# Drug-induced renal injury

*The kidney plays an important role in the elimination of many drugs and their metabolites.*

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The kidney receives a rich blood flow of 25% of resting cardiac output and plays an important role in the elimination of many drugs and their metabolites. The kidney is therefore exposed to high concentrations of drugs and metabolites, making it vulnerable to drug toxicity. It is therefore not surprising that drug-induced renal injury contributes up to 25% of all cases of acute renal failure. Drug-induced renal injury may cause predictable, cumulative dose-dependent toxicity or idiosyncratic dose-independent toxicity at any time during therapy. Cumulative dose-dependent renal toxicity can be anticipated and prevented, but idiosyncratic renal toxicity cannot. A basic understanding of drug-induced renal injury will help to better understand drug-induced renal toxicity and allow for a vigilant approach when prescribing drugs with potential renal toxicity. Renal injury may occur in various renal compartments: the renal vascular supply, the glomerulus, the tubulointerstitium where extensive tubular-peritubular caplliary exchange of solutes takes place, and the collecting ducts. However, it may be more useful from a clinical point of view to classify drug-induced renal toxicity into four major renal syndromes:

- acute renal failure
- chronic renal failure
- glomerulonephritis
- tubulopathies.

These major renal syndromes are discussed in further detail below (see summary in Table I).

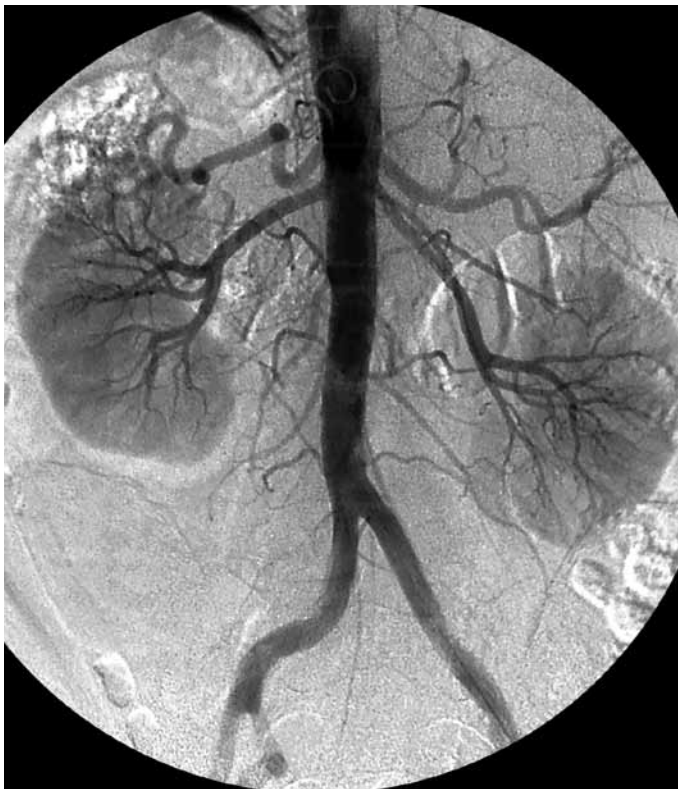
***… drug-induced renal injury contributes up to 25% of all cases of acute renal failure.***

## Acute renal failure

Drugs can cause acute renal failure by causing pre-renal, intrinsic or post-renal toxicity.

### Pre-renal failure

Drugs cause pre-renal failure by impairing glomerular haemofiltration. Drugs can reduce the renal blood perfusion by modulating the vasomotor tone of the afferent (pre-glomerular) or efferent (post-glomerular) arterioles and decrease glomerular filtration rate with subsequent renal failure. Patients who already have compromised renal perfusion (heart failure or volume depletion) are most at risk. Adequate intraglomerular pressure is maintained by prostaglandin-mediated afferent vasodilatation and angiotensin II-mediated efferent vasoconstriction. Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARBs) decrease renal blood perfusion by inhibiting angiotensin II-mediated vasoconstriction at the efferent arteriole. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin-induced afferent arterial dilatation. As the renal parenchyma is normal, but the renal blood flow is impaired, patients will present with low urine output, low sodium excretion and high osmolality. The urea:creatinine ratio is usually more than 20 as the low urine flow facilitates a disproportionate urea reabsorption relative to creatinine. The urine sediment is clear.



### Intrinsic renal failure

Tubular necrosis, interstitial nephritis or thrombotic angiopathy are common causes of parenchymal drug-induced renal injury.

Aminoglycoside antibiotics and amphotericin B are commonly used drugs that cause dose-related acute tubular necrosis. **Acute tubular necrosis** is usually caused by direct drug toxicity, but prolonged impaired renal perfusion as described above may also cause tubular damage. Microscopically, tubular necrosis is recognised by degenerative and regenerative tubular changes. Patients present with a sudden rise in creatinine concentration, and develop oliguria if the offending drug is continued. Urinary sodium excretion is increased and urinary sediment contains granular casts and renal epithelial cells. The injury is dose dependent and generally resolves with discontinuation of the causative drug.

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Up to 15% of drug-induced acute renal failure is caused by hypersensitivity reactions that cause renal tubular and interstitial inflammation. Many drug classes can potentially cause **tubulointerstitial**

**Table I. Mechanisms of drug-induced kidney injury, with some examples**

| | |
|---|---|
| **Acute renal failure** | |
| **Pre-renal failure** | |
| Impaired glomerular haemofiltration | |
| ACE inhibitors | Important clinical and laboratory findings: |
| Angiotensin receptor blockers | Urinary sodium excretion decreased |
| NSAIDs | Urinary sediment: clear |
| COX-2 inhibitors | |
| Diuretics | |
| Calcineurin inhibitors (cyclosporin, tacrolimus) | |
| **Intrinsic renal causes** | |
| Acute tubular necrosis | |
| Aminoglycosides | Important clinical and laboratory findings: |
| Amphotericin B | Sudden rise in creatinine |
| Cisplatin | Urinary sodium excretion increased |
| Radiocontrast media | Urinary sediment: granular casts and renal epithelial cells |
| Tubulointerstitial nephritis | |
| Antibiotics (penicillins, cephalosporins, sulphonamides, fluoroquinolones, rifampicin) | Important clinical and laboratory findings: |
| NSAIDs | Sudden rise in creatinine |
| Thiazide diuretics | Systemic manifestations of a hypersensitivity reaction: e.g. fever, rash and eosinophilia |
| Lithium | Urinary sediment: white blood cells (often eosinophils) and casts and proteinuria |
| Proton-pump inhibitors | |
| Anti-epileptic drugs (phenytoin, valproic acid, carbamazepine) | |
| Allopurinol | |
| Thrombotic microangiopathy | |
| Calcineurin inhibitors (cyclosporin, tacrolimus) | Important clinical and laboratory findings: |
| Chemotherapeutic drugs (mitomycin C, bleomycin, cisplatin) | Sudden rise in creatinine |
| Oestrogen-containing oral contraceptives | Fever, haemolytic anaemia, thrombocytopenia, renal impairment and neurological dysfunction |
| Clopidogrel | |
| Quinine | |
| **Obstructive causes** | |
| Crystal-induced tubulointerstial disease/ obstructive uropathy | |
| Acyclovir | Important clinical and laboratory findings: |
| Indinavir | Urinary sediment: red and white blood cells, granular casts and characteristic drug crystals |
| Sulphonamides | |
| Methotrexate | |
| Ciprofloxacin | |
| Sodium phosphate | |
| **Chronic renal failure** | |
| Tubulointerstitial nephritis | |
| Lithium | Important clinical and laboratory findings: |
| NSAIDs | Gradually declining renal function |
| **Nephrotic syndrome** | |
| Glomerular disease | |
| NSAIDs | Important clinical and laboratory findings: |
| Lithium | Marked proteinuria, may be accompanied by haematuria and hypertension |
| Interferon α and β | |
| Pamidronate | |
| Sirolimus | |
| **Tubulopathies** | |
| Fanconi's syndrome | |
| Tenofovir | Important clinical and laboratory findings: |
| | Proteinuria, phosphaturia, glycosuria and bicarbonate wasting |

NSAIDs – non-steroidal anti-inflammatory drugs; ACE – angiotensin-converting enzyme; COX – cyclo-oxygenase.

**nephritis**, including antibiotics (e.g. penicillins and cephalosporins), NSAIDs and anti-epileptic drugs. Drugs or their metabolites act as haptens and bind to the tubular basement membrane or the interstitial matrix to form antigens. A T cell-mediated delayed hypersensitivity reaction follows. Patients may present with systemic manifestations of a hypersensitivity reaction such as fever, rash, and eosinophilia, even though the symptoms may start insidiously, with lower back pain and malaise being the only symptoms. White blood cells and casts are frequently found in the urine. On special staining the white cells in the urine will

often be found to be eosinophils, which is helpful in diagnosing drug-induced toxicity. Proteinuria may occur when cytokines are released by infiltrating T cells, resulting in increased glomerular permeability.

Drugs, such as the immunosuppressants cyclosporine and tacrolimus, chemotherapeutic drugs bleomycin and cisplatin, clopidogrel, oestrogen-containing oral contraceptives and quinine may cause thrombosis in the afferent renal arteriole and glomerulus. **Thrombotic microangiopathy** is the inclusive term for thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS) as there is a shared pathogenesis and overlap in clinical features. Patients present with a pentad of fever, haemolytic anaemia, thrombocytopenia, renal impairment and neurological dysfunction. Although the clinical picture may vary, patients with TTP primarily present with neurological symptoms, while in patients with HUS the renal impairment dominates. Patients may present with haematuria, proteinuria and granular casts in the urine.

***Analgesics are widely prescribed and can cause renal toxicity when used acutely or chronically.***

**Obstructive causes**

Drugs may precipitate within the renal tubules either as crystals or stones and cause renal obstruction. The clinical features can either be due to renal failure from crystal deposition or nephrolithiasis that results in urinary obstruction and colic. Risk factors that predispose patients to obstructive renal failure include severe volume depletion, underlying renal impairment, bolus drug administration and metabolic derangements such as metabolic acidosis or alkalosis. Drugs implicated in crystal formation include acyclovir, sulphonamides, methotrexate, indinavir, the potassium-sparing diuretic triamterene and large doses of vitamin C. Examination of the urine will show red and white blood cells, granular casts and characteristic drug crystals.

## Chronic renal failure

Drug-induced chronic renal failure presents with a slow progressive elevation of creatinine concentration and usually microscopically as a tubulointerstitial nephritis. Tubulointerstitial nephritis is characterised by interstitial fibrosis, tubular atrophy and inflammation. While repeated or prolonged acute tubulointerstitial nephritis can lead to chronic tubulointerstitial disease, only a few drugs, such as lithium and NSAIDs, are associated with chronic tubulointerstitial nephritis without acute episodes.

## Glomerulonephritis

Nephrotic syndrome is caused by glomerular dysfunction and is marked by heavy proteinuria. Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are primarily caused by podocyte dysfunction. NSAIDs, lithium, pamidronate, sirolimus, and interferon α and β are implicated. Membranous glomerulonephritis (MGN) is characterised by subepithelial immune complex deposits in the glomerular basement membrane. MGN may be caused by NSAIDs, penicillamine and captopril.

Commonly prescribed drugs implicated in renal toxicity are discussed below.

## Analgesics

Analgesics are widely prescribed and can cause renal toxicity when used acutely or chronically. NSAIDs may impair glomerular filtration by inhibiting renal vasodilator prostaglandins and cause acute renal failure as described above. NSAID-induced tubulointerstitial nephritis tends not to present with systemic findings of hypersensitivity and is associated with proteinuria in the nephrotic range in most cases. Although it was anticipated that COX-2 inhibitors would spare the vasodilatory action of COX-1-mediated prostaglandins, they have been associated with renal toxicity. Paracetamol lacks peripheral prostaglandin inhibition, but may cause acute tubular necrosis in overdose.

## Tenofovir

Tenofovir is a nucleotide reverse transcriptase inhibitor currently used as part of first-line antiretroviral treatment. Tenofovir has been associated with renal tubular toxicity, with the main site of toxicity being the proximal tubule. Tenofovir causes Fanconi's syndrome characterised by proteinuria, phosphaturia, glycosuria (with normal blood glucose) and bicarbonate wasting. Risk factors for developing tenofovir-induced renal toxicity include pre-existing renal disease, concomitant use of nephrotoxic drugs, low body weight and older age. However, tenofovir-induced renal toxicity can occur in patients with no obvious risk factors and it is important to monitor all patients on tenofovir treatment for renal dysfunction.

## Lithium

Acute lithium-induced renal injury may present as early as 8 weeks after treatment initiation and cause a reduced urinary concentrating capacity. Nephrogenic diabetes insipidus is the most common adverse effect of lithium therapy and may occur in up to 40% of patients. The current understanding is that lithium accumulates intracellularly in the collecting duct and inhibits the glycogen synthase kinase type 3β enzyme responsible for water and sodium transport. The cell subsequently becomes insensitive to the actions of aldosterone and

***Acute lithium-induced renal injury may present as early as 8 weeks after treatment initiation.***

vasopressin and water and sodium diuresis follows. Lithium also causes a progressive chronic tubulointerstitial renal disease after 10 - 20 years of treatment which may be detected early by monitoring renal function regularly. Detection of lithium-induced renal impairment in a well-controlled psychiatric patient raises a therapeutic dilemma and the decision to substitute lithium with another mood stabilizer should be made jointly by the patient, psychiatrist and nephrologist.

## Amphotericin B

Amphotericin B is widely used for the management of fungal infections including cryptococcus because of its broad spectrum of activity. Renal impairment during amphotericin B use has been reported to be as high as 80%. Amphotericin B may cause renal impairment by two mechanisms: binding to tubular epithelial cells causing cell swelling and lysis, ultimately resulting in tubular dysfunction, and activating vasoconstrictive prostaglandins in the afferent arteriole. Risk factors for amphotericin B-induced renal toxicity include volume depletion, pre-existing renal impairment, use of concomitant nephrotoxins, and high single and cumulative doses. Volume replacement before the amphotericin B dose, longer infusion times and use of lipid-based formulations might minimise amphotericin B nephrotoxicity.

## Aminoglycosides

Aminoglycoside antibiotics cover Gram-negative infections and are well known for their renal toxicity. Renal toxicity is caused by proximal tubular injury that leads to cell necrosis. Renal toxicity can be minimised by preventing volume depletion, avoiding concomitant nephrotoxic drugs, frequent monitoring of creatinine and therapeutic drug monitoring.

Drug-induced renal injury can be minimised by following a few general principles.

## Principles to minimise drug-induced renal injury

- **Identify patients at risk**

Patient risk factors linked to drug-induced renal injury are highlighted above. Prescribe potentially nephrotoxic drugs with caution in high-risk patients and weigh the nephrotoxic risk against the therapeutic benefit.

- **Take precautions**

Nephrotoxicity can be reduced by taking drug-specific precautions. For example, amphotericin B should only be administered to normovolaemic patients and liposomal

formulations should be used if available. Frequently measure aminoglycoside trough concentrations and renal function and adjust the dose as required or prescribe alternative drugs. A continuous decrease in glomerular filtration rate shortly after ACE-I initiation should raise the suspicion of bilateral renal artery stenosis and ACE-I should be avoided in these patients.

- **Frequently monitor renal function**

Frequent renal function monitoring will allow for the early detection of drug-induced renal injury. Beware of relying on the creatinine concentration alone to give an indication of renal function, as a value in the laboratory reference range could be falsely reassuring. Creatinine concentrations should be adjusted for weight, age or gender using formulae to estimate the glomerular filtration rate to give a more accurate indication of the renal function. The Cockroft and Gault formula and the Modification of Diet in Renal Disease (MDRD) are the most widely used formulae to estimate renal function.

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## IN A NUTSHELL

- Up to 25% of acute renal failure is drug induced.
- Drug-induced renal injury can present as acute renal failure, chronic renal failure, nephrotic syndrome or tubulopathy.
- Drug-induced renal injury can be minimised by identifying high-risk patients and evaluating the nephrotoxic risk against the therapeutic benefit of administering the drug.
- Take drug-specific precautions to minimise drug-induced renal injury.
- Frequently calculate the renal function by using a formula to calculate the estimated glomerular filtration rate such as the Cockroft and Gault formula and the Modification of Diet in Renal Disease (MDRD), which is often reported by laboratories as the eGFR.

# Case report

### Deadly herbicide ingestion

A 27-year-old man committed suicide by drinking 1- 2 gulps of a blue-green herbicide, paraquat (Gramoxone). He presented with signs of corrosive mucosal damage, mild transaminitis and acute renal impairment. A diagnosis of paraquat poisoning was delayed, as he initially told health care workers that he had ingested glyphosate (Roundup). He developed type 1 respiratory failure due to pulmonary oedema. Although he had a mitral valve replacement 16 years ago and defaulted follow-up and treatment, he was not in cardiac failure. Over a period of 2 weeks his renal function and transaminitis resolved, but his respiratory function gradually worsened despite his X-ray infiltrates clearing. He died 22 days after paraquat ingestion owing to probable lung fibrosis.

Paraquat ingestion, even one or two gulps, is potentially deadly. Patients with acute, severe fulminant toxicity (more than 40 mg/kg ingested) present with multi-organ failure and die within hours. Patients typically present initially with corrosive damage followed by renal and hepatocellular toxicity within 2 - 3 days. Paraquat accumulates preferentially in pneumocytes. Several days after ingestion irreversible pulmonary fibrosis follows, causing severe morbidity and ultimately mortality.

Treatment consists of initial aggressive management to prevent absorption: activated charcoal should be administered and gastric lavage can be considered within 30 minutes - 1 hour of ingestion, keeping in mind the high risk of perforation. Ipecac is contraindicated. Experimental data indicate that cyclophosphamide and steroids may minimise pulmonary toxicity if administered within 24 hours. Oxygen may increase lung injury by providing oxygen free radicals. Paraquat ingestion is a notifiable condition.

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