Renal Tubular Acidosis (RTA)

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Renal Tubular Acidosis (RTA)

- Renal tubular acidosis (RTA) is a condition in which there is a defect in renal excretion of hydrogen ion, or reabsorption of bicarbonate, or both, which occurs in the absence of or out of proportion to an impairment in the glomerular filtration rate
- Thus, RTA is distinguished from the renal acidosis that develops as a result of advanced chronic kidney disease
- The term “renal tubular acidosis” was coined by Pines and Mudge in their studies published in 1951
- These renal tubular abnormalities can occur as an inherited disease or can result from other disorders or toxins that affect the renal tubules.

TYPES OF RTA

Proximal RTA (type 2)

- Isolated bicarbonate defect
- Fanconi syndrome

Distal RTA (type 1)

- Classic type
- Hyperkalemic distal RTA
- **Hyperkalemic RTA (Type 4)**

Physiology of Renal Acidification

- Kidneys excrete 50-100 meq/day of non carbonic acid generated daily
- This is achieved by H+ secretion at different levels in the nephron
- The daily acid load cannot be excreted as free H+ ions
- Secreted H+ ions are excreted by binding to either buffers, such as HPO_4^{2-} and creatinine, or to NH_3 to form NH_4^+
- The extracellular pH is the primary physiologic regulator of net acid excretion.

Renal Acid-Base Homeostasis

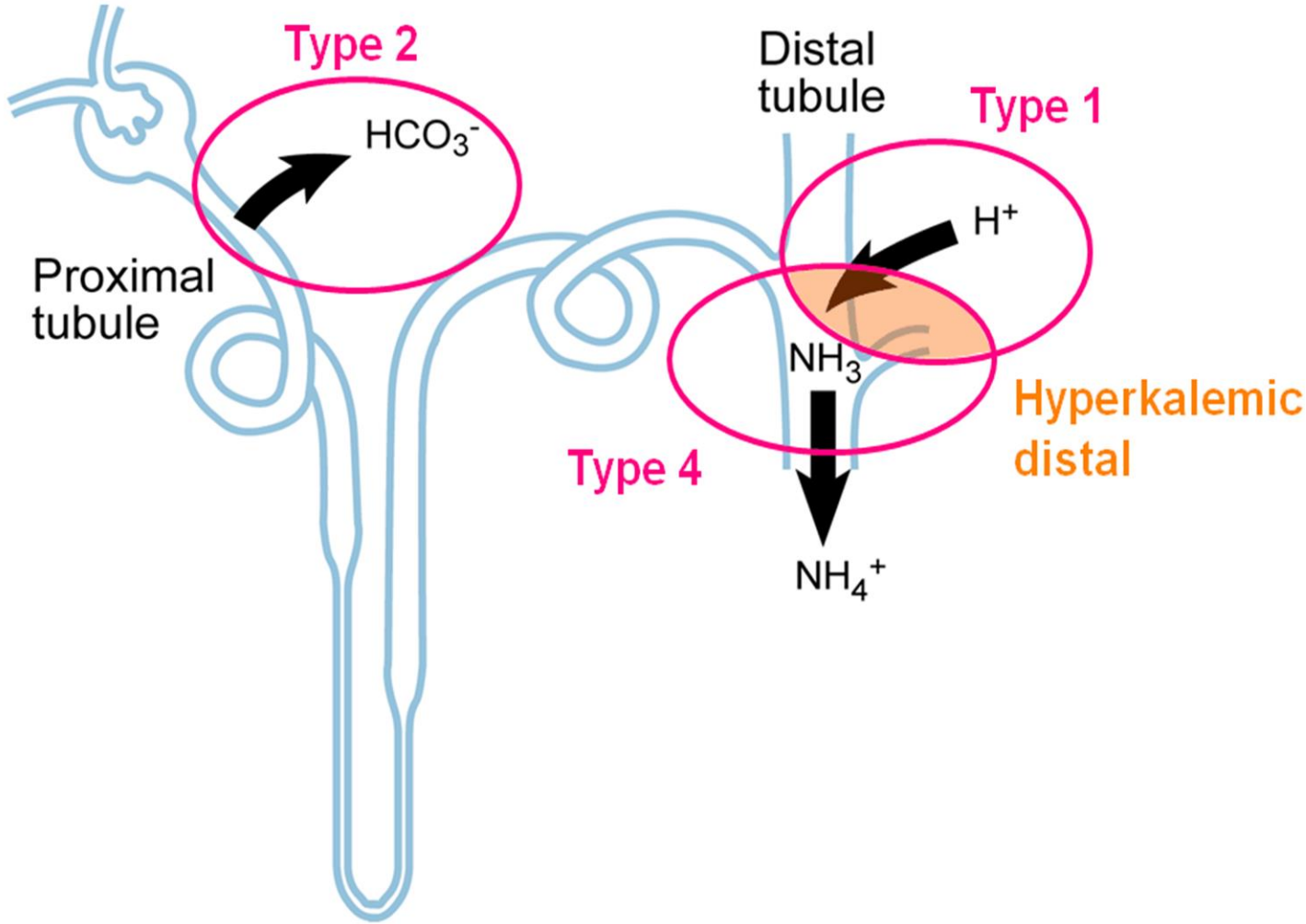
Can be broadly divided into 2 processes

1. Proximal tubular absorption of HCO_3^- (Proximal acidification)
2. Distal Urinary acidification

   -Reabsorption of remaining HCO_3^- that escapes proximally.

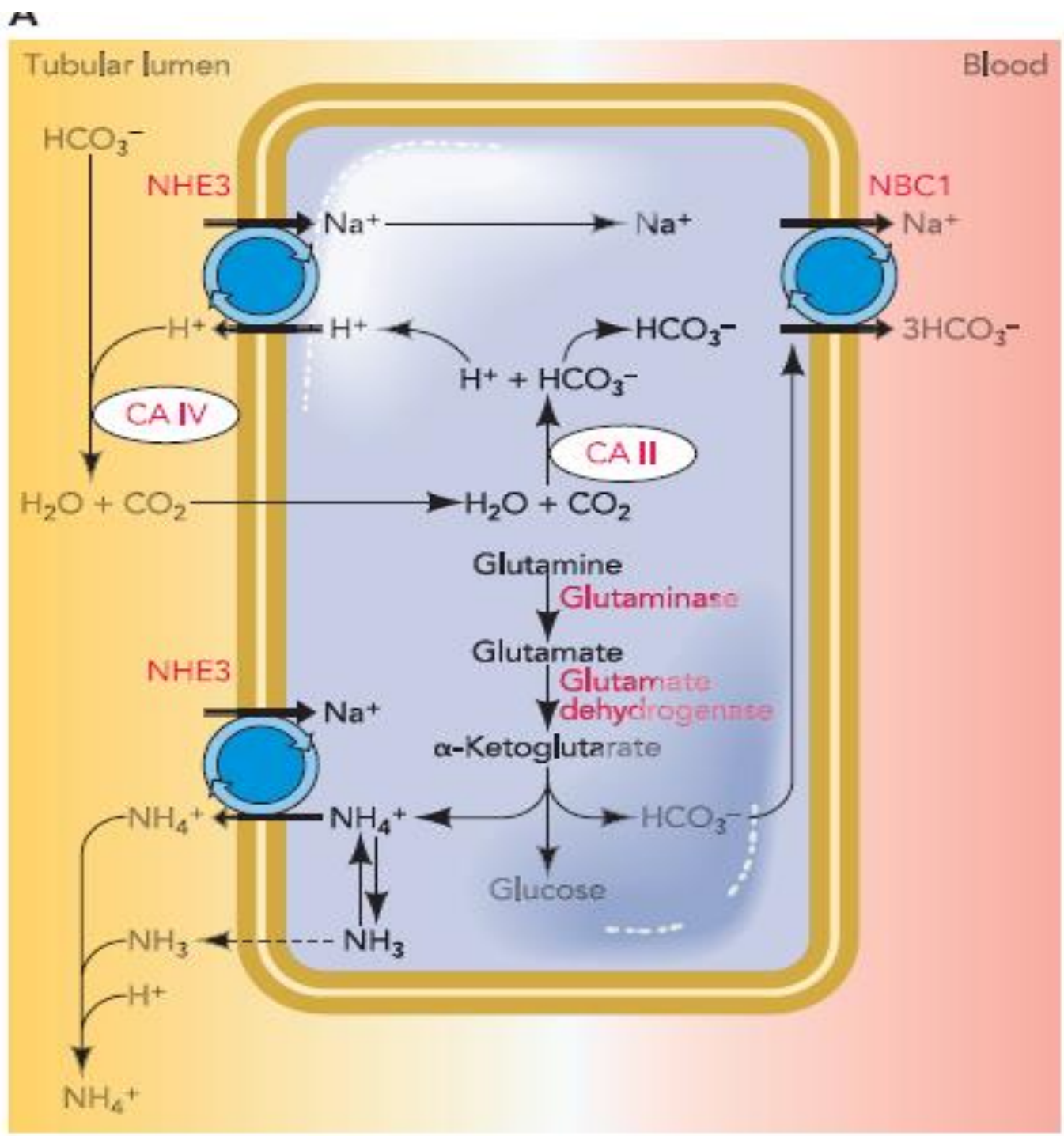
   -Excretion of fixed acids through buffering & Ammonia recycling and excretion of NH_4^+.

Acid excretion mechanisms in renal tubule



Proximal Tubule Physiology

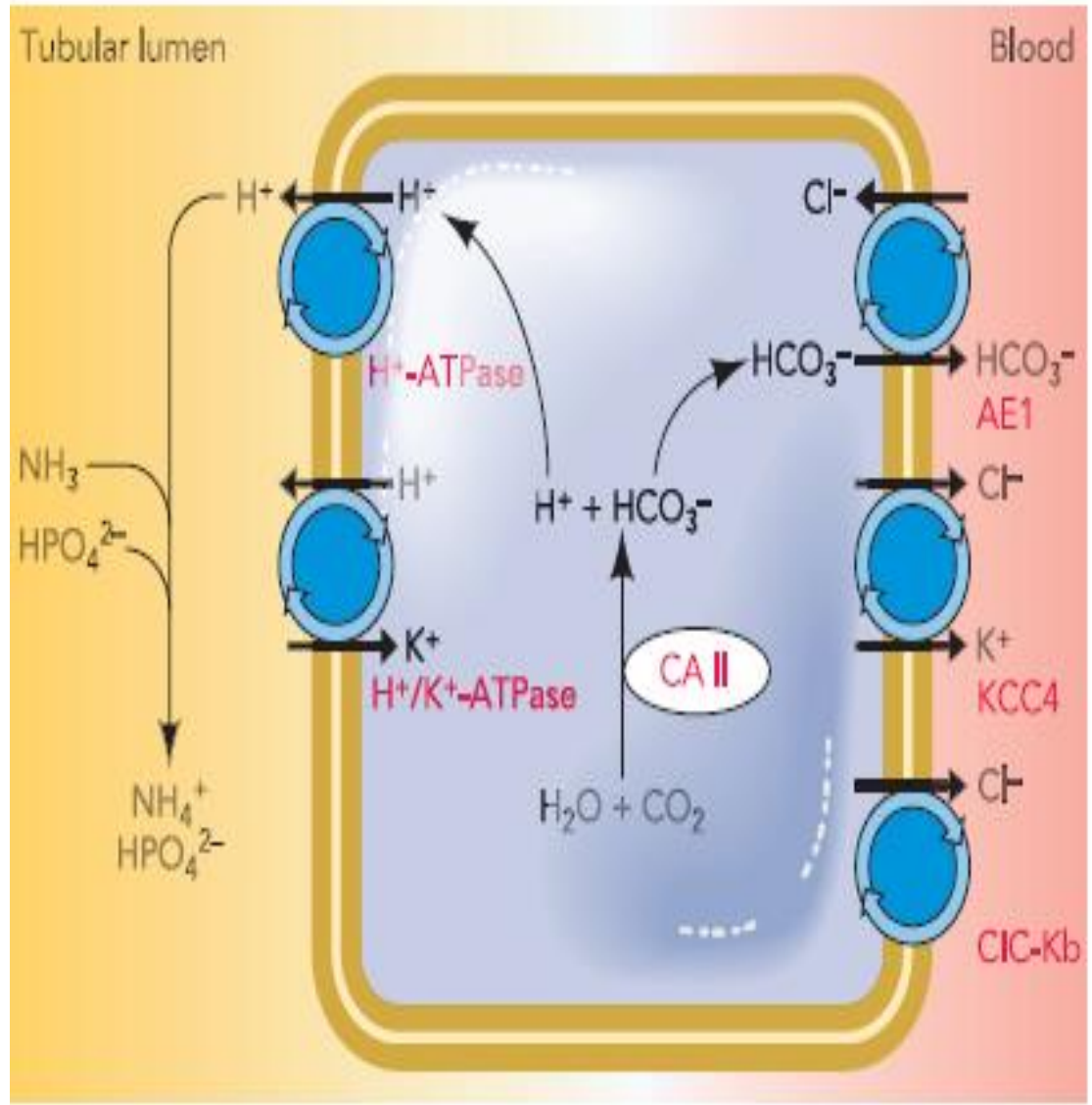
- Proximal tubule contributes to renal acidification by *H+ secretion into the tubular lumen* through NHE3 transporter and by *HCO3- reabsorption*
- Approx. 85% of filtered HCO_3^- is absorbed by the proximal tubule
- The remaining 15 % of the filtered HCO3- is reabsorbed in the thick ascending limb and in the outer medullary collecting tubule.


A
Tubular lumen
Blood
HCO_3^-
NHE3
Na^+
Na^+
NBC1
Na^+
H^+
H^+
HCO_3^-
$3HCO_3^-$
$H^+ + HCO_3^-$
CA IV
CA II
$H_2O + CO_2$
$H_2O + CO_2$
Glutamine
Glutaminase
Glutamate
NHE3
Glutamate dehydrogenase
Na^+
α-Ketoglutarate
NH_4^+
NH_4^+
HCO_3^-
Glucose
NH_3
NH_3
H^+
NH_4^+

DISTAL ACIDIFICATION

- Alpha-Intercalated Cells are thought to be the main cells involved with H^+ secretion in the CT
- This is accomplished by an apically placed H^+-K^+-ATPase and H^+-ATPase with a basolateral Cl^-/HCO_3^- exchanger and the usual basolateral Na^+ - K^+ ATPase

B


Tubular lumen
Blood
H+
H+
H+-ATPase
Cl-
HCO3-
HCO3-
AE1
NH3
HPO4 2-
H+
H+ + HCO3-
Cl-
K+
H+/K+-ATPase
CA II
K+
KCC4
NH4+
HPO4 2-
H2O + CO2
Cl-
ClC-Kb

Non Secretory Defects Causing Distal RTA

- **Gradient defect**: backleak of secretd H+ ions. Ex. Amphotericin B
- **Voltage dependent defect:** impaired distal sodium transport ex. Obstructive uropathy, sickle cell disease, CAH, Lithium and amiloride etc.
- This form of distal RTA is associated with hyperkalemia(Hyperkalemic distal RTA)

DISTAL RTA

- A high urinary pH (5.5) is found in the majority of patients with a secretory dRTA.
- Excretion of ammonium is low as a result of less NH_4^+trapping. This leads to a positive urine anion gap.
- Urine PCO_2 does not increase normally after a bicarbonate load reflecting decreased distal hydrogen ion secretion.
- Serum potassium is reduced in 50% of patients. This is thought to be from increased kaliuresis to offset decreased H^+ and H-K-ATPase activity.

Type of RTA	Subtype and Inheritance	Age at Presentation	Clinical Features	Protein	Gene(s)	OMIM
Distal (type 1)	Dominant	Older/adult	Mild/compensated metabolic acidosis Hypokalemia (variable) Hypercalciuria Hypocitraturia Nephrolithiasis Nephrocalcinosis Sometimes rickets/ osteomalacia Secondary erythrocytosis	AE1	*SCL4A1*	179800
	Recessive	Childhood	Metabolic acidosis with hemolytic anemia Only reported in Southeast Asian populations	AE1	*SCL4A1*	602722
	Recessive with early onset hearing loss	Infancy/childhood	Metabolic acidosis Early nephrocalcinosis Vomiting/dehydration Growth retardation Rickets Bilateral sensorineural hearing loss, from childhood	B1 subunit of H^+-ATPase	*ATP6V1B1*	267300
	Recessive with later onset hearing loss	Infancy/childhood	As above, but later onset hearing loss in some (a few with normal hearing)	a4 subunit of H^+-ATPase	*ATP6V0A4*	602722
Proximal (type 2)	Recessive with ocular abnormalities	Infancy	Metabolic acidosis Hypokalemia Ocular abnormalities (band keratopathy, cataracts, glaucoma) Growth retardation Defective dental enamel Intellectual impairment Basal ganglia calcification	NBC1	*SLC4A4*	604278
Combined proximal and distal (type 3)	Recessive with osteopetrosis	Infancy/childhood	Metabolic acidosis Hypokalemia Osteopetrosis Blindness Deafness Early nephrocalcinosis	CA II	*CA2*	259730

Diagnosis of RTA
Determination of the urine anion gap

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

Normal < 0

Urine anion gap

= Measured cations - Measured anions

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

= Unmeasured anions - unmeasured cations

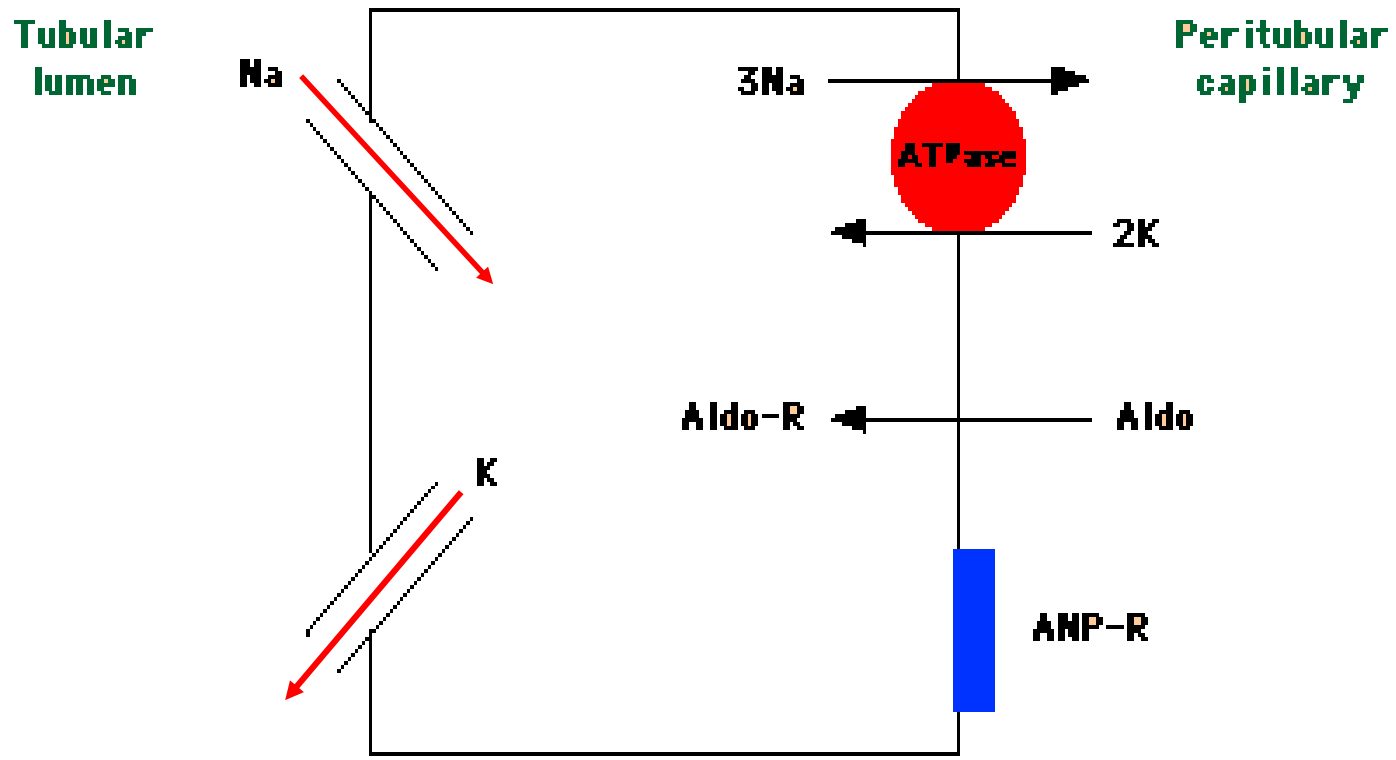
Sulfate
Phosphate
Bicarbonate
Organic anions

Calcium
Magnesium
NH_4^+

Aldosterone and Renal acidification

- Favors H+ and K+ secretion through enhanced sodium transport.
- Recruits more amiloride sensitive sodium channels in the luminal membrane of the collecting tubule.
- Enhances H+-ATPase activity in cortical and medullary collecting tubules.
- Aldosterone also has an effect on NH_4^+ excretion by increasing NH_3 synthesis

Principal Cells



Summary

- H+ secretion, bicarbonate reabsorption and NH4+ production occur at the proximal tubule.
- Luminal CA IV is present in the luminal membrane at this site and in MCT.
- NH4+reabsorption occurs at TAL of loop of Henle and helps in ammonia recycling that facilitates NH4+excretion at MCT.
- H+ secretion occurs in the CCT either dependent or independent of Na availability and in the MCT as an independent process.

Approach

- Determination of the urinary pH (freshly voided morning sample)
- Estimation of the urine anion gap (UAG)
- Determination if there is generalized proximal tubular dysfunction
- Measurement of the fractional excretion of bicarbonate using a bicarbonate titration or loading test

Approach

- The urine pH will generally be <6.0 in proximal RTA, and <5.3 following an acid loading test.
- Urine anion gap will be negative in PRTA and positive in distal RTA (DRTA).
- It is rare to have nephrocalcinosis or stones in PRTA.
- Urinary calcium and citrate excretion will be normal in PRTA.
- Fractional excretion of phosphorus less than 15%, normal urinary amino acid excretion and absence of glycosuria excludes Fanconi syndrome.
- Urine-to-blood PCO_2 will be >20 mm Hg in PRTA and <20 mm Hg in DRTA.
- The renal bicarbonate threshold is important for identifying a defect in tubular reabsorption of bicarbonate.

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	
Other		Fanconi syndrome	Nephro-calcinosis		

Proximal RTA (type II)

- Impaired reabsorption of bicarbonate (HCO_3^-) in the proximal tubule with a decreased renal HCO_3^- threshold (normal: infants, 22 mmol/L; children/adults, 26 mmol/L).
- Even though the serum [HCO_3^-] is low, the urinary pH can remain maximally acidified owing to distal acidification, the latter a result of adequate excretion of ammonium.
- With normalization of the plasma [HCO_3^-] by administration of sodium bicarbonate or citrate, the urine will become more alkaline due to increased bicarbonate delivery to the distal tubule, resulting in a fractional excretion of bicarbonate greater than 15%.

Distal RTA

- Inability to excrete the normal nonvolatile acid load of diet and metabolism because of impaired hydrogen ion secretion in the α-intercalated cells of the collecting tubules in the cortex and outer medulla
- The defect is most commonly due to a voltage abnormality; less commonly, there may be inherent transporter (eg, [H+]-ATPase) dysfunction
- Regardless, distal RTA is characterized by the inability to lower the urine pH maximally (ie, ≤5.5) under the stimulus of systemic acidemia in the setting of otherwise normal GFR; the proximal bicarbonate reclamation is quantitatively normal

A 54-year-old male with a 12 year history of Type 2 diabetes mellitus maintained on insulin, and proliferative diabetic retinopathy, is referred because of proteinuria.

Laboratory studies:

Serum sodium	140 mEq/L
Serum potassium	6.0 mEq/L
Serum chloride	112 mEq/L
Serum bicarbonate	19 mEq/L
Blood urea nitrogen	27 mg/dL
Serum creatinine	1.6 mg/dL
Serum glucose	206 mg/dL

Urinalysis shows 3+ proteinuria.

Case A8

The most likely cause of this patient's metabolic acidosis is:

A. Diarrhea due to diabetic autonomic neuropathy

B. Diabetic ketoacidosis

C. Chronic renal failure

D. Type I renal tubular acidosis

E. Type IV renal tubular acidosis

Case A8

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	
Other		Fanconi syndrome	Nephro-calcinosis		

Type IV RTA (hyporeninemic hypoaldosteronism)

Hyperkalemia (disproportionate to level of GFR)

Non-gap metabolic acidosis with normal urine acidifying ability

Mild CRF

Often underlying tubulointerstitial disease:

- Diabetes mellitus
- SLE, obstruction, myeloma/amyloid, HIV etc.
- *NSAIDs*

A 22-year-old male with HIV infection was started on HAART three months ago. His medications are didanosine, tenofovir and lopinavir.

Serum sodium	141 mEq/L
Serum potassium	3.4 mEq/L
Serum chloride	115 mEq/L
Serum bicarbonate	18 mEq/L
Serum glucose	76 mg/dL
Blood urea nitrogen	7 mg/dL
Serum creatinine	0.4 mg/dL
Serum calcium	8.6 mg/dL
Serum phosphorus	0.9 mg/dL
Serum uric acid	1.7 mg/dL

Urinalysis: pH 6.0, specific gravity 1.015, 3+ glucose, trace protein

Urine phosphorus	25 mg/dL
Urine creatinine	38 mg/dL

Case A9

The most likely cause of this patient acid-base disturbance is:

A. HIV-related diarrhea

B. D-lactic acidosis

C. Didanosine-induced lactic acidosis

D. Hepatic failure-associated renal tubular acidosis

E. Tenofovir toxicity

Case A9

Serum bicarbonate is 18 mEq/L

Anion gap = 141 - 115 - 18 = 8

Probably non-gap metabolic acidosis

Urine pH 6, serum K 3.4

Inappropriately alkaline urine and hypokalemia suggests Type I or II renal tubular acidosis

Case A9

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	
Other		Fanconi syndrome	Nephro-calcinosis		

F_EPO_4 = (25 x 0.4)/(0.9 x 38) = 29% (normal 5-15%)

Renal phosphate wasting

Glycosuria despite normoglycemia, hypouricemia

Fanconi syndrome

Cause:

Tenofovir

Case A9

Fanconi syndrome & ARF 2° to nucleotide-analog reverse transcriptase inhibitors

- Acyclic nucleoside phosphonates: adefovir (22-50%), cidofovir (12% ARF, 1% Fanconi), tenofovir (2-4%)
- Transported into prox. tubule by organic anion transporter (OAT1), causing mitochondrial toxicity
- Both Fanconi syndrome and ARF (due to ATN)
- Can be induced by drug interaction (most pts with tenofovir toxicity were on ritonavir)
- Can be induced by renal insufficiency (all renally excreted)
- Can occur 3 wk to 18 mth after start of Rx

38-year-old woman with dry eyes and polyarthritis. The serum potassium is 3.4 mEq/L, the urine pH is 6.5 and the urine sodium is 28 mEq/L, potassium 50 mEq/L and chloride 57 mEq/L.

A. Proximal (Type II) renal tubular acidosis

B. Classic distal (Type I) renal tubular acidosis

C. Hyporeninemic hypoaldosteronism (Type IV renal tubular acidosis)

D. Gastrointestinal bicarbonate loss

E. Toluene intoxication

Case A10

- So the hypokalemia, the high urine pH, the positive urine anion gap, all suggest a type 1 renal tubular acidosis and then just to make it even easier, it sounds like a case of Sjogren, the number one cause of a type 1 renal tubular acidosis in adults. Okay, so B is correct.

56-year-old Hispanic male with Type II diabetes mellitus, diabetic nephropathy, and chronic renal insufficency with a serum Cr of 2.3 mg/dL. He is unable to tolerate angiotensin-converting enzyme inhibitors due to hyperkalemia. The urine pH is 5.0 and the urine sodium is 43 mEq/L, potassium 13 mEq/L and chloride 41 mEq/L.

A. Proximal (Type II) renal tubular acidosis

B. Classic distal (Type I) renal tubular acidosis

C. Hyporeninemic hypoaldosteronism (Type IV renal tubular acidosis)

D. Gastrointestinal bicarbonate loss

E. Toluene intoxication

Case A11

- The urine pH is 5, urine sodium is 43, potassium 13, and chloride 41. Same selection, pick the one that is most likely to be causing the metabolic acidosis and in this case the hyperkalemia.

26-year-old woman with osteosarcoma of the humerus, undergoing chemotherapy with ifosfamide. The serum potassium is 2.3 mEq/L, glucose 97 mg/dL, phosphate 1.5 mg/dL. The urinalysis shows pH 7.0, 1+ protein, 2+ glucose. The urine sodium is 27 mEq/L, potassium 48 mEq/L and chloride 56 mEq/L.

A. Proximal (Type II) renal tubular acidosis

B. Classic distal (Type I) renal tubular acidosis

C. Hyporeninemic hypoaldosteronism (Type IV renal tubular acidosis)

D. Gastrointestinal bicarbonate loss

E. Toluene intoxication

Case A13

- Proximal renal tubular acidosis. So this sounds like a Fanconi syndrome. Again, major clue is glycosuria despite normal glycemia, low potassium, non-gap acidosis, positive urine anion gap. The high urine pH is probably from bicarbonate wasting and the clue here is the patient has been treated with iphosphamide which is a major cause of a proximal renal tubular acidosis. It does also cause a distal renal tubular acidosis sometimes, but again the fact that this patient has glycosuria and also I should mention quite severe hypophosphatemia, suggests that it is more likely a proximal renal tubular acidosis

24-year-old man with Type I diabetes mellitus complicated by diabetic nephropathy, chronic renal failure with a serum Cr of 1.8 mg/dL, potassium 3.0 mg/dL, autonomic neuropathy and chronic diarrhea. The urine sodium is 10 mEq/L, potassium 14 mEq/L and chloride 36 mEq/L.

A. Proximal (Type II) renal tubular acidosis

B. Classic distal (Type I) renal tubular acidosis

C. Hyporeninemic hypoaldosteronism (Type IV renal tubular acidosis)

D. Gastrointestinal bicarbonate loss

E. Toluene intoxication

Case A14

- So you recognize that this is a negative urine anion gap so the cause of the acidosis is not renal tubular acidosis, has to be a non-renal cause, which in this case is presumably from the diarrhea itself