

# Fluid, electrolyte and acid–base disorders associated with antibiotic therapy

R. Zietse, R. Zoutendijk and E. J. Hoorn

**Abstract** | Antibiotics are among the most frequently prescribed drugs in medicine. Their use, however, is often limited by associated renal toxic effects. The most common manifestation of these toxic effects is decreased glomerular filtration rate. However, they can also occur while renal function remains near to normal. This Review focuses on antibiotic-associated fluid, electrolyte and acid–base disorders that do not greatly reduce glomerular filtration. Renal tubules can be affected by antibiotics at various locations. In the proximal tubule, toxic effects of tetracyclines and aminoglycosides can result in complete proximal tubular dysfunction, also known as Fanconi syndrome. Aminoglycosides (and capreomycin) can also affect the loop of Henle and lead to a Bartter-like syndrome. In the collecting ducts, antibiotics can cause a diverse range of disorders, including hyponatremia, hypokalemia, hyperkalemia, renal tubular acidosis, and nephrogenic diabetes insipidus. Causative antibiotics include trimethoprim, amphotericin B, penicillins, ciprofloxacin, demeclocycline and various antitubercular agents. Here, we describe the mechanisms that disrupt renal tubular function. Integrated with the physiology of each successive nephron segment, we discuss the receptors, transporters, channels or pores that are affected by antibiotics. This insight should pave the way for pathophysiology-directed treatment of these disorders.

Zietse, R. *et al.* *Nat. Rev. Nephrol.* 5, 193–202 (2009); doi:10.1038/nrneph.2009.17

## Introduction

The introduction of antibiotic treatment counts as one of the great medical achievements of the 20<sup>th</sup> century. Compared to early treatments with chemical compounds, antibacterial antibiotics are highly effective and have a favorable adverse-effect profile.

Renal clearance of a drug, and/or its metabolites, is an important mechanism for the elimination of antibiotics. This pharmacokinetic property determines the risk of adverse effects to the kidneys and, therefore, kidney function should be monitored in patients who receive high doses of these drugs. Despite the large therapeutic window for most of these agents, renal impairment often occurs, as revealed by an impaired glomerular filtration rate. Even when little impairment in this rate is seen, however, antibiotic-associated renal damage might still be present. Additionally, renal failure due to tubular necrosis or interstitial nephritis has been described as a consequence of treatment with several classes of antibiotics, such as aminoglycosides and vancomycin. However, antibiotic-induced acute renal failure is not discussed further in this article because that topic has been extensively reviewed elsewhere.<sup>1,2</sup>

The nature of the damage depends on the renal handling of the drug. Although most antibiotics are cleared by glomerular filtration, tubular function can be disrupted in any part of the entire nephron; consequently, most renal toxic effects occur further downstream, in

the tubules. For instance, treatment with aminoglycosides is associated with contraction and proliferation of glomerular mesangial cells,<sup>3</sup> but most histological abnormalities associated with administration of these agents occur in the proximal tubule.<sup>4</sup> Gentamicin is the best-studied of this class of drugs, but several studies have documented similar effects of tobramycin on proximal tubular histology.

Following glomerular filtration, the renal tubules determine the ultimate composition of the urine according to physiological demands. Vast amounts of water and solutes are reabsorbed along the nephron, and substances that are not readily filtered are added to urine by active tubular secretion. Subtle abnormalities in tubular reabsorption or secretion that may not lead to overt renal failure can result in a wide variety of abnormal electrolyte profiles<sup>5</sup> and lead to severe disorders related to fluid, electrolyte and/or acid–base balance. For example, hypokalemia and hyperkalemia can both cause serious cardiac arrhythmias, muscle weakness and death. Hypokalemia has also been associated with rhabdomyolysis and intestinal ileus, among other conditions.<sup>5</sup> Finally, physicians should bear in mind that many infections can induce abnormalities of renal tubular function, which further complicates the management of these patients.

In this Review we focus on the tubular dysfunctions that lead to fluid, electrolyte and acid–base disturbances in the context of a partly preserved glomerular filtration rate. Topics are discussed in relation to each successive

Department of Nephrology, Erasmus Medical Centre, Rotterdam, The Netherlands (R Zietse, R Zoutendijk, EJ Hoorn).

Correspondence: R Zietse, Department of Nephrology, Erasmus Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands (r.zietse@erasmusmc.nl)

## Competing interests

The authors declared no competing interests.

**Key points**

- Renal tubular function can be affected by antibiotic treatment without a concurrent reduction in glomerular filtration rate
- Hypokalemia is a frequent complication of antimicrobial therapy
- Treatment with aminoglycosides can affect renal tubular function in several ways and can lead to hypokalemia, as well as acidosis and alkalosis
- If unexpected disturbances in electrolyte and/or acid–base balance occur in a patient, their prescribed medications should be carefully checked

**Table 1** | Fluid, electrolyte and acid–base disturbances caused by antibiotic treatment

Clinical disturbance and relevant drugs	Frequency	Mechanism	Reference
<b>Hyponatremia</b>			
Trimethoprim	Rare	Blocks ENaCs	57
Ciprofloxacin	Rare	Vasopressin release by increased intracranial pressure	97
<b>Hypernatremia</b>			
Amphotericin B	Rare	Downregulation of aquaporin 2	74
Demeclocycline	Frequent	Reduced vasopressin-stimulated water transport	82
<b>Hypokalemia</b>			
Amphotericin B	Frequent	Disruption of cell membrane, leading to potassium leak	66
Penicillin	Frequent	Nonreabsorbable anion	84
Aminoglycosides	Frequent	Bartter-like syndrome by CaSR stimulation	18
Capreomycin	Frequent	Bartter-like syndrome by CaSR stimulation	45
<b>Hyperkalemia</b>			
Trimethoprim	Frequent	Blocks ENaCs	54,55
Penicillin	Rare	Potassium load	102
Amphotericin B	Rare	Shift to the extracellular compartment	103
<b>High-anion-gap metabolic acidosis</b>			
Penicillins	Rare	Pyroglutamate acidosis	96
Linezolid	Rare	Mitochondrial toxicity	90
Virtually all antibiotics	Rare	D-Lactic acidosis (enteric bacterial overgrowth)	92
<b>Non-anion-gap metabolic acidosis</b>			
Tetracyclines	Rare	Fanconi syndrome	89
Aminoglycosides	Rare	Fanconi syndrome	26
Trimethoprim	Frequent	Blocks ENaCs	64
Amphotericin B	Frequent	Disruption of cell membrane, leading to proton leak	66
<b>Metabolic alkalosis</b>			
Aminoglycosides	Rare	Bartter-like syndrome by CaSR stimulation	18
Capreomycin	Rare	Bartter-like syndrome by CaSR stimulation	45

Abbreviations: CaSR, calcium-sensing receptor; ENaC, epithelial sodium channel.

region of the nephron; we briefly present the physiology of each segment and describe the pathophysiology of antibiotic-induced changes (Table 1) in terms of renal reabsorption of water and ions of sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>) and hydrogen (H<sup>+</sup>). The renal tubular effects of antiretroviral drugs, which can cause Fanconi syndrome and nephrogenic diabetes insipidus,<sup>6</sup> are beyond the scope of this Review.

**Proximal tubule**

**Physiology**

In the proximal tubule 50–80% of the filtrate is reabsorbed. The main mechanism of sodium reabsorption involves sodium hydrogen exchanger type 3 (NHE-3), via which Na<sup>+</sup> enters the cell in exchange for H<sup>+</sup> secreted into the tubular fluid, and the basolateral Na<sup>+</sup>,K<sup>+</sup>-ATPase (Figure 1), which pumps Na<sup>+</sup> out of the cell and into the interstitium.<sup>7</sup> Carbonic anhydrase converts H<sup>+</sup> and bicarbonate ions in the tubular fluid to carbonic acid, which dissociates into water and carbon dioxide. Water and carbon dioxide are subsequently reabsorbed through aquaporin 1 water channels in the apical plasma membrane.<sup>8</sup> Intracellular carbonic anhydrase converts the water and carbon dioxide back to H<sup>+</sup> and bicarbonate ions; H<sup>+</sup> is secreted into the tubular fluid again and the bicarbonate ions are transported across the basolateral membrane.

Derangement of this process may lead to proximal (type II) renal tubular acidosis.<sup>9</sup> Another role of the proximal tubule in acid–base balance is in ammonia-genesis (the formation of NH<sub>4</sub><sup>+</sup> from glutamine).<sup>8</sup> Several solutes, such as phosphate, glucose and amino acids, are reabsorbed in the proximal tubule by secondary, active, sodium-coupled cotransporters, and consequently antibiotics that disrupt Na<sup>+</sup> influx into renal tubular cells also disturb reabsorption of these solutes. K<sup>+</sup>, calcium ions (Ca<sup>2+</sup>) and magnesium ions (Mg<sup>+</sup>) are reabsorbed in the proximal tubule through solvent drag, (paracellular) diffusion and apparent active transport.<sup>10</sup>

**Antibiotic-induced effects**

The two main groups of antibiotics that can affect proximal tubular function and cause fluid and electrolyte disorders are the aminoglycosides and tetracyclines (Figure 1).

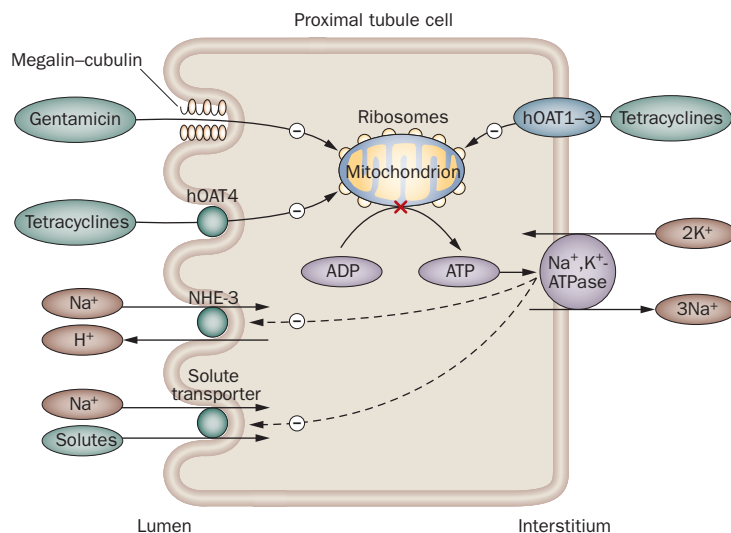
Aminoglycosides act therapeutically by binding to prokaryotic ribosomes and inhibiting bacterial protein synthesis.<sup>11</sup> In the kidney, aminoglycosides are freely filtered and subsequently reabsorbed in the proximal tubule by megalin, a low-affinity, high-capacity, endocytic receptor,<sup>12</sup> with subsequent attachment of the antibiotic to phospholipid membranes.<sup>13</sup> Thus, receptor-mediated endocytosis has an important role in the accumulation of aminoglycosides in the proximal tubule. Mitochondrial ribosomes seem to be more sensitive to aminoglycosides than do cytosolic ribosomes or those bound to the endoplasmic reticulum, perhaps because mitochondria are thought to be derived from (and in

many ways resemble) bacteria.<sup>14</sup> The inhibition of microsomal protein synthesis is an early manifestation of gentamicin's nephrotoxic effects, which occur well before the induction of necrosis in proximal tubular cells.<sup>14</sup> Localization of aminoglycosides to the mitochondrion results in mitochondrial dysfunction and impaired generation of ATP,<sup>15</sup> which in turn reduces the activity of the basolateral  $\text{Na}^+, \text{K}^+$ ATPase. Several other mechanisms of aminoglycoside-induced toxic effects in renal tubular cells have been proposed, such as inhibition of the phosphatidylinositol cascade<sup>16</sup> and lysosomal instability,<sup>17</sup> but these processes might only be involved in late-stage disease when extensive damage has occurred. Aminoglycosides can also affect individual cellular transporters; in rats, gentamicin 80 mg/kg per day for 7 days led to decreased expression of NHE-3 in the proximal tubule.<sup>18</sup>

Aminoglycosides induce proteinuria and enzymuria in humans<sup>19</sup> and animal models.<sup>20</sup> Long-term administration of 80 mg/kg per day gentamicin to rats resulted in a more than fivefold increase in urinary total protein excretion and increased excretion of enzymes associated with the brush-border membrane.<sup>20</sup> In proximal tubule cells the activity of enzymes involved in the citric acid cycle was markedly reduced. This observation seems to confirm previous findings that gentamicin-induced toxic effects on the proximal tubule primarily result from damaged mitochondrial function and ATP production. Since endocytosis is an energy-dependent process, impaired mitochondrial functioning could also explain the increase in proteinuria seen in aminoglycoside-treated patients.

Gentamicin can stimulate the extracellular calcium-sensing receptor (CaSR) in the thick ascending limb of the loop of Henle<sup>21</sup> and, therefore, identification of this receptor in the apical membrane of the proximal tubule is of potential interest with regard to gentamicin toxicity.<sup>22,23</sup> *In vitro*, administration of aminoglycosides initially causes alterations in cellular signaling and proliferation of cells that express the CaSR, followed by apoptosis.<sup>24</sup> Gentamicin-induced cell death could be prevented by administration of a CaSR antagonist.<sup>25</sup> However, the physiological function or functions of the CaSR in the proximal tubule and its putative involvement in aminoglycoside toxicity remain unclear.

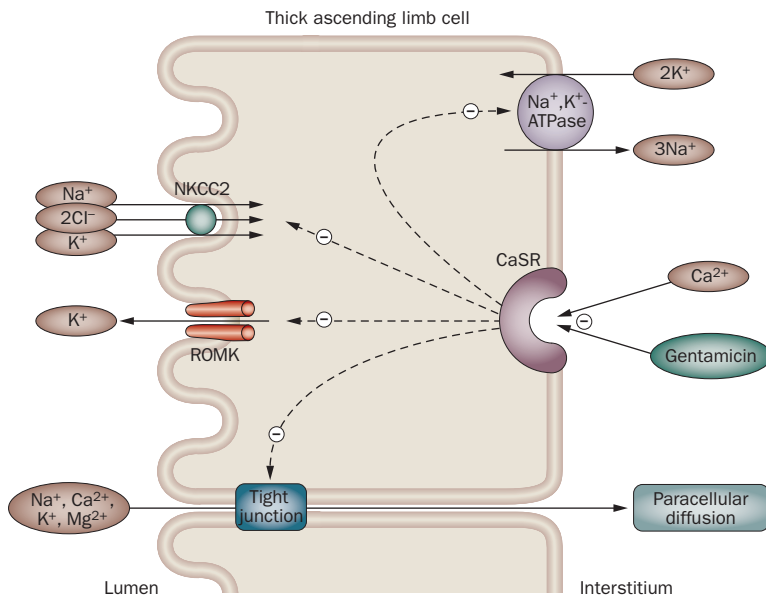
Disturbances of proximal tubular function associated with aminoglycosides either affect isolated transport mechanisms or have a generalized nature that is referred to as Fanconi syndrome. Although this syndrome is usually accompanied by a reduction in glomerular filtration rate, several patients with preserved renal function have been described.<sup>26</sup> Generally, tubular function is restored after discontinuation of the drug.<sup>27</sup> An early indication of aminoglycoside-induced disturbances in proximal tubular function is increased urinary excretion of amino acids.<sup>28</sup> In patients with cystic fibrosis, *N*-acetyl- $\beta$ -D-glucosaminidase (a lysosomal enzyme present in renal proximal tubule cells) has been



**Figure 1** | Antibiotics that affect proximal tubule cells. Gentamicin enters the cell through the megalin-cubulin system, while tetracyclines enter via apical or basolateral organic anion transporters. Gentamicin and tetracyclines can impair the function of mitochondrial ribosomes and interfere with the conversion of ADP to ATP. Consequently, these antibiotics inhibit the  $\text{Na}^+, \text{K}^+$ -ATPase pump, which is dependent upon ATP, and also indirectly (dashed lines) inhibit NHE-3 and other sodium-dependent solute transporters, including transporters for amino acids, uric acid and glucose. Abbreviations: H<sup>+</sup>, hydrogen ions; hOAT, organic anion transporter; K<sup>+</sup>, potassium ions; Na<sup>+</sup>, sodium ions; NHE-3, sodium hydrogen exchanger 3.

advocated as a sensitive urinary marker of aminoglycoside-induced tubular damage.<sup>29</sup> Interestingly, in mouse models of gentamicin-induced nephrotoxic effects, cellular accumulation of gentamicin and increased urinary excretion of *N*-acetyl- $\beta$ -D-glucosaminidase was prevented by treatment with cationic proteins and their peptide fragments, which stopped gentamicin from binding to the endocytic receptor, megalin.<sup>30</sup> Moreover (also in mice), megalin deficiency offers protection from aminoglycoside accumulation in the proximal tubule.<sup>12</sup> Megalin proteins can become saturated with bound aminoglycosides. This saturation can be exploited by employing once-daily doses of aminoglycosides, which has been shown to limit their toxic effects.<sup>31</sup>

A second group of antibiotic agents implicated in Fanconi syndrome is the tetracyclines. Proximal tubular damage can sometimes be induced by tetracycline metabolites within 1 week of starting treatment.<sup>32,33</sup> Tetracyclines may enter the proximal tubular epithelial cell through organic anion transporters, either across the basolateral or the apical plasma membranes (Figure 1).<sup>34</sup> Ribosomes are the main intracellular target of tetracycline. Although this drug binds to eukaryotic ribosomes with an affinity at least 15 times lower than that for bacterial ribosomes,<sup>35</sup> its renal toxic effects are likely to result largely from partial inhibition of ribosomal protein synthesis.<sup>36</sup> Like aminoglycosides, tetracyclines preferentially affect mitochondrial ribosomes owing to their resemblance to bacterial ribosomes.<sup>37</sup> Histological examination of kidney tissue after tetracycline



**Figure 2** | Antibiotics that affect the thick ascending limb of the loop of Henle. Gentamicin, other aminoglycosides and capreomycin can stimulate the CaSR. This stimulation can disrupt electrolyte transport via inhibition of four different pathways that involve NKCC2, ROMK, Na<sup>+</sup>,K<sup>+</sup>-ATPase and/or paracellular diffusion. Inhibition of these transport mechanisms leads to increased urinary excretion of Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup> and Ca<sup>2+</sup>, and associated electrolyte disorders. Abbreviations: Ca<sup>2+</sup>, calcium ions; CaSR, calcium-sensing receptor; Cl<sup>-</sup>, chloride ions; K<sup>+</sup>, potassium ions; Mg<sup>2+</sup>, magnesium ions; Na<sup>+</sup>, sodium ions; NKCC2, the kidney-specific Na<sup>+</sup>,K<sup>+</sup>,Cl<sup>-</sup> symporter, now termed solute carrier family 12 member 1; ROMK, renal outer medullary potassium channel.

treatment showed a striking vacuolization of the proximal tubule epithelium.<sup>38</sup>

The main clinical presentation of tetracycline toxic effects is hypokalemia secondary to increased distal delivery of sodium bicarbonate.<sup>33</sup> Glucosuria, aminoaciduria, and phosphaturia are also seen, consistent with Fanconi syndrome.

Amphotericin B induces enzymuria (that is, significantly increased urinary excretion of *N*-acetyl- $\beta$ -D-glucosaminidase,  $\beta$ -glucuronidase, alanine aminopeptidase and  $\gamma$ -glutamyltransferase) in rats. This finding suggests that proximal tubular damage is present.<sup>39</sup> No clinical occurrences of Fanconi syndrome have, however, been reported in patients treated with this drug.

**Thick ascending limb Physiology**

The thick ascending limb of the loop of Henle performs several tasks. It is water-impermeable, but is a major site for reabsorption of Na<sup>+</sup>, K<sup>+</sup> and chloride ions (Cl<sup>-</sup>) through kidney-specific Na<sup>+</sup>,K<sup>+</sup>,Cl<sup>-</sup> symporter channels (NKCC2, now renamed solute carrier family 12, member 1).<sup>7</sup> Removal of these ions from the lumen contents results in increased medullary osmolality, which provides the driving force for water reabsorption in the collecting duct. The reabsorption of Na<sup>+</sup> and subsequent recycling of K<sup>+</sup> to the lumen via the apical ATP-sensitive

inward-rectifier potassium channel (ROMK) leads to the luminal positive charge required for the paracellular reabsorption of divalent cations, such as Ca<sup>2+</sup>.

In Bartter syndrome, Na<sup>+</sup>, K<sup>+</sup> and Cl<sup>-</sup> transport are impaired because of an autosomal-recessive mutation in genes that encode the Na<sup>+</sup>,K<sup>+</sup>,Cl<sup>-</sup> symporters NKCC1 and NKCC2, ROMK, or basolateral chloride channels (*SLC12A2*, *SLC12A1*, *KCNJ1* and others).<sup>40</sup> Reabsorption of Na<sup>+</sup> and Ca<sup>2+</sup> is closely linked in this nephron segment and, consequently, the activities of both NKCC2 and ROMK are influenced by serum Ca<sup>2+</sup> concentrations. In the thick ascending limb of the loop of Henle, the CaSR is present on the basolateral epithelial cell membrane. Increased serum Ca<sup>2+</sup> levels stimulate this receptor and lead to reductions in secondary, active reabsorption of Na<sup>+</sup>, which reduces the luminal positive driving force and results in increased urinary calcium excretion.<sup>22</sup>

**Antibiotic-induced effects**

A Bartter-like syndrome characterized by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalcemia and serum creatinine levels within the normal range has been described in patients treated with aminoglycosides.<sup>41,42</sup> Gentamicin, a polyvalent, cationic molecule, is thought to activate the CaSR in the thick ascending limb of the loop of Henle (Figure 2) and the distal convoluted tubule. Thus, aminoglycoside treatment can lead to abnormalities that resemble those seen in patients with autosomal-dominant hypocalcemia,<sup>43</sup> which is caused by gain-of-function mutations in the *CASR* gene.<sup>21</sup> This condition is also termed type V Bartter syndrome.<sup>40</sup> Studies of gentamicin administration in rats showed increased excretion of Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and Mg<sup>+</sup>. At a dose of 40 mg/kg, gentamicin decreased the expression of NKCC1 in the thick ascending limb of the loop of Henle and induced a Bartter-like syndrome (Figure 2).<sup>18</sup> These findings are also compatible with an effect of gentamicin on the basolateral CaSR.

Among patients who develop a Bartter-like syndrome, most are female. In all such patients, the clinical symptoms always resolve when aminoglycosides are withdrawn.<sup>21</sup> The dose above which this effect of gentamicin on the thick ascending limb of the loop of Henle occurs varies widely (for example, some case reports noted total gentamicin doses of 1.2–2.6 g).<sup>21</sup> In a prospective study performed in 127 consecutive patients treated with aminoglycosides, we observed hypokalemia in 13% of the patients, whereas the incidence of Bartter-like syndrome was 2% (R Zietse, R Zoutendijk and EJ Hoorn, unpublished data).

Multidrug regimens used to treat tuberculosis are frequently associated with hypokalemia.<sup>44</sup> Although multiple factors in individuals with tuberculosis could lead to hypokalemia, its occurrence is strongly associated with the use of capreomycin. This drug, similarly to gentamicin, may induce a Bartter-like syndrome, in which renal wasting of Na<sup>+</sup> and Cl<sup>-</sup> results in volume depletion, hyperaldosteronism and hypokalemia.<sup>45</sup>

## Distal convoluted tubule

### Physiology

As part of the 'aldosterone-sensitive' distal nephron, the distal convoluted tubule is involved in electroneutral reabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$  through the thiazide-sensitive sodium-chloride cotransporter.<sup>7</sup> Throughout the connecting tubule, the epithelial  $\text{Na}^+$  channel (ENaC) is expressed, which, when activated by aldosterone, leads to a transmembrane voltage potential that is negative on the apical side.<sup>46</sup> This electrochemical driving force is important in the secretion of  $\text{K}^+$  ions. Although  $\text{H}^+$  ions undergo active transport towards the lumen by  $\text{H}^+$ -ATPase, the luminal negative charge is also important for effective secretion of  $\text{H}^+$  in the distal parts of the nephron.

The distal convoluted tubule is the only site of transcellular magnesium reabsorption, where  $\text{Mg}^{2+}$  enter the cell through apical transient receptor potential cation channel subfamily M member 6 (TRPM6).<sup>47</sup> This channel seems to interact with the thiazide-sensitive sodium-chloride cotransporter, as absent or inhibited activity of this cotransporter leads to downregulation of TRPM6 and results in hypomagnesemia.<sup>48</sup>

### Antibiotic-induced effects

Gentamicin might affect the distal convoluted tubule as well as upstream nephron segments, since magnesium wasting is a common adverse effect of aminoglycoside treatment. A causal relationship between gentamicin administration and magnesium wasting has been suggested by studies in nonhuman primates.<sup>49</sup> In healthy human individuals, gentamicin caused an immediate, transient, and substantial increase in fractional renal excretion of  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$ , which could be consistent with altered transport of these ions in the distal convoluted tubule.<sup>50</sup> From studies performed in an immortalized mouse distal convoluted tubule cell line, Kang *et al.*<sup>51</sup> concluded that gentamicin acts through an effect on the extracellular polyvalent-cation-sensing receptor, which is present in distal convoluted tubule cells.

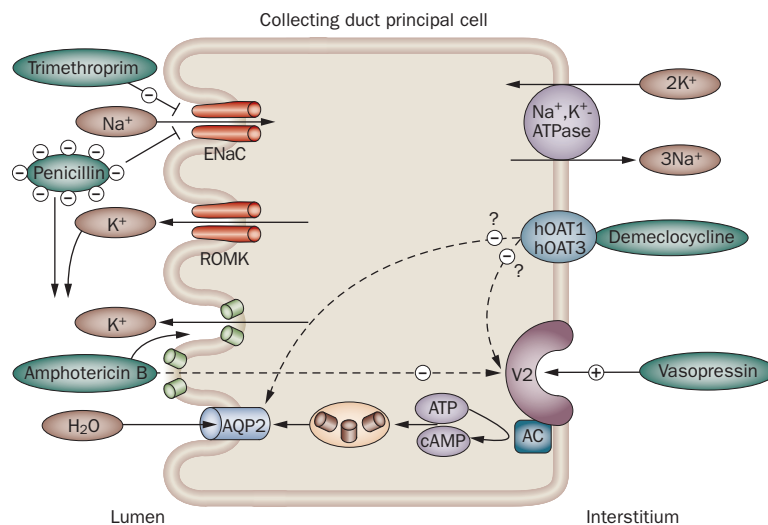
## Collecting duct

### Physiology

Functionally, the collecting duct can be divided into cortical and medullary parts. The medullary collecting duct can be further subdivided into inner and outer regions.

The cortical collecting duct is part of the aldosterone-sensitive segment of the nephron. The main means of cation transport throughout the whole aldosterone-sensitive segment is  $\text{Na}^+$  entry from the luminal fluid through ENaCs, which leads to a transmembrane voltage potential that is negative on the lumen side, and to  $\text{K}^+$  secretion through the ROMK channel (Figure 3).

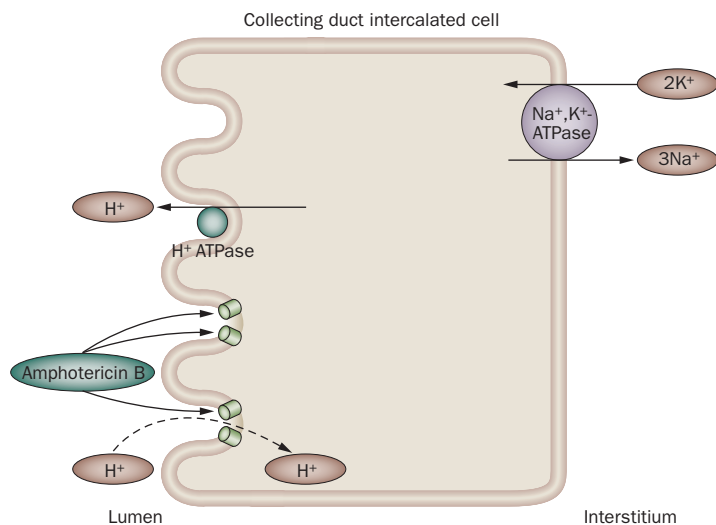
Both the inner and outer medullary collecting ducts are essential to determine the concentration of the urine. An increase in serum osmolality leads to the release of vasopressin by the pituitary gland. Vasopressin acts on its



**Figure 3** | Antibiotics that affect collecting-duct principal cells. Trimethoprim blocks ENaCs similarly to amiloride, which causes  $\text{Na}^+$  wasting, reduced kaliuresis, and distal renal tubular acidosis (because  $\text{H}^+$  excretion decreases). Penicillin acts as a nonreabsorbable anion that maintains a luminal negative charge if aldosterone-driven  $\text{Na}^+$  reabsorption is increased. This negative charge stimulates  $\text{K}^+$  secretion and may cause hypokalemia. Demeclocycline and amphotericin B both cause nephrogenic diabetes insipidus, by inhibiting vasopressin-stimulated V2–AQP2 signaling. Amphotericin B creates pores in cell membranes; once inside, it inhibits  $\text{G}_s\alpha$  proteins and/or adenylate cyclase. These pores leak  $\text{K}^+$ , which induces hypokalemia. How demeclocycline disrupts vasopressin–aquaporin signaling is unknown, but it probably enters the cell via hOAT1 or hOAT3. Abbreviations: AC, adenylate cyclase; AQP2, aquaporin 2; cAMP, cyclic AMP; ENaC, epithelial sodium channel (amiloride-sensitive sodium channel); hOAT, organic anion transporter;  $\text{K}^+$ , potassium ions;  $\text{Na}^+$ , sodium ions; V2, vasopressin 2 receptor.

receptor V2 on the basolateral membrane of the principal cells in the collecting duct (Figure 3), which results in the insertion of aquaporin 2 in the apical plasma membrane. In concert with the constitutively expressed aquaporin 3 and aquaporin 4 channels on the basolateral membrane, these water channels enable the reabsorption of water, driven by the osmotic gradient between the lumen and interstitium. Moreover, in mouse studies, stimulation of V2 increased urea reabsorption through increased expression of urea transporters in the inner medullary collecting duct, which increases the ability of the kidney to reabsorb water.<sup>52</sup>

Finally, the collecting duct is important in maintenance of the acid–base balance (Figure 4). Both the cortical and inner medullary collecting ducts contain a subset of specialized, intercalated cells that express  $\text{H}^+$ -ATPase and  $\text{H}^+$ , $\text{K}^+$ -ATPase.  $\text{H}^+$  in these cells are actively transported to the lumen. Whereas the proximal tubule contributes to acid–base homeostasis by the reabsorption of filtered bicarbonate, this distal nephron segment is able to produce 'new' bicarbonate, which is essential to buffer the net 50–70 mmol per day of  $\text{H}^+$  that is ingested or produced by degradation of protein. Failure of distal  $\text{H}^+$  secretion leads to distal (type I) renal tubular acidosis.<sup>53</sup>



**Figure 4** | Antibiotics that affect collecting duct intercalated cells. Amphotericin B can create pores in the cell membrane. These pores allow a backflux of H<sup>+</sup> into the cell, which inhibits urinary H<sup>+</sup> excretion and, therefore, results in distal renal tubular acidosis. Abbreviations: H<sup>+</sup>, hydrogen ions; K<sup>+</sup>, potassium ions; Na<sup>+</sup>, sodium ions.

#### Antibiotic-induced effects

All the transport mechanisms in the collecting ducts can be affected by a variety of antibiotics, including trimethoprim, amphotericin B, penicillins, and demeclocycline (Figures 3 and 4).

Hyperkalemia is a common adverse effect of treatment with trimethoprim, which is frequently prescribed in combination with sulfamethoxazole (one part to five parts) as co-trimoxazole.<sup>54,55</sup> Less frequently, administration of trimethoprim leads to renal tubular Na<sup>+</sup> wasting that may induce hypovolemia-induced vasopressin release and hyponatremia.<sup>54,56</sup> Trimethoprim acts on the apical membrane of the cortical collecting duct, where it inhibits Na<sup>+</sup> influx via ENaCs, which decreases the net driving force for K<sup>+</sup> exit across the apical cell membrane and results in inhibition of K<sup>+</sup> secretion.<sup>57</sup> Renal failure increases the risk of trimethoprim-induced hyperkalemia, but potassium excretion was also decreased in healthy volunteers with normal renal function who received this drug.<sup>58</sup>

On the basolateral membrane of the cortical collecting duct, trimethoprim inhibits Na<sup>+</sup>, K<sup>+</sup>-ATPase,<sup>59</sup> which further reduces the kidney's ability to excrete potassium. Two strategies have been employed to ameliorate trimethoprim-induced antidiuresis. One strategy is to increase distal urine flow by the infusion of saline and administration of a loop diuretic (such as furosemide); the other is alkalization of the urine, for example with acetazolamide.<sup>60,61</sup> Only cationic trimethoprim competes with Na<sup>+</sup> for ENaC transport.<sup>62</sup> Thus, increased urinary pH decreases the concentration of positively charged trimethoprim and reduces its antidiuretic effect.<sup>62</sup> The voltage effect of inhibition of ENaCs also affects the ability of the distal nephron to excrete H<sup>+</sup>.

Indeed, treatment with trimethoprim might also result in voltage-dependent distal renal tubular acidosis.<sup>63</sup>

Amphotericin B is an effective drug for the treatment of systemic fungal infections. It alters the permeability of fungal cell membranes by binding to ergosterol in the lipid bilayer. Unfortunately, amphotericin B can also bind to cholesterol in mammalian cell membranes, and the altered ion permeability that results is the cause of a vast spectrum of renal toxic effects.<sup>64</sup> Such effects occur in a considerable number of patients treated with amphotericin B. For example, Wingard *et al.*<sup>65</sup> observed doubling of serum creatinine levels in 53% of treated patients, and creatinine levels exceeded 221 μmol/l in 29% of patients. Several mechanisms have been proposed to explain the reduction in glomerular filtration rate induced by amphotericin B. Although the mediator of this effect is as yet unclear, amphotericin B administration is associated with renal vasoconstriction and a reduction in renal blood flow. Other potential mechanisms, such as a reduction of the glomerular ultrafiltration coefficient and renal tubular toxic effects, have also been proposed.<sup>64</sup>

Obviously, a reduction in glomerular filtration rate following treatment with amphotericin B can be associated with disturbances of the fluid and electrolyte balance. Owing to the effects of this drug on membrane permeability to monovalent cations, however, it can have a marked, direct effect on tubular function without concomitant azotemia. A common renal tubular side effect of amphotericin B therapy is potassium wasting that leads to hypokalemia.<sup>66</sup> Occasionally, hypokalemia can be so severe that it results in rhabdomyolysis.<sup>67</sup>

Amphotericin B increases membrane permeability to K<sup>+</sup> in various tissues.<sup>64</sup> As renin and aldosterone levels do not increase during amphotericin B treatment,<sup>68</sup> alterations in the permeability of tubular cells in the distal nephron are likely, which cause a passive flux of K<sup>+</sup> down its electrochemical gradient. The induction of hypokalemia may further aggravate the renal tubular toxic effects induced by amphotericin B;<sup>69</sup> consequently, the development of hypokalemia must be recognized early and potassium supplementation should be started if necessary. Amphotericin B nephrotoxic effects are likely to be worse in patients who have depletion of potassium<sup>69</sup> or sodium<sup>68</sup> before treatment with this agent is initiated. Both amiloride and spironolactone reduce requirements for potassium supplementation in patients receiving amphotericin B.<sup>70,71</sup> Patients who have marked proteinuria (>3 g/l) seem to have a reduced risk of renal tubular toxic effects caused by amphotericin B,<sup>73</sup> an effect that may be related to a reduced concentration of free amphotericin B in tubular fluid as a consequence of free protein binding to this drug.

This ionic 'leakiness' of the distal nephron is also presumed to cause the distal renal tubular acidosis in patients treated with amphotericin B (Figure 4). In studies that used turtle bladders, Steinmetz *et al.*<sup>73</sup> demonstrated that although H<sup>+</sup> secretion was markedly reduced by administration of amphotericin B, it was not greatly affected when passive electrochemical transport

across the epithelium was minimized by abrogation of the transmembrane  $H^+$  concentration gradient. These results suggest that the impaired urine acidification associated with amphotericin B administration is caused by increased passive permeability of the luminal membrane and increased back-diffusion of  $H^+$ , rather than by failure of active transport.

Polyuria and nephrogenic diabetes insipidus due to a reduction in the concentrating ability of the kidney is another frequent finding in patients receiving amphotericin B.<sup>74</sup> Concomitant hypokalemia may be one of the causative factors, as it is known to inhibit vasopressin-stimulated water permeability in the collecting duct.<sup>75</sup> However, a renal concentration defect has also been shown in patients treated with amphotericin B who had serum potassium levels in the normal range.<sup>76</sup> Use of liposomal amphotericin B does not seem to prevent the development of nephrogenic diabetes insipidus.<sup>77</sup> *In vitro*, amphotericin B caused a partial inhibition of vasopressin-stimulated water permeability and urea transport in the inner medullary collecting ducts of rats.<sup>78</sup> Also, in rats, amphotericin B decreased the abundance of aquaporin 2 water channels, probably because it inhibited adenyl cyclase and/or G proteins.<sup>79</sup> Amphotericin-B-induced renal tubular toxic effects are not limited to one side effect, as this drug has been reported to cause combined renal tubular acidosis and nephrogenic diabetes insipidus.<sup>80</sup>

Nephrogenic diabetes insipidus is a well-known renal adverse effect of demeclocycline, a group I tetracycline derivative. Demeclocycline is thought to enter the principal cell in the collecting duct through renal organic anion transporter channels hOAT1 and hOAT3, located on the basolateral membrane (Figure 3).<sup>81</sup> In toad bladders, demeclocycline inhibits vasopressin-induced water flow.<sup>82</sup> In fact, demecocycline is often used to treat the syndrome of inappropriate secretion of antidiuretic hormone rather than for its antimicrobial properties.<sup>83</sup> Where in the vasopressin–aquaporin signaling cascade this drug interferes, however, is unknown.

Generally, the therapeutic window for penicillin use is large and drugs in this class have few toxic effects other than hypersensitivity-mediated disorders. Hypokalemia has been reported to occur in patients receiving penicillin derivatives,<sup>84</sup> and is thought to develop because these drugs act as nonreabsorbable anions, which maintain a transmembrane potential gradient that is negative on the lumen side (despite decreased distal delivery of  $Cl^-$ ) in the cortical collecting duct.<sup>85</sup> This effect may be augmented by volume depletion, which leads to increased aldosterone synthesis and potassium secretion. A low urinary  $Cl^-$  concentration is considered a diagnostic feature of hypokalemia due to a nonreabsorbable anion. We have, however, reported a case of flucloxacillin-induced hypokalemia in a patient who had a high urinary  $Cl^-$  concentration.<sup>86</sup> This observation suggests that other mechanisms, such as solute diuresis, are also involved.

The CaSR is present on the apical membranes of the principal cells in the collecting duct. Stimulation of this

receptor by calcium decreases the vasopressin-induced expression of aquaporin 2 water channels and leads to a decrease in urine-concentrating ability.<sup>87</sup> Although this receptor can also be stimulated by aminoglycosides, nephrogenic diabetes insipidus has not been reported in patients receiving this class of agents. Polyuria secondary to a renal concentrating defect has been reported in aminoglycoside-treated patients,<sup>88</sup> but this symptom probably results from the well-characterized effects of these agents on functions of the thick ascending limb of the loop of Henle.<sup>19</sup>

### Extrarenal toxic effects of antibiotics

Not all electrolyte and acid–base disturbances caused by antibiotics are a result of perturbed renal tubular function. In some patients, use of a tetracycline has been associated with lactic acidosis, possibly through an adverse effect on mitochondrial function.<sup>89</sup> This adverse effect may be more frequent when tetracyclines are used in combination with other drugs that affect mitochondrial function, such as antiviral drugs or metformin. Another antibiotic associated with lactic acidosis (after long-term use) is linezolid.<sup>90</sup> In this case, metabolic acidosis also seems to result from the inhibition of mitochondrial protein synthesis.<sup>91</sup> Antimicrobial therapy can also cause acid–base disorders that are not specific to this class of drugs, such as D-lactic acidosis related to antibiotic-associated enteric overgrowth of *Lactobacillus acidophilus*.<sup>92,93</sup> Differentiation between metabolic acidosis related to lactic acidosis and that related to renal tubular acidosis is important, and may be achieved by calculating the serum anion gap. When serum lactate measurements are normal in the presence of an increased anion gap, D-lactic acidosis may be present.<sup>93</sup>

Penicillins might cause high-anion-gap acidosis through disturbance of the  $\gamma$ -glutamyl cycle, which leads to rising serum concentrations of 5-oxoproline or pyroglutamate.<sup>94</sup> This adverse effect is, however, less frequent than with other antimicrobials or paracetamol. Pyroglutamic acidosis during penicillin treatment has been reported by several authors<sup>95,96</sup> and should, therefore, be considered in patients receiving penicillin if a high-anion-gap metabolic acidosis develops.

During treatment with ciprofloxacin, central nervous system side effects can be associated with hyponatremia, possibly owing to increased vasopressin release resulting from an increase in intracranial pressure.<sup>97</sup> In a group of patients with seizures related to the use of quinolones, hyponatremia was present in approximately one-third of the cases.<sup>98</sup>

Hyponatremia has also been described in patients treated with antitubercular agents, such as rifabutin,<sup>99</sup> capreomycin<sup>100</sup> and ethionamide.<sup>101</sup> Differentiation between hyponatremia caused by these agents and that related to other causes, such as the tuberculosis infection itself, adrenal insufficiency, syndrome of inappropriate antidiuresis and cerebral salt wasting is, however, difficult.

**Table 2** | Diagnostic features and treatment of antibiotic-associated renal-tubule disorders

Antibiotics and relevant disorders	Diagnostic features	Treatment <sup>a</sup>
<i>Aminoglycosides and tetracyclines</i>		
Proximal RTA or Fanconi syndrome	Non-anion-gap metabolic acidosis, hypokalemia with or without hypouricemia, hypophosphatemia, glucosuria, tubular proteinuria	Supplementation of potassium, bicarbonate and/or phosphate
Bartter-like syndrome	Hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalcemia natriuresis	Supplementation of potassium, magnesium and/or calcium, isotonic saline
<i>Amphotericin B</i>		
Distal RTA	Non-anion-gap metabolic acidosis, hypokalemia	Supplementation of bicarbonate and/or potassium
Hypokalemia	Urinary potassium loss	Supplementation of potassium, amiloride, spironolactone
Hyperkalemia	Potassium shift out of cells (no specific diagnostic test available)	Calcium (with arrhythmia), glucose–insulin, cation-exchange resin, isotonic saline
<i>Amphotericin B and demeclocycline</i>		
Nephrogenic diabetes insipidus	Synthetic-vasopressin-resistant polyuria, hyponatremia may be present	Thiazide diuretics, amiloride, low sodium and protein diet
<i>Trimethoprim</i>		
ENaC blockade	Hyperkalemia with or without hyponatremia	Isotonic saline, alkalization of the urine
Distal RTA	Non-anion-gap metabolic acidosis	Bicarbonate
<i>Penicillin</i>		
Hypokalemia	Typically low urine chloride and high urine potassium	Potassium supplementation
Hyperkalemia	High potassium in drug in patient with impaired kaliuresis	Calcium (with arrhythmia), glucose–insulin, cation-exchange resin, isotonic saline
Pyroglutamic acidosis	High-anion-gap metabolic acidosis	Discontinuation of the drug
<i>Tetracyclines and linezolid</i>		
Lactic acidosis	High-anion-gap metabolic acidosis with elevated lactate	Discontinuation of the drug

<sup>a</sup>Discontinuation of the offending antibiotic should always be considered, depending on the severity of the renal tubular disorder. The choice to start the treatments listed below should also depend on the clinical significance and severity of the disorder. Abbreviations: ENaC, epithelial sodium channel; RTA, renal tubular acidosis.

Rapid administration of large amounts of semi-synthetic penicillin derivatives and amphotericin B has been associated with acute hyperkalemia.<sup>102,103</sup> The underlying causes seem to be the potassium load in penicillin G and a shift from the intracellular to the extracellular compartment, respectively.

**Differential diagnosis and treatment**

Proximal and distal renal tubular acidosis fall into the category of metabolic acidosis that is not associated with an increased anion gap. When proximal renal tubular acidosis is part of Fanconi syndrome, in which hypophosphatemia, hypouricemia and tubular glucosuria and proteinuria are also present, it can be easily distinguished from distal renal tubular acidosis. If proximal tubular acidosis is isolated, however, differentiation is more difficult and relies on calculation of fractional bicarbonate excretion during infusion. Treatment is generally with bicarbonate therapy, but this approach might worsen hypokalemia in proximal renal tubular acidosis because a bicarbonate diuresis can cause potassium wasting; potassium bicarbonate is another option.<sup>80</sup> In all the causes of hypokalemia we have discussed, renal potassium loss is central to the pathogenesis.

Thus, assessment of urinary potassium excretion can be extremely useful; a (spot) urine potassium:creatinine ratio is the best indicator of renal potassium wasting. In patients with polyuria, a low urine osmolality and absence of a response to synthetic vasopressin is diagnostic for nephrogenic diabetes insipidus.

**Conclusions**

Several groups of patients are at risk of developing renal side effects of antimicrobial agents, including those with an impairment of renal function or volume depletion. Here, we have reviewed the many electrolyte disturbances that can be induced by commonly prescribed antimicrobial agents. Many of these adverse effects are dose-dependent and quite frequent (Table 1); consequently, the prudent physician should closely monitor serum electrolyte composition and acid–base balance during the treatment of infections. Readily available parameters in serum and urine can be used in diagnosis of the different fluid, electrolyte and acid–base disorders. If one of these disorders is suspected, assessing a broad range of electrolytes, including levels of creatinine, urea, sodium, chloride, potassium, magnesium, calcium, phosphate, bicarbonate,

uric acid, osmolality and/or albumin in serum and in urine, might facilitate diagnosis. Table 2 summarizes the diagnostic features and treatment options for fluid, electrolyte, and acid–base disorders caused by antibiotics. Dose adjustment and therapeutic drug monitoring are imperative. In caring for these patients, however, the ultimate decision to make is whether the characteristics of the infection for which the antibiotics are given outweigh the adverse effects caused by this treatment.

### Review criteria

In our literature search strategy we used the Medical Subject Headings (MeSH) “antibiotics”, “water–electrolyte imbalance”, “acid–base imbalance” and “kidney tubules”. In addition, PubMed was searched for the specific names of common antibiotics and groups of antibiotics as well as the specific names of fluid, electrolyte, and acid–base disorders.

- Rougier, F. *et al.* Aminoglycoside nephrotoxicity. *Curr. Drug Targets Infect. Disord.* **4**, 153–162 (2004).
- Gonzalez, E. *et al.* Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int.* **73**, 940–946 (2008).
- Martinez-Salgado, C., Lopez-Hernandez, F. J. & Lopez-Novoa, J. M. Glomerular nephrotoxicity of aminoglycosides. *Toxicol. Appl. Pharmacol.* **223**, 86–98 (2007).
- Rodríguez-Barbero, A., Lopez-Novoa, J. M. & Arevalo, M. Involvement of platelet-activating factor in gentamicin nephrotoxicity in rats. *Exp. Nephrol.* **5**, 47–54 (1997).
- Brown, R. S. Potassium homeostasis and clinical implications. *Am. J. Med.* **77**, 3–10 (1984).
- Izzedine, H., Launay-Vacher, V. & Deray, G. Antiviral drug-induced nephrotoxicity. *Am. J. Kidney Dis.* **45**, 804–817 (2005).
- Knepper, M. A. & Brooks, H. L. Regulation of the sodium transporters NHE3, NKCC2 and NCC in the kidney. *Curr. Opin. Nephrol. Hypertens.* **10**, 655–659 (2001).
- Boron, W. F. Acid–base transport by the renal proximal tubule. *J. Am. Soc. Nephrol.* **17**, 2368–2382 (2006).
- Igarashi, T. *et al.* Unraveling the molecular pathogenesis of isolated proximal renal tubular acidosis. *J. Am. Soc. Nephrol.* **13**, 2171–2177 (2002).
- Giebisch, G., Krapf, R. & Wagner, C. Renal and extrarenal regulation of potassium. *Kidney Int.* **72**, 397–410 (2007).
- Davies, J. & Davis, B. D. Misreading of ribonucleic acid code words induced by aminoglycoside antibiotics. The effect of drug concentration. *J. Biol. Chem.* **243**, 3312–3316 (1968).
- Schmitz, C. *et al.* Megalin deficiency offers protection from renal aminoglycoside accumulation. *J. Biol. Chem.* **277**, 618–622 (2002).
- Beauchamp, D., Gourde, P. & Bergeron, M. G. Subcellular distribution of gentamicin in proximal tubular cells, determined by immunogold labeling. *Antimicrob. Agents Chemother.* **35**, 2173–2179 (1991).
- Bennett, W. M. *et al.* Microsomal protein synthesis inhibition: an early manifestation of gentamicin nephrotoxicity. *Am. J. Physiol.* **255**, F265–F269 (1988).
- Weinberg, J. M., Harding, P. G. & Humes, H. D. Mechanisms of gentamicin-induced dysfunction of renal cortical mitochondria. II. Effects on mitochondrial monovalent cation transport. *Arch. Biochem. Biophys.* **205**, 232–239 (1980).
- Ramsammy, L. S., Josepovitz, C. & Kaloyanides, G. J. Gentamicin inhibits agonist stimulation of the phosphatidylinositol cascade in primary cultures of rabbit proximal tubular cells and in rat renal cortex. *J. Pharmacol. Exp. Ther.* **247**, 989–996 (1988).
- Powell, J. H. & Reidenberg, M. M. Further studies of the response of kidney lysosomes to aminoglycosides and other cations. *Biochem. Pharmacol.* **32**, 3213–3220 (1983).
- Sassen, M. C. *et al.* Dysregulation of renal sodium transporters in gentamicin-treated rats. *Kidney Int.* **70**, 1026–1037 (2006).
- Nix, D. E. *et al.* Assessment of the enzymuria resulting from gentamicin alone and combinations of gentamicin with various  $\beta$ -lactam antibiotics. *Ann. Pharmacother.* **31**, 696–703 (1997).
- Banday, A. A. *et al.* Time dependent effects of gentamicin on the enzymes of carbohydrate metabolism, brush border membrane and oxidative stress in rat kidney tissues. *Life Sci.* **82**, 450–459 (2008).
- Chou, C. L. *et al.* Acquired Bartter-like syndrome associated with gentamicin administration. *Am. J. Med. Sci.* **329**, 144–149 (2005).
- Riccardi, D. *et al.* Localization of the extracellular  $Ca^{2+}$ /polyvalent cation-sensing protein in rat kidney. *Am. J. Physiol.* **274**, F611–F622 (1998).
- Ward, D. T., McLarnon, S. J. & Riccardi, D. Aminoglycosides increase intracellular calcium levels and ERK activity in proximal tubular OK cells expressing the extracellular calcium-sensing receptor. *J. Am. Soc. Nephrol.* **13**, 1481–1489 (2002).
- Ward, D. T. *et al.* Aminoglycosides induce acute cell signaling and chronic cell death in renal cells that express the calcium-sensing receptor. *J. Am. Soc. Nephrol.* **16**, 1236–1244 (2005).
- Gibbons, C. E. *et al.* Calcium-sensing receptor antagonism or lithium treatment ameliorates aminoglycoside-induced cell death in renal epithelial cells. *Biochim. Biophys. Acta* **1782**, 188–195 (2008).
- Alexandridis, G., Liberopoulos, E. & Elisaf, M. Aminoglycoside-induced reversible tubular dysfunction. *Pharmacology* **67**, 118–120 (2003).
- Melnick, J. Z., Baum, M. & Thompson, J. R. Aminoglycoside-induced Fanconi's syndrome. *Am. J. Kidney Dis.* **23**, 118–122 (1994).
- Ghiculescu, R. A. & Kubler, P. A. Aminoglycoside-associated Fanconi syndrome. *Am. J. Kidney Dis.* **48**, e89–e93 (2006).
- Etherington, C. *et al.* Measurement of urinary *N*-acetyl- $\beta$ -D-glucosaminidase in adult patients with cystic fibrosis: before, during and after treatment with intravenous antibiotics. *J. Cyst. Fibros.* **6**, 67–73 (2007).
- Watanabe, A. *et al.* Targeted prevention of renal accumulation and toxicity of gentamicin by aminoglycoside binding receptor antagonists. *J. Control Release* **95**, 423–433 (2004).
- Nagai, J. & Takano, M. Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity. *Drug Metab. Pharmacokinet.* **19**, 159–170 (2004).
- Hemstreet, B. A. Antimicrobial-associated renal tubular acidosis. *Ann. Pharmacother.* **38**, 1031–1038 (2004).
- Babu, E. *et al.* Human organic anion transporters mediate the transport of tetracycline. *Jpn. J. Pharmacol.* **88**, 69–76 (2002).
- Montoliu, J. *et al.* Lactic acidosis and Fanconi's syndrome due to degraded tetracycline. *Br. Med. J. (Clin. Res. Ed.)* **283**, 1576–1577 (1981).
- Budkevich, T. V., El'skaya, A. V. & Nierhaus, K. H. Features of 80S mammalian ribosome and its subunits. *Nucleic Acids Res.* **36**, 4736–4744 (2008).
- Connell, S. R. *et al.* Ribosomal protection proteins and their mechanism of tetracycline resistance. *Antimicrob. Agents Chemother.* **47**, 3675–3681 (2003).
- Wirmer, J. & Westhof, E. Molecular contacts between antibiotics and the 30S ribosomal particle. *Methods Enzymol.* **415**, 180–202 (2006).
- Izzedine, H. *et al.* Drug-induced Fanconi's syndrome. *Am. J. Kidney Dis.* **41**, 292–309 (2003).
- Inselmann, G., Balaschke, M. & Heidemann, H. T. Enzymuria following amphotericin B application in the rat. *Mycoses* **46**, 169–173 (2003).
- Hebert, S. C. Bartter syndrome. *Curr. Opin. Nephrol. Hypertens.* **12**, 527–532 (2003).
- Shiah, C. J. *et al.* Acute muscular paralysis in an adult with subclinical Bartter's syndrome associated with gentamicin administration. *Am. J. Kidney Dis.* **24**, 932–935 (1994).
- Landau, D. & Kher, K. K. Gentamicin-induced Bartter-like syndrome. *Pediatr. Nephrol.* **11**, 737–740 (1997).
- Pollak, M. R. *et al.* Autosomal dominant hypocalcaemia caused by a  $Ca^{2+}$ -sensing receptor gene mutation. *Nat. Genet.* **8**, 303–307 (1994).
- Shin, S. *et al.* Hypokalemia among patients receiving treatment for multidrug-resistant tuberculosis. *Chest* **125**, 974–980 (2004).
- Steiner, R. W. & Omachi, A. S. A Bartter's-like syndrome from capreonycin, and a similar gentamicin tubulopathy. *Am. J. Kidney Dis.* **7**, 245–249 (1986).
- Ecelbarger, C. A. & Tiwari, S. Sodium transporters in the distal nephron and disease implications. *Curr. Hypertens. Rep.* **8**, 158–165 (2006).
- Alexander, R. T., Hoenderop, J. G. & Bindels, R. J. Molecular determinants of magnesium homeostasis: insights from human disease. *J. Am. Soc. Nephrol.* **19**, 1451–1458 (2008).

48. Nijenhuis, T. *et al.* Enhanced passive  $\text{Ca}^{2+}$  reabsorption and reduced  $\text{Mg}^{2+}$  channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. *J. Clin. Invest.* **115**, 1651–1658 (2005).
49. Finton, C. K. *et al.* Gentamicin-induced hypomagnesemia. *Am. Surg.* **49**, 576–578 (1983).
50. Elliott, C., Newman, N. & Madan, A. Gentamicin effects on urinary electrolyte excretion in healthy subjects. *Clin. Pharmacol. Ther.* **67**, 16–21 (2000).
51. Kang, H. S. *et al.* Aminoglycosides inhibit hormone-stimulated  $\text{Mg}^{2+}$  uptake in mouse distal convoluted tubule cells. *Can. J. Physiol. Pharmacol.* **78**, 595–602 (2000).
52. Fenton, R. A. & Knepper, M. A. Mouse models and the urinary concentrating mechanism in the new millennium. *Physiol. Rev.* **87**, 1083–1112 (2007).
53. Kamel, K. S. *et al.* A new classification for renal defects in net acid excretion. *Am. J. Kidney Dis.* **29**, 136–146 (1997).
54. Mori, H. *et al.* Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim–sulfamethoxazole. *Intern. Med.* **42**, 665–669 (2003).
55. Perazella, M. A. Trimethoprim is a potassium-sparing diuretic like amiloride and causes hyperkalemia in high-risk patients. *Am. J. Ther.* **4**, 343–348 (1997).
56. Ahn, Y. H. & Goldman, J. M. Trimethoprim–sulfamethoxazole and hyponatremia. *Ann. Intern. Med.* **103**, 161–162 (1985).
57. Muto, S. *et al.* Effect of trimethoprim–sulfamethoxazole on  $\text{Na}^+$  and  $\text{K}^+$  transport properties in the rabbit cortical collecting duct perfused *in vitro*. *Nephron Physiol.* **102**, p51–p60 (2006).
58. Don, B. R. The effect of trimethoprim on potassium and uric acid metabolism in normal human subjects. *Clin. Nephrol.* **55**, 45–52 (2001).
59. Eiam-Ong, S., Kurtzman, N. A. & Sabatini, S. Studies on the mechanism of trimethoprim-induced hyperkalemia. *Kidney Int.* **49**, 1372–1378 (1996).
60. Perazella, M. A. Trimethoprim-induced hyperkalemia: clinical data, mechanism, prevention and management. *Drug Saf.* **22**, 227–236 (2000).
61. Reiser, I. W. *et al.* Reversal of trimethoprim-induced antidiuresis. *Kidney Int.* **50**, 2063–2069 (1996).
62. Schreiber, M. *et al.* Antidiuretic action of trimethoprim is minimized by raising urine pH. *Kidney Int.* **49**, 82–87 (1996).
63. Lin, S. H. *et al.* Reversible voltage-dependent distal renal tubular acidosis in a patient receiving standard doses of trimethoprim sulfamethoxazole. *Nephrol. Dial. Transplant.* **12**, 1031–1033 (1997).
64. Sawaya, B. P., Briggs, J. P. & Schnermann, J. Amphotericin B nephrotoxicity: the adverse consequences of altered membrane properties. *J. Am. Soc. Nephrol.* **6**, 154–164 (1995).
65. Wingard, J. R. *et al.* Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin. Infect. Dis.* **29**, 1402–1407 (1999).
66. Burges, J. L. & Birchall, R. Nephrotoxicity of amphotericin B, with emphasis on changes in tubular function. *Am. J. Med.* **53**, 77–84 (1972).
67. Lucas da Silva, P. S., Iglesias, S. B. & Waisberg, J. Hypokalemic rhabdomyolysis in a child due to amphotericin B therapy. *Eur. J. Pediatr.* **166**, 169–171 (2007).
68. Gerkens, J. F. & Branch, R. A. The influence of sodium status and furosemide on canine acute amphotericin B nephrotoxicity. *J. Pharmacol. Exp. Ther.* **214**, 306–311 (1980).
69. Bernardo, J. F. *et al.* Potassium depletion potentiates amphotericin-B-induced toxicity to renal tubules. *Nephron* **70**, 235–241 (1995).
70. Wazny, L. D. & Brophy, D. F. Amiloride for the prevention of amphotericin B-induced hypokalemia and hypomagnesemia. *Ann. Pharmacother.* **34**, 94–97 (2000).
71. Ural, A. U. *et al.* Spirinolactone: is it a novel drug for the prevention of amphotericin B-related hypokalemia in cancer patients? *Eur. J. Clin. Pharmacol.* **57**, 771–773 (2002).
72. Mohan, S. *et al.* Proteinuria lowers the risk of amphotericin B-associated hypokalaemia. *J. Antimicrob. Chemother.* **60**, 690–693 (2007).
73. Steinmetz, P. R. & Lawson, L. R. Defect in urinary acidification induced *in vitro* by amphotericin B. *J. Clin. Invest.* **49**, 596–601 (1970).
74. Barbour, G. L. *et al.* Vasopressin-resistant nephrogenic diabetes insipidus. A result of amphotericin B therapy. *Arch. Intern. Med.* **139**, 86–88 (1979).
75. Frokiaer, J. *et al.* Pathophysiology of aquaporin-2 in water balance disorders. *Am. J. Med. Sci.* **316**, 291–299 (1998).
76. Butler, W. T. *et al.* Nephrotoxicity of amphotericin B: early and late effects in 81 patients. *Ann. Intern. Med.* **61**, 175–187 (1964).
77. Canada, T. W., Weavind, L. M. & Augustin, K. M. Possible liposomal amphotericin B-induced nephrogenic diabetes insipidus. *Ann. Pharmacother.* **37**, 70–73 (2003).
78. Yano, Y., Monteiro, J. L. & Seguro, A. C. Effect of amphotericin B on water and urea transport in the inner medullary collecting duct. *J. Am. Soc. Nephrol.* **5**, 68–74 (1994).
79. Kim, S. W. *et al.* Amphotericin B decreases adenyl cyclase activity and aquaporin-2 expression in rat kidney. *J. Lab. Clin. Med.* **138**, 243–249 (2001).
80. Hoorn, E. J. & Zietse, R. Combined renal tubular acidosis and diabetes insipidus in hematological disease. *Nat. Clin. Pract. Nephrol.* **3**, 171–175 (2007).
81. El-Sheikh, A. A., Masereeuw, R. & Russel, F. G. Mechanisms of renal anionic drug transport. *Eur. J. Pharmacol.* **585**, 245–255 (2008).
82. Hirji, M. R. & Mucklow, J. C. Transepithelial water movement in response to carbamazepine, chlorpropamide and demeclocycline in toad urinary bladder. *Br. J. Pharmacol.* **104**, 550–553 (1991).
83. Kinzie, B. J. Management of the syndrome of inappropriate secretion of antidiuretic hormone. *Clin. Pharm.* **6**, 625–633 (1987).
84. Brunner, F. P. & Frick, P. G. Hypokalaemia, metabolic alkalosis, and hypernatraemia due to “massive” sodium penicillin therapy. *Br. Med. J.* **4**, 550–552 (1968).
85. Lipner, H. I. *et al.* The behavior of carbenicillin as a nonreabsorbable anion. *J. Lab. Clin. Med.* **86**, 183–194 (1975).
86. Hoorn, E. J. & Zietse, R. Severe hypokalaemia caused by flucloxacillin. *J. Antimicrob. Chemother.* **61**, 1396–1398 (2008).
87. Bustamante, M. *et al.* Calcium-sensing receptor attenuates AVP-induced aquaporin-2 expression via a calmodulin-dependent mechanism. *J. Am. Soc. Nephrol.* **19**, 109–116 (2008).
88. Gordon, J. A. *et al.* The renal concentrating defect after gentamicin administration in the rat. *J. Lab. Clin. Med.* **101**, 903–910 (1983).
89. Blazes, D. L. & Decker, C. F. Symptomatic hyperlactataemia precipitated by the addition of tetracycline to combination antiretroviral therapy. *Lancet Infect. Dis.* **6**, 249–252 (2006).
90. Wiener, M. *et al.* Lactic acidosis after treatment with linezolid. *Infection* **35**, 278–281 (2007).
91. De Vriese, A. S. *et al.* Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin. Infect. Dis.* **42**, 1111–1117 (2006).
92. Coronado, B. E., Opal, S. M. & Yoburn, D. C. Antibiotic-induced D-lactic acidosis. *Ann. Intern. Med.* **122**, 839–842 (1995).
93. Halperin, M. L. & Kamel, K. S. D-lactic acidosis: turning sugar into acids in the gastrointestinal tract. *Kidney Int.* **49**, 1–8 (1996).
94. Fennes, A. Z. *et al.* Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. *Clin. J. Am. Soc. Nephrol.* **1**, 441–447 (2006).
95. Peter, J. V. *et al.* An unusual cause of severe metabolic acidosis. *Med. J. Aust.* **185**, 223–225 (2006).
96. Rolleman, E. J. *et al.* Guilty as charged: unmeasured urinary anions in a case of pyroglutamic acidosis. *Neth. J. Med.* **66**, 351–353 (2008).
97. Adler, D. *et al.* SIADH consecutive to ciprofloxacin intake. *Eur. J. Intern. Med.* **15**, 463–464 (2004).
98. Kushner, J. M., Peckman, H. J. & Snyder, C. R. Seizures associated with fluoroquinolones. *Ann. Pharmacother.* **35**, 1194–1198 (2001).
99. Chitre, M. M. & Berenson, C. S. Idiosyncratic rifabutin-induced leukopenia and SIADH: case report and review. *Pharmacotherapy* **21**, 493–497 (2001).
100. Holmes, A. M., Hesling, C. M. & Wilson, T. M. Capreomycin-induced serum electrolyte abnormalities. *Thorax* **25**, 608–611 (1970).
101. Nakashita, T. & Motojima, S. Case of SIADH caused by ethionamide in a patient with pulmonary tuberculosis [Japanese]. *Kekkaku* **81**, 731–735 (2006).
102. Thiele, A. & Rehman, H. U. Hyperkalemia caused by penicillin. *Am. J. Med.* **121**, e1–e2 (2008).
103. Barcia, J. P. Hyperkalemia associated with rapid infusion of conventional and lipid complex formulations of amphotericin B. *Pharmacotherapy* **18**, 874–876 (1998).