Renal Tubular Acidosis - A quick guide (2) Vikas Parekh, M.D.

What is a RTA?
It is the development of a metabolic acidosis due to a defect in the ability of the renal tubules to either reabsorb bicarbonate or increase hydrogen excretion in response to an acidemia. All RTAs are characterized by a non anion gap metabolic acidosis.

What is the kidney supposed to do to keep acid-base balance?
1. Reabsorb filtered bicarbonate – this is 90% a proximal tubule function primarily via Na+-H+ exchange. Normally you should reabsorb almost all your bicarbonate so the urine will have a PH of 4.5-5.0. (The other 10% is reabsorbed in the distal tubule.)
2. Excrete acid- this is a distal tubule function – hydrogen ions (acid – from breakdown of sulfur containing amino-acids) need to be excreted into the urine, but you can't just dump hydrogen into the urine because you'd get a pH of less than 2.5 – that would hurt coming out and destroy the tubule cells - So the urine is buffered with ammonia (excreted as ammonium by the kidney). This happens in the collecting duct cells.

What are the types of RTA?
Type 1 or Distal RTA – inability to excrete hydrogen ions is the big defect (and since hydrogen is buffered with ammonia you'll have less ammonium as well in urine)
-Most common cause in adults is autoimmune disorders (sjogrens, RA etc) also Ampho B, Lithium, Ifosfamide, Cirrhosis, Obstruction (may be hyperkalemic).
-Basically can't acidify your urine despite acidemia (Urine pH>5.5) and usually serum bicarb is very low (i.e less than 12 meq/L)

Type 2 or Proximal RTA – difficulty with bicarbonate resorption when the plasma bicarb is above a threshold
-Usually associated with more generalized proximal tubular dysfunction so called "Fanconi syndrome" with bicarbonaturia, glucosuria, phosphaturia, uricosuria, proteinuria, aminoaciduria
-The most common cause of Fanconi in adults is light chain excretion from myeloma which basically gum up the proximal tubule cells, the use of carbonic anhydrase inhibitors (acetazolamide), or the use of Ifosfamide chemotherapy. Other less common causes include: heavy metal toxicity, Vit D deficiency, Renal txp, genetic disorders (Cystinosis, glycogen storage dz, wilsons).
-Basically the kidney has a reduced reabsorbtive capacity for bicarb of about 16-18 meq/L (normal is about 25 meq/L) - this means serum bicarb will end up near this level since you'll dump into urine until you get to threshold

Type 4 or Hypoaldosteronism – impaired ability to generate ammonia and thus limited ability to buffer acid
-Either due to aldo deficiency or resistance to aldo action (chronic tubulointerstitial dz, K-sparing diuretics)
-Most common form is hyporenin-hypoaldo state seen with mild-mod renal insufficiency (especially diabetic). Also of course adrenal insufficiency or meds such as ACEI, aldactone, high dose trimethoprim, pentamidine, can also see sometimes with obstuctive uropathy.

How do you diagnose them? Need to have an unexplained non-anion gap metabolic acidosis
i.e NO GI Loss, NO Exogenous Acid (i.e. TPN)

Type 1 RTA: Suspect in any patient with a non-anion gap acidosis, very low serum HCO3 and a urine pH that is inappropriately high above 5.3 in adults and 5.6 in kids.
-There are however, other possible causes to exclude for this combo of low serum HCO3, high urine PH, non-gap acidosis and these are: Significant volume depletion (decreased distal sodium delivery can impair hydrogen excretion – because hydrogen excretion is dependent on electrical gradient – thus you can get metabolic acidosis , Hypokalemia –which increases urinary ammonium excretion (you can see HypoKalemia with both type I RTA and diarrhea), UTI with urea-splitting organism.

To evaluate further you can:
1. Check Urine Sodium –if its less than 25 suspect volume depletion
2.Check Urine anion gap – this indirectly estimates urine ammonium – which is proxy for acid secretion (Urine cation gap is Na+K –Cl , the gap is made up by ammonium NH4+ and a negative gap meaning ammonium is

present). The gap should be negative in diarrhea and HypoK while it is positive in Type 1 RTA due to impaired excretion of hydrogen (ammonium is how we excrete hydrogen).
-Potassium is usually low (but not always) – the etiology of hypokalemia is most likely due to increased secretion of potassium in distal tubule in response to decreased hydrogen excretion which is the defect in Type I RTA – basically potassium is secreted instead of hydrogen to maintain electroneutrality that is needed to balance sodium resorption.
-Symptoms: kidney stones, nephrocalcinosis due to chronic acidosis resulting in bone resorption/renal resorption of calcium

Type 2 RTA: urine pH here is variable it depends on if the patient is getting bicarb and what their acid load is overall. Urine pH will be above 5.3 if they are getting bicarb – as excess bicarb is spilled into urine, but it can be less than 5.3 if they are not getting bicarb and have an acidic diet
-Look for other proximal tubular defects: glucosuria (with normal serum glu), proteinuria, hypophosphatemia, hyporuricemia…
-Definitive dx: raise plasma bicarb by giving IV infusion -→urine pH will get very high (above 7.5) once you get serum bicarb up over the low resorptive threshold (i.e above 16-18) seen in this RTA. Also the fractional excretion of HCO3 will be high - above 15% (calculate like FeNA but subsitute HCO3 in the equation)
(as opposed to Type I RTA where the urine pH won't change much since you will reabsorb the bicarb and the FeHCO3 will be 3% or less when you do a bicarb infusion)

Type 4 RTA:
Associated with Hyperkalemia (since aldo regulates potassium secretion). Urine pH less 5.3 and bicarb that isn't that low (usually circa 17). Potential diagnosis by checking renin and aldo levels in patient with above features.(Hypo aldo/hypo renin) although if due to aldo resistance aldo/renin levels may be OK. Urine anion gap (see type I RTA) usually positive due to impaired ammonium excretion. (can also consider calculated Trans-tubular potassium gradient or TTKG – if below 5 than this suggest hypoaldo state (ie. Impaired potassium secretion) – TTKG = (Urine K+ x Posm) / (Plasma K+ x U osm)
Must be sure there is : NO GI Loss, NO Exogenous Acid (i.e. TPN)

Treatment:
-Type 1 RTA: Yes in kids (to let them grow) and in adults (to reduce calcium loss/stones) Give them Bicarb – usually give either NaHCo3 or Sodium Citrate.
-Type 2 RTA: Yes in kids to let them grow, sometimes in adults if they have bone disease (phosphate wasting) Give them Bicarb as well – but you may have to give them a lot of it. Because the more you give, the more spills into urine and you get an induced diuresis, often leading to hypokalemia. Sometimes you can add a thiazide diuretic which by causing volume depletion can enhance proximal resorption of sodium and secondarily bicarb.
-Type 4 RTA: Treat only in some cases: i.e. adrenal insufficiency give them back mineralocorticoid (i.e. florinef) Rarely replace those with hyporenin-hypoaldo due to problems with htn/edema….usually just go with low K+ diet and a diuretic to help keep the K+ down (obviously not a K+ sparing diuretic).

	Type I RTA	**Type 2 RTA**	**Type 4 RTA**
Primary Defect	Impaired distal acidification	Reduced Proximal bicarb reabsorption	Decreased aldo effect resulting in decreased ammonium production
Plasma Bicarb	Usually very low (<12)	Usually medium-low (14-18)	Usually mildly low (>17)
Urine pH	Greater than 5.3	Variable, is greater than 5.3 if above reabsorptive threshold for bicarb	Usually less than 5.3
Plasma K+	Usually Low, but corrects with alkali theapy	Low and gets worse with bicarb due to diuresis	Increased due to impaired excretion (low aldo)
Fractional excretion HCo3 if plasma HCo3 >20	Less than 3%	High usually >15%	Less than 3%