acidosis in kidney disease [created by Paul 15/12/07]

general

- Metabolic acidosis occurs with both acute and chronic renal failure and with other types of renal damage. The anion gap may be normal or may be elevated.
- If the renal damage affects both glomeruli and tubules, the acidosis is a high-anion gap acidosis. It is due to failure of adequate excretion of various acid anions due to the greatly reduced number of functioning nephrons.
- If the renal damage predominantly affects the tubules with minimal glomerular damage, a different type of acidosis may occur. This is called Renal Tubular Acidosis (RTA) and this is a normal anion gap or hyperchloraemic type of acidosis. The GFR may be normal or only minimally affected.
- Renal tubular acidosis is a form of hyperchloraemic metabolic acidosis which occurs when the renal damage primarily affects tubular function without much effect on glomerular function. The result is a decrease in H+ excretion which is greater than can be explained by any change in GFR. If glomerular function (ie GFR) is significantly depressed, the retention of fixed acids results in a high anion gap acidosis.
- Three main clinical categories or 'types' of renal tubular acidosis (RTA) are now recognised but the number of possible causes is large. The mechanism causing the defect in ability to acidify the urine and excrete acid is different in the three types.
- Incomplete forms of RTA also occur. The arterial pH is normal in these patients and acidosis develops only when an acid load is present.

comparison of RTA types

Comparison of Major Types of RTA			
	Type 1	Type 2	Type 4
Hyperchloraemic acidosis	Yes	Yes	Yes
Minimum Urine pH	>5.5	<5.5 (but usually >5.5 before the acidosis becomes established)	<5.5
Plasma potassium	Low-normal	Low-normal	High
Renal stones	Yes	No	No
Defect	Reduced H^+ excretion in distal tubule	Impaired HCO_3 reabsorption in proximal tubule	Impaired cation exchange in distal tubule

Distal (Type 1) Renal Tubular Acidosis

General
- This is also referred to as classic RTA or distal RTA.
- The problem here is an inability to maximally acidify the urine. Typically urine pH remains > 5.5 despite severe acidaemia ([HCO3] < 15 mmol/l).
- Some patients with less severe acidosis require acid loading tests (eg with NH4Cl) to assist in the diagnosis. If the acid load drops the plasma [HCO3] but the urine pH remains > 5.5, this establishes the diagnosis.

General Classification of Causes of type 1 RTA
(i)Hereditary (genetic)
(ii) Autoimminue diseases (eg Sjogren's syndrome, SLE, thyroiditis)
(iii) Disorders which cause nephrocalcinosis (eg primary hyperparathyroidism, vitamin D intoxication)
(iv) Drugs or toxins (eg amphotericin B, toluene inhalation)
(v) Miscellaneous - other renal disorders (eg obstructive uropathy)

Pathophysiological Mechanisms in Reduced H+ Secretion in Distal Tubule
(i) "Weak pump"
- Inability for H+ pump to pump against a high H+ gradient
(ii) "Leaky membrane"
- Back-diffusion of H+ [eg This occurs in RTA due amphotericin B]
(iii) "Low pump capacity"
- Insufficient distal H+ pumping capacity due to tubular damage.

Investigation
- Typical findings are an inappropriately high urine pH (usually > 5.5), low acid secretion and urinary bicarbonate excretion despite severe acidosis. Renal sodium wasting is common and results in depletion of ECF volume and secondary hyperaldosteronism with increased loss of K+ in the urine.
- The diagnosis of type 1 RTA is suggested by finding a hyperchloraemic acidosis in association with an alkaline urine particularly if there is evidence of renal stone formation.
Note: If [HCO3 > 15 mmol/l, then acid loading tests are required to establish the diagnosis.

Treatment
- Treatment with NaHCO3 corrects the Na+ deficit, restores the extracellular fluid volume and results in correction of the hypokalaemia. Typical alkali requirements are in the range of 1 to 4 mmol/kg/day. K+ supplements are only rarely required. Sodium and potassium citrate solutions can be useful particularly if hypokalaemia is present. Citrate will bind Ca++ in the urine and this assists in preventing renal stones.

Proximal (Type 2) Renal Tubular Acidosis

General
- Type 2 RTA is also called proximal RTA because the main problem is greatly impaired reabsorption of bicarbonate in the proximal tubule.
- At normal plasma [HCO3], more than 15% of the filtered HCO3 load is excreted in the urine. When acidosis is severe and HCO3 levels are low (eg <17 mmols/l), the urine may become bicarbonate free.

Features
- Symptoms are precipitated by an increase in plasma [HCO3]. The defective proximal tubule cannot reabsorb the increased filtered load and the distal delivery of bicarbonate is greatly increased. The H+ secretion in the distal tubule is now overwhelmed by attempting to reabsorb bicarbonate and the net acid excretion decreases. This results in urinary loss of HCO3 resulting in systemic acidosis with inappropriately high urine pH. The bicarbonate is replaced in the circulation by Cl-.
- The increased distal Na+ delivery results in hyperaldosteronism with consequent renal K+ wasting. The hypokalaemia may be severe in some cases but as hypokalaemia inhibits adrenal aldosterone secretion, this often limits the severity of the hypokalaemia.
- Hypercalciuria does not occur and this type of RTA is not associated with renal stones.
- During the NH4Cl loading test, urine pH will drop below 5.5.
- Note that the acidosis in proximal RTA is usually not as severe as in distal RTA and the plasma [HCO3] is typically greater than 15 mmol/l.

Causes
- There are many causes but most are associated with multiple proximal tubular defects eg affecting reabsorption of glucose, phosphate and amino acids. Some cases are hereditary.
- Causes include vitamin D deficiency, cystinosis, lead nephropathy, amyloidosis and medullary cystic disease.

Treatment
- Treatment is directed towards the underlying disorder if possible.
- Alkali therapy (NaHCO3) and supplemental K+ is not always necessary. If alkali therapy is required, the dose is usually large (up to 10 mmols/kg/day) because of the increased urine bicarbonate wasting associated with normal plasma levels.
- K+ loss is much increased in treated patients and supplementation is required.
- Some patients respond to thiazide diuretics which cause slight volume contraction and this results in increased proximal bicarbonate reabsorption so less bicarbonate is needed.

Type 3 Renal Tubular Acidosis

- This term is no longer used.
- Type 3 RTA is now considered a subtype of Type 1 where there is a proximal bicarbonate leak in addition to a distal acidification defect.

Type 4 Renal Tubular Acidosis

General
- A number of different conditions have been associated with this type but most patients have renal failure associated with disorders affecting the renal interstitium and tubules. In contrast to uraemic acidosis, the GFR is greater than 20 mls/min.
- a useful differentiating point is that hyperkalaemia occurs in type 4 RTA (but NOT in the other types).

Pathophysiology
- The underlying defect is impairment of cation-exchange in the distal tubule with reduced secretion of both H+ and K+.
- This is a similar finding to what occurs with aldosterone deficiency and type 4 RTA can occur with Addison's disease or following bilateral adrenalectomy.
- Acidosis is not common with aldosterone deficiency alone but requires some degree of associated renal damage (nephron loss) esp affecting the distal tubule.
- The H+ pump in the tubules is not abnormal so patients with this disorder are able to decrease urine pH to < 5.5 in response to the acidosis.

uraemic acidosis

- The acidosis occurring in uraemic patients is due to failure of excretion of acid anions (particularly phosphate and sulphate) because of the decreased number of nephrons. There is a major decrease in the number of tubule cells which can produce ammonia and this contributes to uraemic acidosis.
- Serious acidosis does not occur until the GFR has decreased to about 20 mls/min. This corresponds to a creatinine level of about 0.30-0.35 mmols/l.
- The plasma bicarbonate in renal failure with acidosis is typically between 12 & 20 mmols/l. Intracellular buffering and bone buffering are important in limiting the fall in bicarbonate. This bone buffering will cause loss of bone mineral (osteomalacia).
- Most other forms of metabolic acidosis are of relatively short duration as the patient is either treated with resolution of the disorder or the patient dies. Uraemic acidosis is a major exception as these patients survive with significant acidosis for many years. This long duration is the reason why loss of bone mineral is significant in uraemic acidosis but is not a feature of other causes of metabolic acidosis.