Clinical approach to renal tubular acidosis in adult patients

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**Introduction**

Normal urinary acidification involves bicarbonate reabsorption in the proximal tubules and hydrogen ion excretion in the distal tubules. Impairment of any of these critical functions leads to renal tubular acidosis (RTA). All forms of RTA are characterised by a normal anion gap metabolic acidosis (see Table 1).

The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis (1).

The serum anion gap gap is:

$$[Na^{+}] + [Cl^{-} - HCO_{3}^{-}]$$

Pseudo normalisation of the elevated anion gap secondary to severe hypoalbuminaemia must be carefully ruled out (in general, each 1 g/dl decline in serum albumin from the normal value of 4.5 g/dl, decreases the serum anion gap by 2.5 mEq/l). Once normal anion gap metabolic acidosis is confirmed, the urine anion gap is calculated to indirectly estimate the urine NH$_4^+$ levels (2).

The urine anion gap is:

$$[\text{urine } Na^{+} + \text{urine } K^{+}] - \text{urine } Cl^{-}$$

High urine chloride levels leading to a negative gap are typically accompanied by high amounts of NH$_4^+$, as seen with gastrointestinal and proximal renal bicarbonate wasting. A positive urine anion gap suggests the possibility of distal RTAs resulting in lower amounts of NH$_4^+$ and chloride in the urine (3).

Gastro-intestinal losses of bicarbonate (diarrhoea, urinary diversion procedures and fistulas) should be ruled out by detailed history and physical examination.

Although alkaline urine pH is variably seen in all three types of RTAs, only patients with complete type I distal RTA have a urine pH > 5.3 even during periods of severe metabolic acidosis. By contrast, urine pH transiently becomes acidic in both type II and type IV RTAs till the extra acid load is excreted into the urine (see Figure 1 and Table 1).

**Basic principles of acid–base balance**

The kidneys have a major role in regulating the H$^+$ ion concentration or pH of the body fluids. In a healthy individual, the arterial pH of the extra cellular fluid (ECF) has a range of 7.38–7.42 and this corresponds to the H$^+$ ion concentration of 42–38 nmol/l (0.00004 mmol/l).

The major threats to the pH of the body fluids are from the acids formed in the metabolism of carbohydrates, fats and proteins consumed in a daily diet (4,5). These metabolic acids can be divided into three categories.
Volatile acids
When there is adequate tissue perfusion in the presence of insulin, oxidation of carbohydrates and fats yield carbon dioxide (CO₂), as the major end product. CO₂ reacts with water to form carbonic acid (H₂CO₃), which in turn, can dissociate to form H⁺ and HCO₃⁻:

\[
\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^-.
\]

Carbon dioxide is called a volatile acid, as it can be excreted via the lungs. All acids other than H₂CO₃ are non-volatile acids, hence they are not excreted by the lungs.

Organic acids
These acids are formed from incomplete metabolism of carbohydrates (e.g. lactate) and fats (e.g. ketones) when there is poor tissue perfusion and insulin deficiency. Organic acids are considered non-volatile acids and they consume bicarbonate for conversion into CO₂.

Fixed acids
Fixed acids are typically produced from protein metabolism;
- Sulphuric acid from sulphur containing amino acids methionine and cysteine.
- Phosphoric acid from the metabolism of phospholipids, nucleic acids, phospholipoproteins and phosphoglycerides.
- Amino acids glutamate and aspartate have both COO⁻ and NH₃⁺ groups at physiological pH and oxidation of these groups will result in production of equal amounts of bicarbonate and ammonium.

The liver is the major net producer of fixed acids from protein metabolism. It also removes excess NH₄⁺ by urea synthesis and also transports ammonia to kidneys via glutamine. For each ammonium converted to urea in the liver, a single molecule of bicarbonate is consumed:

\[
2\text{NH}_4^+ + 2\text{HCO}_3^- = \text{Urea} + \text{CO}_2 + 3\text{H}_2\text{O}.
\]
A typical protein rich western diet would yield approximately 100 mmol (1–1.5 mmol/kg) H+ every day. It represents a 25,000-fold increase in basal H+ concentration and could be disastrous unless excreted by the kidneys.

As the non-volatile acids are buffered for the most part by the bicarbonate buffer system, the body is left with an overall deficit of HCO3−. To maintain acid-base balance, the kidneys must not only reclaim all the filtered HCO3−, but also generate new HCO3−. Most of the filtered HCO3− is reabsorbed in the proximal tubules and generation of new HCO3− occurs in the distal and collecting tubules during the excretion of H+.

Normally, 80–85% of the filtered bicarbonate is reabsorbed in the proximal tubule with the help of the enzyme carbonic anhydrase (CA; 6). Epithelial cells of the proximal tubule synthesize H2CO3 via CA. H2CO3 then ionizes into H+ and HCO3−. The process of Na+–H+ exchange recreates H2CO3 in the lumen and NaHCO3 in the cell, which is absorbed into the peritubular venous blood. The net effect is the reabsorption of one molecule of HCO3− and one molecule of Na+ from the tubular lumen into the blood stream for each molecule of H+ secreted (7). This mechanism does not lead to the net excretion of any H+ from the body as the H+ is consumed in the reaction with the filtered bicarbonate in the tubular lumen.

Proximal tubule is also the major site of ammonia synthesis from amino acid glutamine (8). Most of the proximally secreted ammonia is removed from the tubular fluid by the thick ascending loop of Henle into the medullary interstitium and is later secreted into the collecting tubules.

Around 10% of the filtered bicarbonate is reabsorbed in the loop of Henle and the remaining 5–10% is reabsorbed in the collecting tubules. The process of bicarbonate reabsorption in the distal tubule involves an HCO3Cl− exchanger. Principal cells reabsorb Na+ via the epithelial Na+ channels causing an electronegative tubular lumen, which favours the secretion of both K+ (principal cells) and H+ (intercalated cells) into the lumen.

Hydrogen ion secretion from the intercalated cells in the distal convoluted tubule involves the H+-ATPase pump. Although this proton secretory pump is under direct influence of aldosterone, acid excretion can occur indirectly by the negative charge created by Na+ reabsorption in the cortical collecting tubules. In comparison, the process of hydrogen ion excretion in the medullary collecting tubules is sodium independent (9).

Figure 1 Algorithm for diagnosing RTA. RTA, renal tubular acidosis; NH4+Cl−, ammonium chloride; AG, anion gap

Hyperchloremic Normal Anion Gap Metabolic Acidosis

- Fe HCO3 > 15%
- Urine pH >5.3
- IV Sodium Bicarbonate load
- Proximal (type II) RTA, Confirmed
- Voltage defect
  - Confirmed
  - E.g.; Sickle cell disease
- Hypokalemia and unchanged K excretion after diuretics
- H-ATPase pump defect confirmed
  - E.g.; Sjogren’s syndrome
- Urine pH persistently >5.3
- Type I RTA, Confirmed
- Check U-B pCO2 & Urine K before and after diuretics
- Urine-Blood pCO2 difference > 25 mm

- Proximal (type II) RTA with serum HCO3 above threshold
- Type IV RTA
  - Confirmed
  - E.g.; Diabetes
- Type IV RTA
  - Confirmed
  - E.g.; Amphotericin B

- Proximal (type II) RTA with serum HCO3 below threshold
- Type IV RTA
  - Confirmed
  - E.g.; Diabetes
- Type IV RTA
  - Confirmed
  - E.g.; Amphotericin B

- Proximal (type II) RTA
  - Urine AG –ve
  - Type I RTA
  - Confirmed
- Hypokalemia and increased K excretion after diuretics
- Type IV RTA
  - Confirmed
  - E.g.; Diabetes
- Type IV RTA
  - Confirmed
  - E.g.; Amphotericin B

- Type I RTA
  - Confirmed
  - E.g.; Diabetes
- Type IV RTA
  - Confirmed
  - E.g.; Diabetes
- Type IV RTA
  - Confirmed
  - E.g.; Amphotericin B

- Urine AG +ve
- Urine pH >5.3
- Distal RTA’s
- Urine AG +ve
- Urine pH >5.3
- Acidity of glomerular Insufficiency

- Urine AG +ve
- Urine pH <5.3
- Proximal (type II)
  - RTA
  - Confirmed
- Distal RTA’s
- Acidity of glomerular Insufficiency

- Urine AG +ve
- Urine pH <5.3
- Acidity of glomerular Insufficiency

- Urine AG +ve
- Urine pH <5.3
- Acidity of glomerular Insufficiency
Distal tubules secrete the daily acid load as H⁺ ions generated within the cells from the dissociation of H₂O (H₂O = H⁺ and OH⁻ ions). These OH⁻ ions combine with CO₂ to form HCO₃⁻ ions by intracellular CA. Thus, secretion of each H⁺ ion into the lumen is associated with generation of one HCO₃⁻ ion within the tubular cell, which is returned to the plasma.

Distal nephrons are capable of actively secreting hydrogen ions against large concentration gradients (Final urine pH may reach 4.4 while blood pH is 7.4) and the distal luminal membrane is normally resistant to passive back diffusion of secreted H⁺ ions (certain drugs can compromise this barrier, resulting in reduced net secretion of acid).

The filtered bicarbonate in the distal tubular lumen combines with the secreted H⁺ ions to form H₂CO₃. As CA is not readily accessible to the collecting tubular lumen, the formed H₂CO₃ slowly dehydrates to CO₂ and H₂O, which are passively reabsorbed and converted into HCO₃⁻ ions inside the cells. This delayed dehydration of H₂CO₃ increases urinary pCO₂ values (> 65 mm) well in excess of that in the blood samples (40 mm). As this increment in urinary pCO₂ is ultimately derived from distally secreted protons, the urine–blood (U–B) pCO₂ difference (> 25 mm) becomes a semi quantitative index of distal nephron acid secretion during bicarbonate loading.

It is important to emphasise that the daily acid load cannot be excreted till all of the filtered HCO₃⁻ has been reabsorbed. H⁺ ions secreted in excess of those required to reabsorb filtered HCO₃⁻ bind with non-bicarbonate buffers in the tubular fluid, most important of which are ammonia and phosphate.

A low pH in the collecting tubule caused by active H⁺ secretion and low bicarbonate concentration greatly augments transfer of ammonia from the medullary interstitium into the luminal fluid. Ammonia buffers the luminal H⁺ ions in the collecting duct and becomes NH₄⁺ in the tubule lumen and is eliminated in the urine. For every molecule of NH₄⁺ excreted, a molecule of HCO₃⁻ is returned to the systemic circulation from the proximal tubule. In the absence of an acidic pH in the collecting tubule, ammonia in the medullary interstitium will be returned to the liver by the systemic circulation where it will be converted to urea, while consuming HCO₃⁻ during the process. Thus, the overall process of HCO₃⁻ regeneration is not complete unless the NH₄⁺ is excreted (10).

The amount of ammonia produced by the proximal tubules can increase markedly in acidosis. This involves synthesis of new enzymes and requires several days for complete adaptation (11). Plasma K⁺ concentration alters ammonia production, which is inhibited by hyperkalaemia and stimulated by hypokalaemia.

Titratable acidity (TA) represents the H⁺ ion, which is buffered by the limited amounts of filtered phosphate in the urine (HPO₄²⁻ + H⁺ = H₂PO₄⁻). In comparison with ammonia, production of phosphate cannot increase significantly in the presence of acidosis. The TA can be measured in the urine from the amount of sodium hydroxide needed to titrate the urine pH back to 7.4, hence the name ‘titratable acidity’ (12). Ammonium is not measured as part of the TA because the high pK value of ammonium prevents H⁺ from being removed from NH₄⁺ during titration to a pH of 7.4.

The net effect of the excretion of one H⁺ is the return of one HCO₃⁻ and one Na⁺ to the blood stream. RTAs result from various forms of congenital and acquired tubular dysfunction resulting in impaired urinary acidification (13). Their differentiating clinical features are described below (see Table 1).

### Proximal renal tubular acidosis (type II RTA)

Type II RTA occurs in two phases (14).

#### The period of transient HCO₃⁻ wasting

When the reabsorption capacity of the proximal tubule is impaired (rather than complete inhibition), less of the filtered HCO₃⁻ is reabsorbed in this segment. The increased distal HCO₃⁻ delivery overwhelms the limited capacity of the distal nephron, leading to bicarbonaturia. This period of transient bicarbonate wasting results in ECF volume contraction and secondary hyperaldosteronism with resulting hypokalaemia. Chloride reabsorption is enhanced secondary to ECF volume contraction. The alkaline collecting tubule lumen reduces net acid excretion causing a hyperchloremic metabolic acidosis as an end result. During this period, FeHCO₃ is high with an alkaline urine pH (> 6) and urine anion gap may be negative.

#### The steady state

Urinary bicarbonate wasting continues until the plasma HCO₃⁻ level reaches a new low level (12–18 meq/l), at which point most of the filtered bicarbonate is reabsorbed as a result of enhanced distal tubular reabsorption, resulting in acidic urine pH (< 5.3). Thus, type II RTA is a self-limiting disorder and the systemic acidosis is not progressive despite total absence of proximal HCO₃⁻ reabsorption (15).

With oral bicarbonate therapy or when challenged with IV sodium bicarbonate infusion, the amount of
bicarbonate in the urine increases (FeHCO$_3$ > 15%) and the urine pH becomes alkaline. Impaired production of NH$_3$ in the proximal tubule may result from diffuse tubular dysfunction, which may lower the rate of NH$_4^+$ excretion into the urine with a positive urine anion gap.

**Aetiology and clinical features of proximal (type II) RTA**

Proximal (type II) RTA in children results from inherited defects in the genes for the transmembrane transporters responsible for proximal acidification (16–18).

Inactivating mutations of the Na$^+$HCO$_3^-$ symporter can cause permanent isolated proximal RTA. As the Na$^+$HCO$_3^-$ symporter is expressed in multiple ocular tissues and pancreas, patients may present with various ocular abnormalities (glaucoma, cataracts) and pancreatitis (19,20). Inactivating mutations of the CA II gene leading to proximal (type II) RTA is typically accompanied by osteoporosis and mental retardation (21). In children, proximal (type II) RTA is also commonly associated with cystinosis and with the chemotherapeutic agent Ifosfamide, which is used in the treatment of several solid tumours.

The two most common causes of proximal (type II) RTA in adults are multiple myeloma and the use of CA inhibitors (22,23). The light chains are resistant to degradation by proteases in lysosomes in the proximal tubular cells and their accumulation is presumably responsible for the tubular impairment (24).

The proximal defect in bicarbonate reabsorption may appear as an isolated defect or as a more generalised impairment of all the substances reabsorbed by the proximal tubule (varying degrees of phosphate, glucose, amino acids, calcium, citrate and uric acid wasting often accompanies the bicarbonate wasting). The latter form is called Fanconi syndrome and the majority of cases of proximal (type II) RTA are manifested by this abnormality (25) (Table 2).

Type II RTA causes osteomalacia, rickets in children and osteopenia, pseudofractures in adults in about 20% of the patients (26).

Despite high calcium excretion in patients with proximal (type II) RTA, nephrocalcinosis is rare, because the following factors limit the amount of free calcium available to precipitate with phosphate or oxalate: (i) concomitant excretion of citrate, which can form soluble complexes with calcium, and (ii) acidic distal tubular urine pH in steady state increases the solubility of calcium phosphate.

### Table 2  Common causes of proximal (type II) RTA

<table>
<thead>
<tr>
<th>Isolated defect</th>
<th>Generalised defect (Fanconi syndrome)</th>
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<tbody>
<tr>
<td>Autosomal dominant proximal RTA from unknown gene mutation</td>
<td>Primary (genetic)</td>
</tr>
<tr>
<td>Autosomal recessive sodium-bicarbonate symporter (NBC1) protein mutation in SLC4A4 gene</td>
<td>Inborn errors of metabolism (cystinosis, Wilson’s disease, galactosemia, hereditary fructose intolerance, methylmalonic academia, glycogen storage diseases)</td>
</tr>
<tr>
<td>Inherited carbonic anhydrase II deficiency caused by mutations in CA2 gene – associated with mental retardation, cerebral calcifications and osteopetrosis (Sly syndrome)</td>
<td>Dysproteinemic states (myeloma, monoclonal gammopathy)</td>
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<tr>
<td>Drugs (acetazolamide)</td>
<td>Secondary hyperparathyroidism with chronic hypocalcaemia, vitamin D deficiency</td>
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<td></td>
<td>Tubulointerstitial diseases (Sjogren’s syndrome, medullary cystic disease, renal transplantation)</td>
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<td></td>
<td>Nephrotic syndrome</td>
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<tr>
<td></td>
<td>Amyloidosis</td>
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<tr>
<td></td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
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<td></td>
<td>Toxins (lead, mercury, copper, cadmium, glue sniffing)</td>
</tr>
<tr>
<td></td>
<td>Drugs (outdated tetracycline, ifosfamide, cisplatin, gentamycin, valproic acid)</td>
</tr>
</tbody>
</table>

**Diagnosis and treatment of proximal (type II) RTA**

The presence of type II RTA should be suspected in any patient with an unexplained normal anion gap metabolic acidosis, even if the urine pH is below 5.3 and urine anion gap may be negative or positive (see Figure 1).

When patients in the steady state are treated with alkali therapy (IV sodium bicarbonate 0.5–1.0 meq/kg/h), the plasma HCO$_3^-$ increases above the threshold and bicarbonaturia ensues resulting in urine pH $> 7.5$ and FeHCO$_3$ $> 15–20\%$ (27):

$$\text{FeHCO}_3^- = \frac{\text{Urine HCO}_3^- \times \text{Plasma Cr}}{\text{Plasma HCO}_3^- \times \text{Urine Cr}} \times 100.$$

As distal renal tubules have substantial bicarbonate reabsorptive capacity, the plasma bicarbonate concentration usually does not fall below 12 meq/l in patients with proximal (type II) RTA. As the exogenous alkali is rapidly excreted in the urine, high doses (10–30 mEq/kg/day) of citric acid/sodium citrate (Bicitra; Ortho-Mcneil-Janssen pharmaceuticals, Inc., Titusville, NJ) are required to restore adequate serum bicarbonate levels. Citrate is rapidly metabolised to HCO$_3^-$ and is better tolerated than HCO$_3^-$ solutions.
Correcting the HCO₃⁻ to near-normal values (22–24 mEq/l) is desirable in children to preserve normal growth, but not required in adults. Patients with proximal (type II) RTA tend to become hypokalemic once alkali therapy is initiated. When the plasma HCO₃⁻ concentration is normalised, the high distal delivery of bicarbonate induces kaliuresis, requiring large supplements of K⁺ (28).

When large doses of alkali are ineffective or poorly tolerated, the addition of a distal diuretic may increase the proximal reabsorption of sodium along with bicarbonate secondary to volume depletion. Amiloride is preferred over thiazides because of the potassium sparing effect (29).

**Classic distal renal tubule acidosis (type I RTA)**

The characteristic feature of classic RTAs is an inability to acidify the urine maximally (to less than pH 5.3) in the face of systemic acidosis (13,30). In most patients with classic RTA, the urine pH is around 6.5, reflecting the unabsorbed normal distal load of bicarbonate.

The causes of type I RTA can be grouped as hypokalaemic and hyperkalaemic forms (see Table 3):

**Hypokalaemic type I RTA**

- Impaired net secretion of H⁺ ions. As a result of the defects in the basolateral membrane ATPase. This could be genetic or acquired because of diseases like Sjogren’s syndrome. This results in reduced acid excretion despite normal aldosterone effect on H⁺-ATPase pump.
- Increased permeability of the luminal membranes to secreted protons. This results in back diffusion of H⁺ ions despite the presence of an effective pump. This gradient defect is classically seen in patients treated with Amphotericin B (31). Before the back diffusion occurs, the secreted H⁺ ions in the tubular lumen bind with HCO₃⁻ to form H₂CO₃. As there is no luminal CA, H₂CO₃ is slowly dehydrated to CO₂ and water and this results in transient high urine pCO₂ levels in the urine. This is the only type of classic RTA with high urine pCO₂ levels (> 65 mmHg) and corresponding high urine-blood pCO₂ difference (> 25 mmHg).

Patients with the above conditions tend to have urinary potassium wasting and hypokalaemia prior to therapy because sodium reabsorption in the collecting tubules occurs more in exchange with potassium, as the net distal hydrogen ion secretion is diminished. Chronic metabolic acidosis results in less bicarbonate reabsorption by the proximal tubule, which in turn results in less proximal sodium reabsorption. Increased sodium wasting in the urine results in secondary hyperaldosteronism leading to hypokalaemia.

Concurrent decreased activity of the second proton pump (H⁺ K⁺ ATPase) in the intercalated cells is

<table>
<thead>
<tr>
<th>Table 3 Common causes of type I RTA</th>
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<tbody>
<tr>
<td><strong>Hypokalaemic classic renal tubular acidosis</strong></td>
</tr>
<tr>
<td>Calcium induced Tubular damage</td>
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<tr>
<td>Idiopathic hypercalciuria</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
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<tr>
<td>Hypervitaminosis D</td>
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<tr>
<td>Medullary sponge kidney</td>
</tr>
<tr>
<td>Drugs and Toxins</td>
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<tr>
<td>Amphotericin B</td>
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<tr>
<td>Ifosfamide</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Analgesic abuse</td>
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<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Toluene</td>
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<tr>
<td><strong>Idiopathic causes</strong></td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
</tr>
<tr>
<td>Wilson’s disease</td>
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<tr>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td><strong>Hyperkalaemic classic renal tubular acidosis</strong></td>
</tr>
<tr>
<td>Decreased effective intravascular volume of any cause</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
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<tr>
<td>Renal transplant rejection</td>
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</tbody>
</table>

RTA, renal tubular acidosis; SLE, systemic lupus erythematosus.
sometimes seen along with defective primary proton pump activity. As the main function of this pump is to reabsorb potassium in states of depletion, its inhibition may promote urinary K⁺ wasting.

**Hyperkalaemic type I RTA (voltage-dependent defect)**

Normal gradient-driven proton secretion requires a higher number of cations in the cell compared with the lumen, creating a transepithelial negative voltage gradient. This negative gradient can be altered by the following conditions:

- **Reduced distal sodium delivery as a result of enhanced proximal tubule reabsorption.** Seen in conditions with decreased effective arterial volume (CHF, nephrotic syndrome, cirrhosis) and also any cause of marked volume depletion.
- **Reduced distal sodium reabsorption.** Seen when sodium channels are blocked by use of drugs (Amiloride, Triamterene, Lithium, Trimethoprim or Pentamidine) or by urinary tract obstruction. Patients with sickle cell disease and lupus nephritis may present with hyperkalaemic variant of classic RTA (33,34).

As a consequence of increased intraluminal sodium, the distal tubular lumen becomes relatively less electronegative compared with the cell (voltage-dependent defect) and transepithelial K⁺ secretion is impaired leading to hyperkalaemia (32). The pathogenesis of metabolic acidosis is the result of the unfavourable voltage, which impairs H⁺ secretion by the intercalated cells or the inhibition of ammonium production and transport as a consequence of hyperkalaemia. These patients have normal aldosterone levels and normal amounts of H⁺-ATPase in the intercalated cells (34).

**Aetiology and clinical features of type I RTA**

The most common causes in adults are autoimmune disorders (Sjogren’s syndrome, rheumatoid arthritis), hypercalciuria, recreational toluene sniffing and drug-induced (amphotericin B) and -marked volume depletion (see Table 3).

In children, type I RTA is most often a hereditary condition. Genetic mutations in the chloride-bicarbonate cotransporter (SLC4A1 gene) and in the apical H⁺-ATPase (ATP6V1B1 and ATP6V0A4 genes) have been identified (35–38).

Patients with Sjögren’s syndrome may reveal complete absence of H⁺-ATPase pumps in the intercalated cells in renal biopsy (39). They also show presence of high titres of autoantibodies directed against CA II enzyme. CA II inhibition further impairs hydrogen ion generation within the cell for secretion into the lumen (40).

Type I RTA is associated with abnormalities in potassium balance, depending on the type of defect. Occasionally, patients with severe hypokalaemia may present with quadriplegia or respiratory arrest (41). Nephrolithiasis is very frequently associated with untreated classic RTA. Chronic persistent metabolic acidosis increases calcium phosphate release from the bone during buffering of excess hydrogen ions and also reduces tubular reabsorption of these ions. The resulting hypercalciuria and hyperphosphaturia lead to the precipitation of calcium phosphate stones.

This process is also promoted by low urinary citrate levels, as citrate normally binds to calcium and is excreted in the urine as calcium citrate (42). Hypocitraturia results from enhanced proximal tubule reabsorption, which is facilitated by acidosis in the proximal tubular cells (43,44).

**Diagnosis and treatment of type I RTA**

The presence of classic RTA should be suspected in any patient with a normal anion gap metabolic acidosis and a urine pH > 5.3. Urinary tract infection with Proteus and other urea-splitting organisms should be excluded, as NH₃ is generated from hydrolysis of urea and can alkalinise the normally formed urine in the urinary bladder.

The characteristic feature of type I RTA is persistent urine pH of > 5.3 even in the presence of a metabolic acidosis induced by NH₄⁺Cl⁻ loading (see Table 1). As oral ammonium chloride administration (100 mg/kg) often induces nausea and vomiting, an alternative test of urinary acidification, which is actually faster and more reliable is the simultaneous oral administration of Furosemide (40 mg) and Fludrocortisone (1 mg) (47). Urinary acidification response to simultaneous furosemide and fludrocortisone is typically seen within 3–4 h.

**Response to loop diuretics and mineralocorticoid**

Loop diuretics increase distal sodium delivery and increased sodium reabsorption in the cortical collecting tubule enhances the luminal electronegativity resulting in more H⁺ and K⁺ ion secretion. Fludrocortisone may be administered along with loop diuretics to further enhance intercalated cell proton secretion (47).

In normal subjects with metabolic acidosis, the expected acidic urine pH (< 5.3) is further lowered by loop diuretics. By contrast, patients with diffuse impairment of the H⁺-ATPase pump will have a persistently
alkaline urine pH, but will show a rise in K+ excretion, reflecting the intact principal cell function (48).

In contrast to hypokalaemic classic distal RTA, patients with hyperkalaemic classic RTA (voltage-dependent defect) do not increase H+ or K+ excretion in response to furosemide (49). Hyperkalaemic type I RTA may appear similar to type IV RTA. However, in type I RTA aldosterone levels are normal and the acidifying defect is more severe, leading to a urine pH that is above 5.3 and a plasma bicarbonate concentration below 15 meq/l. These patients are unable to increase acid or K+ excretion in response to furosemide or fludorcortisone (see Table 4).

**Urine–blood pCO2 difference after bicarbonate loading**

When the distal tubule becomes markedly alkaline after bicarbonate loading, secretion of H+ ions leads to the formation of H2CO3, which dehydrates into CO2 and H2O (45,46). In patients with defective H+ ion secretion, the U–B pCO2 difference is close to that of blood. Higher U–B pCO2 difference (higher pCO2 levels in urine than blood) is seen only in patients with intact H+ ion secretion and with H+ ion back diffusion. Amphotericin B-induced distal RTA is the most common example of such a 'gradient' defect (31).

**Incomplete type I RTA**

Some patients may have an incomplete variant of the disease and retain normal serum bicarbonate levels despite alkaline urine pH. Nephrolithiasis may still occur in them because of hypocitraturia (50). As opposed to complete type I RTA, they retain normal rates of ammonium excretion from possible enhanced production of ammonia by the proximal tubules (51). These patients still fail to excrete the acid load when challenged with ammonium chloride and retain urine pH > 5.3. Recognition of incomplete type I RTA is important in these patients, as the administration of potassium citrate can reduce stone formation.

Correction of acidosis is required to allow normal growth in children, to prevent osteopenia and to minimise nephrolithiasis. Alkali requirements may be equal to 1–3 mEq/kg/day. Citric acid, potassium citrate, sodium citrate (Polycitra; Ortho-Mcneil-Janssen pharmaceuticals, Inc.) are especially useful in this setting (52). Maintenance of normal serum bicarbonate with alkali therapy also raises urinary citrate, lowers the frequency of nephrolithiasis and tends to restore normal growth in children (53).

### Hyperkalaemic type IV renal tubule acidosis

Aldosterone directly stimulates H+ ion secretion by the H+-ATPase pump in the intercalated cells and also K+ ion secretion by the principal cells. By increasing sodium reabsorption, aldosterone increases luminal electronegativity and indirectly increases H+ ion secretion (54).

**Aetiology and clinical features of type IV RTA**

Aldosterone deficiency, resistance or inhibition (Table 5) may result in hyperkalaemic, hyperchlorae-

#### Table 4 Response to diuretics in different types of type I RTA

<table>
<thead>
<tr>
<th>Defect</th>
<th>Urine studies before diuretics</th>
<th>Urine studies after diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine pH</td>
<td>Urine K</td>
</tr>
<tr>
<td>Normal response</td>
<td>&lt; 5.0</td>
<td>Normal</td>
</tr>
<tr>
<td>H+ ion excretion defect</td>
<td>&gt; 5.3</td>
<td>Increased</td>
</tr>
<tr>
<td>H+ ion back diffusion</td>
<td>&gt; 5.3</td>
<td>Increased</td>
</tr>
<tr>
<td>Sodium reabsorptive/voltage defect</td>
<td>&gt; 5.3</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

#### Table 5 Common causes of type IV RTA

<table>
<thead>
<tr>
<th>Aldosterone deficiency</th>
<th>Aldosterone resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>21-hydroxylase deficiency</td>
<td>Sickle cell nephropathy</td>
</tr>
<tr>
<td>Hyporeninemia</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>AIDS</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>Pseudohypoaldosteronism</td>
</tr>
<tr>
<td>IgM monoclonal gammopathy</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Aldosterone inhibition</td>
<td>Drugs that interfere with tubular Na+ channel function</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Amiloride</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Triamterene</td>
</tr>
<tr>
<td>Cyclooxygenase inhibitors</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Heparin</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Lovenox</td>
<td></td>
</tr>
<tr>
<td>Drugs that interfere with basolateral Na+K+ ATPase</td>
<td>Cyclosporine and tacrolimus</td>
</tr>
</tbody>
</table>


Renal tubular acidosis
Renal tubular acidosis (55–60). In addition, the resulting hyperkalaemia impairs renal ammonia synthesis (61). This effect may result from:

- Decrease in ammonium production by the proximal tubule.
- Competitive inhibition of binding of NH4+ to K+ site on the Na+-K+-2Cl− carrier in the loop of Henle.
- Decreased NH4+ concentration in the medullary interstitium.
- Decrease in NH3/NH4+ secretion into outer and inner medullary conducting duct.

As gradient driven H+ ion secretion continues despite the absence of aldosterone, the resulting metabolic acidosis is not as severe as seen in classic RTA. Urine pH becomes acidic during periods of acute metabolic acidosis or NH4+Cl− loading (see Figure 1).

Limitation of basolateral Na+ K+-ATPase activity by cyclosporine and tacrolimus decreases intracellular K+ and the transepithelial potential, which together decrease the driving force for K+ secretion (62).

Hyporeninemic hypoaldosteronism is the most common cause of type IV RTA. Patients with this disorder are usually older diabetics and exhibit mild renal insufficiency.

**Diagnosis and treatment of type IV RTA**

Both the metabolic acidosis and the hyperkalaemia are usually out of proportion to the level of reduction in glomerular filtration rate (GFR). The metabolic acidosis seen with type IV RTA is generally mild and correcting the hyperkalaemia often leads to increased NH4+ excretion and correction of acidosis. Although mineralocorticoid replacement is effective, as most patients with type IV RTA have underlying renal insufficiency, this can exacerbate oedema or hypertension. Loop diuretics often effectively induce renal potassium and salt excretion (63).

**Acidosis of glomerular insufficiency**

The metabolic acidosis seen from reduction in functional renal mass is initially hyperchloremic in nature (GFR, 20–30 ml/min), but converts to the normochloremic, high-AG variety as renal insufficiency progresses and the GFR falls below 15 ml/min (64). The principal defect in net acid excretion in these patients is not an inability to secrete H+ in the distal nephron, but rather an inability to produce or to excrete NH4+ ion. There is impaired net acid excretion when the plasma HCO3− concentration is in the normal range, with preserved ability to lower the urine pH during acidosis. The U–B pCO2 gradient is normal, reflecting the intact distal H+ secretory capacity.

When the net acid excretion is impaired, alkaline salts from bone buffer the positive acid load and this results in progressive dissolution of bone and muscle wasting. Alkali replacement (1–2 mEq/kg/day) to maintain the plasma bicarbonate concentration above 22 meq/l usually restores acid-base equilibrium and prevents acid retention.

**Conclusions**

The presence of RTA should be considered in any patient with an otherwise unexplained normal anion gap metabolic acidosis. The diagnosis of proximal (type II) RTA is made by measurement of the urine pH and fractional bicarbonate excretion during a bicarbonate infusion. The hallmark is urine pH above 7.5 and the appearance of more than 15 per cent of the filtered bicarbonate in the urine when the serum bicarbonate concentration is raised to a normal level. Classic type I distal RTA presents with an inappropriately high urine pH (greater than 5.3) in the presence of acidosis and is often associated with nephrolithiasis. Type IV RTA is because of either aldosterone deficiency or resistance and hyperkalaemia is the primary electrolyte abnormality in these patients.

Serum electrolytes such as blood urea nitrogen, calcium, phosphorus and creatinine should be obtained. A urinalysis is performed for the evaluation of glycosuria and proteinuria. Renal ultrasonography can be performed to identify obstructive uropathies. When nephrolithiasis is present, a 24 h urinary calcium measurement may identify hypercalciuria. The mainstay of therapy in all forms of RTA is bicarbonate replacement with varying dose requirements in each condition. As the prognosis is dependent on the nature of the underlying disease, a thorough diagnostic work up should be carried out for any new onset RTA.

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Renal tubular acidosis

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