary pH >5.5 in hypoaldosteronism
Delta–Delta (Δ–Δ)
Ketoacidosis:
ΔAG–Δ[HCO_3^-]
Lactic acidosis:
Compute the value of [Δ0.6 AG]–[Δ(HCO_3^-)]
If the result is –5 to 5 mmol/liter for either of the above: only high anion-gap metabolic acidosis
>5 mmol/liter: high anion-gap metabolic acidosis as well as metabolic alkalosis
<–5 mmol/liter: high anion-gap metabolic acidosis as well as normal anion-gap acidosis
Osmolal gap
(measured–calculated osmolality) >10 mOsm/kg
(e.g., toxic alcohols)
Calculated serum osmolality:
(2×[Na^+])+[glucose, in mg/dl]/18+(blood urea nitrogen, in mg/dl)/2.8
In standard units
(mmol/liter)=(2×[Na^+])+[glucose]+[urea]

Case

Urine pH	**More than 5.5**
Plasma potassium	Low-normal
FEHco3	less than 5%
UAG	+

Q 1 : which type of RTA ?

Q2:tt?

Resources

- Nelson textbook of pediatrics , 20th edition
- Rudolph’s pediatrics , 23rd edition
- The harriet lane handbook , 21st edition

THANK YOU