

# Review

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**QJM**

## Drug-induced renal Fanconi syndrome

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### Summary

A number of therapeutic drugs are toxic to the kidney proximal tubule (PT) and can cause the renal Fanconi syndrome (FS). The most frequently implicated drugs are cisplatin, ifosfamide, tenofovir, sodium valproate and aminoglycoside antibiotics, and the new oral iron chelator deferasirox has also recently been associated with FS. The incidence of full or partial FS is almost certainly under-estimated due to a lack of appropriate systematic studies, variations in definitions of tubular dysfunction and under-reporting of adverse events. The clinical features of FS are amino aciduria, low molecular weight proteinuria, hypophosphataemia, metabolic

acidosis and glycosuria. The most serious complications are bone demineralization from urinary phosphate wasting and progressive decline in kidney function. Commonly used tests for kidney function such as estimated glomerular filtration rate and urine albumin/creatinine ratio are not sensitive markers of PT toxicity; patients at risk should thus be monitored with more appropriate tests, and drugs should be stopped or reduced in dose if toxicity occurs. Substantial recovery of PT function can occur after withdrawal of therapy, but this can take months and chronic damage may persist in some cases.

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### Introduction

The era of modern medicine has been defined by a huge expansion in pharmacological therapies for previously untreatable conditions; unfortunately, however, some of these drugs can have toxic side effects in the kidney. The proximal tubule (PT) is the first part of the kidney tubule after the glomerulus; many drugs are excreted across the PT and it is the commonest site of toxicity in the kidney. Impairment of normal PT function causes urinary wasting of substances that are predominantly or exclusively reabsorbed at this site—namely amino acids, low molecular weight proteins (LMWPs), phosphate, bicarbonate, glucose and urate<sup>1</sup>—and the clinical

features of the Lignac-de Toni-Debré-Fanconi syndrome (usually abbreviated to FS). The PT also reabsorbs significant amounts of sodium, potassium, chloride, magnesium and calcium, but alternative uptake pathways in the distal tubule can compensate for these losses.

There are many different causes of FS, including hereditary conditions such as cystinosis, mitochondrial cytopathy, tyrosinaemia, fructose intolerance, galactosaemia, Wilson's disease, Dent's disease and Lowe syndrome.<sup>1</sup> Drug toxicity is by far the commonest cause of acquired FS, and this is a significant clinical problem that can limit the development and application of otherwise highly effective therapies. In specialties such as HIV medicine, the increasing

availability of highly potent life-long therapies means that the balance of associated kidney disorders is rapidly shifting from those caused by the disease to those caused by the drug treatments.

## Epidemiology and aetiology

The list of drugs associated with FS continues to grow (Table 1), with the most frequent causes being anti-cancer agents, anti-virals and aminoglycoside antibiotics.<sup>2</sup> Many drugs are taken up by the PT from the blood stream via a range of transporters expressed at the cell surface membranes (such as organic cation and anion transporters and p-glycoprotein<sup>3</sup>). As a result, intracellular drug concentrations can reach high levels in the PT, which probably explains why toxicity in this nephron segment is common. In most cases, the actual incidence of tubular toxicity is unknown and probably under-estimated, due to a lack of systematic studies using appropriate markers of tubular dysfunction and under-reporting of adverse events.

Platinum-containing compounds (cisplatin and carboplatin) and alkylating agents such as ifosfamide are widely used in the treatment of cancer and are established PT toxins.<sup>4–6</sup> Cisplatin is more toxic than carboplatin due to its greater uptake into PT cells. Ifosfamide is structurally related to cyclophosphamide, which is not usually nephrotoxic; the toxicity of ifosfamide *in vivo* is due to rapid uptake into tubular cells via organic cation transporters<sup>7</sup> and the subsequent generation of the toxic metabolite chloroacetaldehyde.<sup>4</sup> Cisplatin and ifosfamide both cause acute PT toxicity, which is often reversible; however, some individuals can develop a chronic tubulopathy, which persists for many years and can be progressive. Estimates of the incidence

of acute toxicity vary widely among reported studies (from 5% to 88% for ifosfamide<sup>4</sup>), but it is clearly a common occurrence. The development of chronic toxicity is highly variable and difficult to predict.

Anti-viral drugs are now a relatively common cause of FS. Nucleoside reverse transcriptase inhibitors (NRTIs) can cause PT toxicity, but it is observed more frequently with the nucleotide reverse transcriptase inhibitors (NtRTIs) adefovir, cidofovir and tenofovir, probably due to the high levels of uptake of these drugs into PT cells via organic anion transporters.<sup>8</sup> While they are undoubtedly highly effective anti-viral agents, the clinical usage of adefovir and cidofovir has been limited historically because of nephrotoxicity, and they are both established causes of FS.<sup>9,10</sup> In contrast, the newer agent tenofovir was thought to be less nephrotoxic, and it is now widely used as first-line therapy for HIV and Hepatitis B infection. Original safety trials showed no significant deleterious effect of tenofovir on serum creatinine and estimated glomerular filtration rate (eGFR)<sup>11</sup>; however, numerous cases of FS have subsequently been reported in patients taking tenofovir.<sup>12,13</sup> Severe toxicity probably only occurs in <1% of patients,<sup>13</sup> but many more have evidence of a milder tubular defect.<sup>14</sup>

Aminoglycoside antibiotics are widely used to treat bacterial infections and are known potent PT toxins with the following rank order: gentamicin > tobramycin > amikacin.<sup>15</sup> They are avidly endocytosed at the PT apical membrane and taken up into lysosomes, where they exert their toxicity. The incidence of nephrotoxicity may be as high as 14% according to some older studies,<sup>16</sup> but this may have improved more recently because of changes in dosing and monitoring strategies.<sup>17</sup>

Sodium valproate is used to treat epilepsy and mood disorders, and numerous cases of FS have

**Table 1** Causes of drug-induced renal FS

Class	Drugs	Indications for use
Alkylating agents	Ifosfamide	Cancer
Aminoglycoside antibiotics	Gentamicin, Amikacin	Gram-negative bacterial infection
Anti-epileptics	Sodium valproate	Seizures, bipolar disorder
Anti-protozoals	Suramin	Trypanosomiasis
Dicarboxylic acids	Fumaric acid	Psoriasis
Iron chelators	Deferasirox	Iron overload (e.g. in thalassemia)
NRTIs	Didanosine, Stavudine	HIV
NtRTIs	Tenofovir, Adefovir, Cidofovir	HIV, Hepatitis B, CMV
Platinum compounds	Cisplatin/carboplatin	Cancer
Salicylates	Aspirin	Analgesia, anti-inflammatory
Tetracycline antibiotics	Degraded tetracycline	Bacterial infection
Tyrosine kinase inhibitors	Imatinib mesylate	Chronic myeloid leukaemia

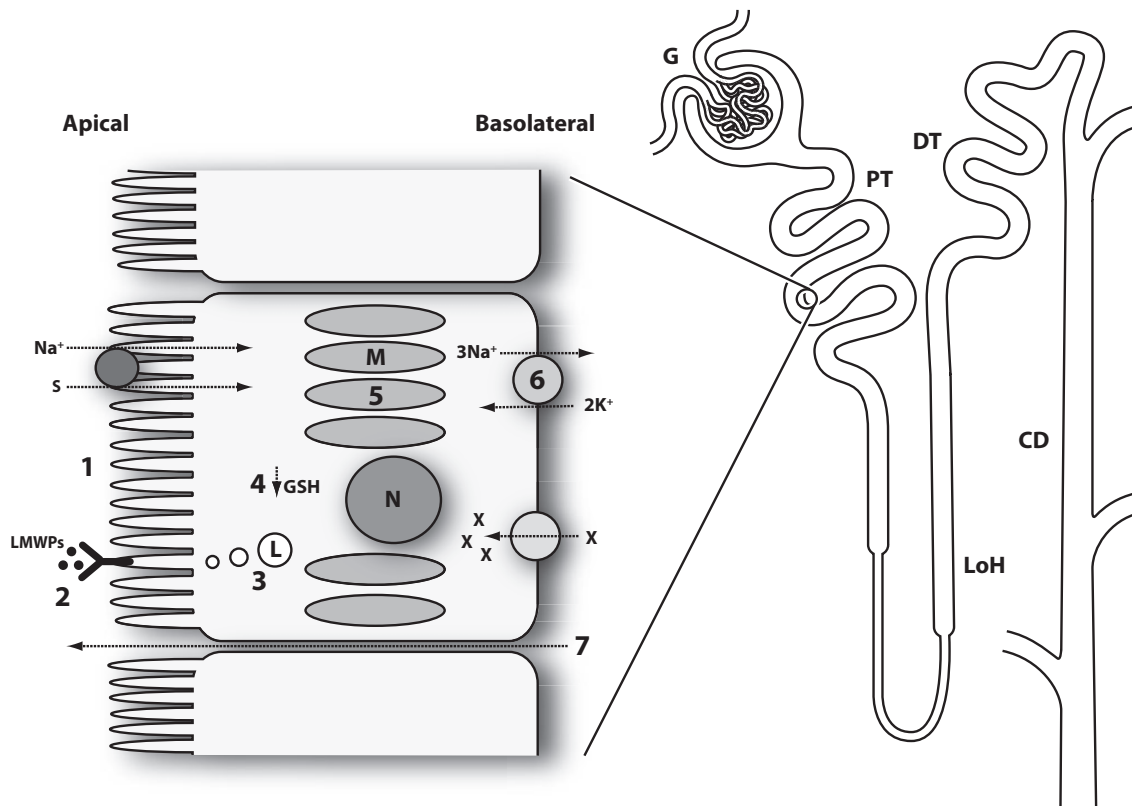
been reported with this drug, mainly in severely disabled patients,<sup>18</sup> while many more patients may develop sub-clinical PT toxicity.<sup>19</sup> Fumaric acid is used topically as a treatment for psoriasis; it is an isomer of maleic acid, which is a potent and rapid cause of experimental FS in rodents,<sup>20</sup> and FS has been described in humans taking fumaric acid.<sup>21</sup> Other agents that can cause FS include salicylates,<sup>22</sup> the anti-parasitic drug suramin,<sup>23</sup> tetracycline antibiotics<sup>24</sup> and tyrosine kinase inhibitors used in the treatment of haematological malignancies.<sup>25</sup>

Deferasirox (Exjade) is a new iron chelator used in patients with a history of multiple blood transfusions (e.g. for hereditary anaemias). Unlike the older parenteral drug deferoxamine, it is administered once daily and orally and is thus more convenient for patients requiring chronic therapy. Nephrotoxicity was noted in phase three studies of deferasirox,<sup>26</sup> and cases of reversible FS have since been reported.<sup>27</sup>

## Pathogenesis

Adult humans typically filter ~180 l of fluid per day through the kidneys; more than 98% of this has to be reclaimed before excretion, and the bulk of reabsorption occurs in the PT. Most solute transport in the PT is coupled directly, or indirectly, to sodium transport (Figure 1). Plasma proteins smaller than albumin (LMWPs) are filtered by the glomerulus and reabsorbed in the PT via receptor-mediated endocytosis. PT cells are densely packed with mitochondria and are dependent on aerobic metabolism to generate sufficient ATP to power solute transport.

FS represents a global breakdown of solute transport in the PT, rather than an isolated problem with a particular transporter. There are many different causes of FS, and the mechanisms through which they all converge on a unified phenotype are largely unknown. Various hypotheses have been proposed



**Figure 1.** Solute transport in the renal PT and possible mechanisms in the pathogenesis of the renal FS. The majority of fluid filtered by the glomerulus (G) is reabsorbed along the PT. Further reabsorption takes place in the loop of Henle (LoH), distal tubule (DT) and collecting duct (CD). Solutes (S) such as amino acids, phosphate and glucose are co-transported across the PT apical membrane with  $\text{Na}^+$ , while LMWPs are taken up by receptor-mediated endocytosis into lysosomes (L). Sodium transport is driven by the basolateral  $\text{Na}^+/\text{K}^+$ -ATPase, which requires ATP generated by mitochondria (M) located in close proximity (N=nucleus). A number of toxic drugs (X) can rapidly accumulate into PT cells from the bloodstream via basolateral transporters and can cause FS. Breakdown of PT solute transport in FS may occur for the following reasons: (1) abnormal fluidity of the apical membrane, (2) impaired endocytosis and recycling of receptors, (3) abnormal lysosomal function, (4) depletion of the anti-oxidant glutathione (GSH), (5) mitochondrial toxicity and decreased ATP synthesis, (6) inhibition of the  $\text{Na}^+/\text{K}^+$ -ATPase and (7) back-leak of solutes through the paracellular pathway or across the apical membrane.

(Figure 1), which may not be mutually exclusive, however, the majority of the available evidence suggests that an underlying defect in PT cell metabolism is the main mechanism via which most drugs cause FS,<sup>2</sup> including cisplatin,<sup>4</sup> gentamicin,<sup>28</sup> ifosfamide,<sup>29</sup> salicylate,<sup>30</sup> tenofovir<sup>12,13</sup> and valproate.<sup>18</sup> Experimental application of mitochondrial toxins blocks PT solute transport,<sup>31</sup> and FS is the commonest renal presentation of patients with mitochondrial cytopathy.<sup>32</sup> Furthermore, the presence of enlarged and dysmorphic mitochondria in the PT is a typical finding in biopsy specimens from patients with drug-induced FS (Figure 2).<sup>12,13</sup>

## Clinical features

The characteristic clinical features of FS are listed in Table 2 and result from urinary wasting of solutes normally reabsorbed in the PT; some patients only exhibit some of these features (partial FS—see below). Phosphate depletion is the most important clinical aspect of FS, because it leads to skeletal demineralization and osteomalacia, which can present with bone pain, fractures and proximal muscle weakness. Unfortunately, by the time patients develop symptoms, bone disease is often quite advanced. Metabolic acidosis in FS is typically mild, with serum bicarbonate maintained  $\geq 15$  mmol/l, as long as distal tubule urinary acidification mechanisms are intact. Fluid (water and sodium) loss leading to symptomatic hypovolaemia is not a common problem in adults, because of compensatory reabsorption in the distal tubule, but some patients may report polyuria.

It is important to note that commonly used tests for chronic kidney disease (CKD), such as creatinine-based eGFR and urine albumin/creatinine ratio, are predominantly measures of glomerular function and are not sensitive markers of PT function.<sup>14,33,34</sup> Patients exposed to tubular toxic drugs may also develop glomerular dysfunction, but this is not always the case, and severe FS can occur in the absence of an increase in serum creatinine.<sup>35</sup> Furthermore, if serum creatinine does rise in FS, it may be due to impaired tubular secretion, rather than an actual change in GFR.<sup>36</sup> Some patients with drug-induced FS also exhibit signs of toxicity in the distal nephron (e.g. hypomagnesaemia and a urinary concentrating defect).

## Diagnosis

The diagnosis of drug-induced FS is usually suggested by a temporal relationship between exposure to a known PT toxin and the development of

tubulopathy. However, with drugs such as tenofovir, toxicity can occur months or even years after establishing patients on treatment.<sup>37</sup> Improvement in PT function after withdrawal of the drug confirms the diagnosis. Methods used to assess kidney function in patients at risk of drug-induced FS are listed in Table 3. Urinary LMWPs such as retinol-binding protein and beta-2-microglobulin are the most sensitive markers of PT dysfunction and provide a quantitative readout of severity.<sup>14,38</sup> Comparison with urinary albumin excretion can help to classify proteinuria as being predominantly of either tubular or glomerular origin<sup>33</sup>; however, assays for tubular proteinuria are not available in all hospitals. Urine protein/creatinine ratio (PCR) does not distinguish the origin of proteinuria, but is more widely available and is typically raised in patients with FS.<sup>37</sup>

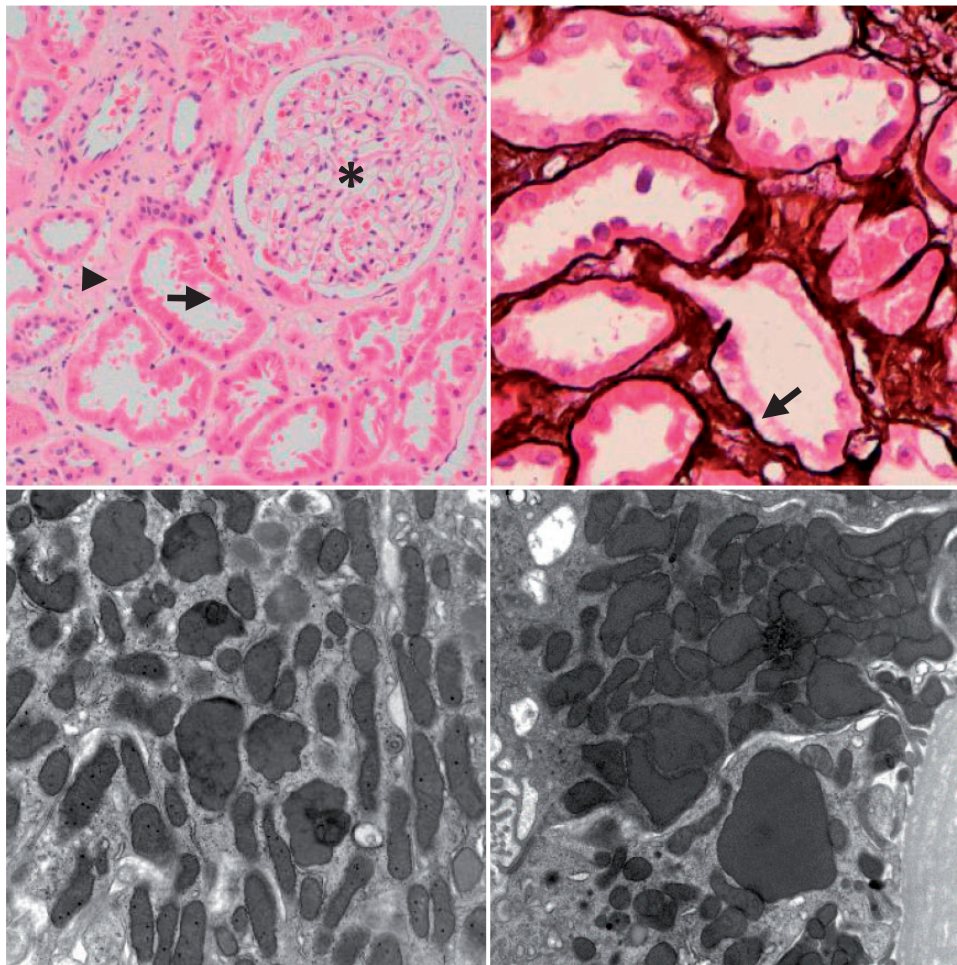
Renal tubular handling of phosphate can be evaluated by calculating either the fractional excretion (normal <20%) or the tubular maximal reabsorption (TmP/GFR, normal >0.8 mmol/l),<sup>39</sup> from paired spot plasma and urine samples of phosphate and creatinine:

- Fractional excretion =  $(\text{Urine}_{\text{phos}} \times \text{Plasma}_{\text{creat}} \times 100) / (\text{Plasma}_{\text{phos}} \times \text{Urine}_{\text{creat}})$ .
- TmP/GFR =  $\text{Plasma}_{\text{phos}} - (\text{Urine}_{\text{phos}} \times \text{Plasma}_{\text{creat}} / \text{Urine}_{\text{creat}})$ .

Alkaline phosphatase is typically increased in patients with reduced bone mineral density, but it can also be raised for other reasons (e.g. liver disease).

Renal ultrasound scanning is of limited use in FS, but may demonstrate non-specific signs of renal damage such as hyperechogenicity of the parenchyma.<sup>40</sup> Kidney uptake of the radionuclide tracer dimercaptosuccinic acid can be decreased as a result of impaired receptor-mediated endocytosis of the tracer in the PT.<sup>41</sup> Radiological features of reduced bone mineral density may be seen on plain X-ray (such as pseudo-fractures) and dual-energy X-ray absorptiometry, while regions of increased radionuclide uptake on bone scintigraphy can be confused with bony metastases.<sup>42</sup>

In some cases, a renal biopsy is performed to assess the extent of acute tubular damage and irreversible tubulointerstitial scarring (Figure 2). There are no histological features specific to FS, but the presence of dysmorphic and swollen mitochondria in the PT is a common finding on electron microscopy in drug-induced FS.<sup>12,13</sup> Other causes to consider in the differential diagnosis of acquired FS include heavy metal exposure (e.g. cadmium, lead), aristolochic acid (contained in some herbal remedies) or paraquat poisoning, glue sniffing, Sjogrens syndrome, mitochondrial cytopathy and light chain disease (myeloma).<sup>1</sup>



**Figure 2.** Typical histological features in kidney biopsies from patients with drug-induced renal FS. Top left panel: light microscopy (20× objective magnification) of haematoxylin and eosin stained tissue from a patient with ifosfamide nephrotoxicity demonstrating damaged and flattened PTs (arrow), interstitial fibrosis (arrowhead) and a normal glomerulus (asterisk). Top right panel: higher magnification (60×) of Periodic Acid-Schiff Methenamine Silver stained tissue demonstrating proximal tubular damage in more detail, including vacuolization of cells (arrow). Bottom panels: swollen and dysmorphic mitochondria are a common finding in proximal tubular cells on electron microscopy in patients with nephrotoxicity due to ifosfamide (left) and tenofovir (right).

**Table 2** Clinical features of the renal FS

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Amino aciduria
Organic aciduria
Low molecular weight proteinuria
Hypophosphataemia
Normoglycaemic glycosuria
Metabolic acidosis
Hypouricaemia
Hypokalaemia
Polyuria

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## Risk factors

In general, drug toxicity in the PT is a dose-related phenomenon. The concentration of drug that PT

cells are exposed to depends on the blood concentration, which in turn is affected by various parameters that are the main identified risk factors for developing FS (Table 4).<sup>4,6,13,43</sup> In spite of the existence of these established risk factors, for many drugs the occurrence of nephrotoxicity still remains highly variable among patients, making it difficult to target monitoring at specific sub-groups. Underlying genetic polymorphisms in membrane transporters and other molecules affecting uptake or handling of drugs in PT cells may play a role in determining risk of toxicity from drugs such as tenofovir<sup>44</sup> and cisplatin.<sup>45</sup> It is important to appreciate that drug safety trials are often performed in relatively healthy patients with few baseline risk factors; therefore, nephrotoxicity may only become apparent when

**Table 3** Methods for assessing kidney function in patients at risk of drug-induced renal FS

Method	Requirements	Comments
Serum creatinine/eGFR	Single blood sample	Measures of glomerular function, not sensitive markers of tubular function. Mild creatinine rises may occur due to impaired tubular secretion.
Isotopic GFR	Radio-isotope injection, multiple blood samples	Accurate measurement of glomerular function.
Fractional excretion or maximal tubular reabsorption of phosphate	Matched blood and urine samples of phosphate and creatinine	Phosphate wasting is an important complication of FS.
Metabolic acidosis	Single blood sample	Usually mild, unless distal tubular urinary acidification is also impaired.
Urinary albumin/creatinine ratio	Spot urine sample	Predominantly a marker of glomerular disease, not sensitive for proximal tubular dysfunction.
Urinary PCR	Spot urine sample	Not specific for tubular disease, but typically increased in FS.
Tubular proteinuria (e.g. retinol-binding protein)	Spot urine sample	The most sensitive marker of PT dysfunction.
Amino aciduria and organic aciduria	Spot urine sample	Typically increased in FS, but not usually used for monitoring purposes.
Dipstick glycosuria	Spot urine sample	Marker of PT dysfunction, but may also be caused by hyperglycaemia.

**Table 4** Risk factors for drug-induced renal FS

Drug dose and duration of therapy
Pre-existing renal impairment
Reduced renal mass (e.g. previous nephrectomy)
Older age or very young
Drug interactions
Low body weight
Volume depletion (e.g. diarrhoea and vomiting)
Underlying pharmacogenetic factors

drugs are subsequently used in wider and more varied populations.<sup>46</sup>

## Monitoring of patients at risk

As noted earlier, widely used tests for CKD such as serum creatinine and eGFR are not sensitive markers of PT dysfunction. This point has been illustrated by the story of tenofovir, in which original safety studies using these parameters reported no evidence of renal toxicity, but multiple cases of tubular toxicity were steadily reported over time.<sup>46</sup> Therefore, to be effective, monitoring should be focused on more appropriate markers, such as tubular proteinuria (if available), urine PCR, phosphate reabsorption and glycosuria. The optimum frequency of

monitoring in any given patient will depend on the specific drug and the extent of baseline risk factors. Various published guidelines are available, for example, The UK Children's Cancer Study Group (<http://www.cclg.org.uk>) recommend that patients exposed to cisplatin or carboplatin should be screened for nephrotoxicity (serum creatinine and magnesium, TmP phosphate) within 6 months of treatment, and within 1 year in the case of ifosfamide, with the frequency of further monitoring dependent on these results (every 5 years if normal). Meanwhile, the British HIV Association ([www.bhiva.org](http://www.bhiva.org)) recommends that patients starting tenofovir should be monitored every 4 weeks in the first year (and every 3 months thereafter) with eGFR, serum phosphate, urine dipstick (for glycosuria) and urine PCR.

## Prevention and treatment

Given that many drugs are renally excreted, it is important to accurately establish baseline kidney function before dosing, particularly with drugs such as cisplatin and ifosfamide. Estimates of GFR using serum creatinine-based formulae are less accurate above 60 ml/min, so isotopic measurements are often performed. Dose reductions can be made with drugs such as tenofovir or gentamicin in

patients with pre-existing CKD. Some nephrotoxic chemotherapy agents are administered with intravenous saline to increase their renal excretion. Specific drugs can be given, such as amifostine (a glutathione analogue), to try and prevent toxicity, but the usefulness of these agents is limited by side effects.<sup>47</sup> Prevention of uptake into the PT by inhibition of drug transporters represents another possible preventive strategy, for example, probenecid, an inhibitor of organic anion transporters, has been used to prevent cidofovir-induced tubular toxicity in patients with CMV infection.<sup>48</sup>

Overall, given that strategies to prevent or treat drug-induced FS are currently limited, the most prudent approach is to use the minimum possible dose to achieve a therapeutic effect and to monitor patients carefully using appropriate markers of PT function. If a patient develops FS while taking a nephrotoxic drug it should be stopped immediately; if this is not possible—for example, if there is no alternative drug and the clinical situation is life-threatening—then a dose reduction should be considered.

In patients with established FS, the main goal of treatment is to prevent complications arising from urinary wasting of solutes. Increased renal loss of amino acids and glucose does not lead to adverse consequences; however, phosphate depletion causes bone demineralization, and oral phosphate supplements and a high phosphate diet can help to compensate for urinary losses. Hypophosphataemia is worsened by vitamin D deficiency, so levels should be checked and supplemented if low. Activation of 25-OH vitamin D to 1,25-OH vitamin D requires 1- $\alpha$ -hydroxylase; this enzyme is located in the PT so patients with FS may also require treatment with alfacalcidol or calcitriol. Bone loss may be compounded by ovarian toxicity and premature menopause in female patients exposed to ifosfamide and cisplatin. Chronic metabolic acidosis probably also contributes to bone disease in FS and is easily corrected with oral sodium bicarbonate.

### **Mild tubular toxicity and partial Fanconi syndrome**

FS represents the most severe grade of drug-induced PT toxicity, short of cell necrosis and acute kidney injury. Many more patients may develop milder degrees of toxicity, such as isolated tubular proteinuria,<sup>14</sup> the significance of which is often unclear. In glomerular kidney diseases, proteinuria (mainly albuminuria) is associated with a poor renal outcome; however, the constituents of tubular proteinuria are

different, and although most patients with hereditary FS develop progressive renal failure over time there are rare exceptions to this.<sup>49</sup> Tubular phosphate handling should be assessed in patients with partial FS, since urinary phosphate wasting can occur even with a normal serum phosphate level.<sup>50</sup> Ultimately, the decision whether to stop therapy should be fully discussed with the patient by the prescribing physician, and will typically depend on the strength of the indication for treatment, the degree of toxicity (and whether it is worsening over time) and the availability of alternative non-nephrotoxic drugs.

### **Prognosis**

The PT has a remarkable capacity to regenerate itself following an insult, and substantial improvement in function can occur after drug-induced FS, provided that the offending agent is withdrawn.<sup>4,37</sup> However, recovery of function can take months and is not always complete, leaving some patients with residual tubular defects. Long-term follow-up of patients exposed to ifosfamide has shown that tubular dysfunction can persist for at least 10 years after therapy has stopped, and can worsen over time in some individuals.<sup>4</sup>

### **Conclusions**

Nephrotoxic potential does not necessarily preclude the use of drugs, especially where the benefits of treatment clearly outweigh the risks; for example, many lives have been saved by the administration of gentamicin in severe Gram-negative bacterial sepsis. However, it is extremely important that doctors using drugs toxic to the PT are aware of this effect and monitor their patients appropriately. If significant toxicity occurs, treatment should be withdrawn before damage becomes severe and irreversible, and the complications of urinary solute wasting should be addressed with particular attention paid to hypophosphataemia and bone health. Although some risk factors for drug-induced FS have been highlighted, in many cases it remains unclear why some patients develop toxicity while others do not, but pharmacogenomics may play a role and more research is required in this area. Further work is also needed to develop new strategies to prevent toxicity or enhance recovery of damaged tubules, or to formulate less toxic analogues of drugs that retain comparable therapeutic efficacy.

As new drugs emerge in the future, it is highly likely that some will be toxic to the PT and cause FS; therefore, it is vital that lessons are learned from past experience, and to be more comprehensive

screening studies for nephrotoxicity in humans should include tests of both glomerular and tubular function.

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