8.5: Renal Tubular Acidosis

8.5.1: Definition

Renal Tubular Acidosis (RTA) is a syndrome due to either a defect in proximal tubule bicarbonate reabsorption, or a defect in distal tubule hydrogen ion secretion, or both. This results in a hyperchloremic metabolic acidosis with normal to moderately decreased GFR. Anion gap is normal. A typical situation where RTA would be suspected is if urine pH is greater than 7.0 despite the presence of a metabolic acidosis.

In contrast, the acidosis that occurs with acute, chronic, or acute on chronic renal failure is a high anion gap metabolic acidosis.

As a general overview to help understand why renal disease can give different types of acidosis consider the following: Acidosis due to renal disease is considered in 2 categories depending on whether the predominant site of renal damage is in the glomeruli or in the tubules.

Renal tubular acidosis is a form of hyperchloremic 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. In contrast, if glomerular function (ie GFR) is significantly depressed (hence 'renal failure'), the retention of fixed acids results in a high anion gap acidosis.

Acidosis and Location of Renal Damage

- Predominantly tubular damage \(\rightarrow\) Normal anion gap acidosis (Renal tubular acidosis - RTA)
  - Distal (or type 1) RTA
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. 1,2

8.5.2: Distal (Type 1) Renal Tubular Acidosis

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.

There are many different causes but the majority of cases can be placed into one of several groups:

General Classification of Causes

- Hereditary (genetic) ³,⁴
- Autoimmune diseases (eg Sjogren's syndrome, SLE, thyroiditis)
- Disorders which cause nephrocalcinosis (eg primary hyperparathyroidism, vitamin D intoxication)
- Drugs or toxins (eg amphotericin B, toluene inhalation)
- Miscellaneous - other renal disorders (eg obstructive uropathy)

The basic problem is reduced H⁺ secretion in the distal nephron but there are several possible mechanisms (see table below).

Pathophysiological Mechanisms in Reduced H⁺ Secretion in Distal Tubule

- "Weak pump" - Inability for H⁺ pump to pump against a high H⁺ gradient
- "Leaky membrane" - Back-diffusion of H⁺ (eg This occurs in RTA due amphotericin B)
- "Low pump capacity" - Insufficient distal H⁺ pumping capacity due to tubular damage.

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.

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 Ca²⁺ in the urine and this assists in preventing renal stones.

**Diagnosis of Distal Renal Tubular Acidosis**

Hyperchloraemic metabolic acidosis associated with a urine pH > 5.5 despite plasma [HCO₃⁻] < 15 mmol/l

*Supportive findings:* hypokalaemia, neprocalcinosis, presence of a disorder known to be associated with RTA (see list in text)

*Note*

If [HCO₃⁻] > 15 mmol/l, then acid loading tests are required to establish the diagnosis.

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**8.5.3: Proximal (Type 2) Renal Tubular Acidosis**

**Pathophysiology**

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. 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 $[\text{HCO}_3^-]$ 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. Other 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 ($\text{NaHCO}_3$) and supplemental $\text{K}^+$ 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. $\text{K}^+$ 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.

**8.5.4: 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.

**8.5.5: Type 4 Renal Tubular Acidosis**

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 ml/min.

**Useful differentiating point:** Hyperkalaemia occurs in type 4 RTA (but NOT in the other types)

The underlying defect is impairment of cation-exchange in the distal tubule with reduced secretion of both $\text{H}^+$ and $\text{K}^+$. 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 $\text{H}^+$ 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.

The table below provides a useful summary of some of the key points in differentiating the types of renal tubular acidosis.
## Comparison of Major Types of RTA

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperchloraemic acidosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Minimum Urine pH</td>
<td>&gt;5.5</td>
<td>&lt;5.5 (but usually &gt;5.5 before the acidosis becomes established)</td>
<td>&lt;5.5</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>Low-normal</td>
<td>Low-normal</td>
<td>High</td>
</tr>
<tr>
<td>Renal stones</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Defect</td>
<td>Reduced H⁺ excretion in distal tubule</td>
<td>Impaired HCO₃⁻ reabsorption in proximal tubule</td>
<td>Impaired cation exchange in distal tubule</td>
</tr>
</tbody>
</table>

Incomplete forms of RTA also occur. The arterial pH is normal in these patients and acidosis develops only when an acid load is present.

## References


