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# Pathophysiologic Mechanisms of Selected Types of Nephrotoxicity

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## Aminoglycoside Nephrotoxicity

Aminoglycosides preferentially affect the proximal tubular cells. These agents are freely filtered by the glomeruli and quickly taken up by the proximal tubular epithelial cells, where they are incorporated into lysosomes after first interacting with phospholipids on the brush border membranes. They exert their main toxic effect within the tubular cell by altering phospholipid metabolism. In addition to their direct effect on cells, aminoglycosides cause renal vasoconstriction.

The 2 critical factors in the development of acute kidney injury (AKI) secondary to aminoglycoside nephrotoxicity are dosing and duration of therapy. Aminoglycoside uptake by the tubules is a saturable phenomenon, so uptake is limited after a single dose. Thus, a single daily large dose is preferable to 3 doses per day. One dose per day presumably causes less accumulation in the tubular cells once the saturation point is reached.<sup>[1, 2]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Amphotericin B Nephrotoxicity

**Amphotericin B** binds to sterols in cell membranes, thereby creating pores that compromise membrane integrity and increase membrane permeability. It binds not only to ergosterol in fungal cell walls but also to cholesterol in human cell membranes; this is what accounts for its nephrotoxicity.

Characteristic electrolyte abnormalities include wasting of potassium and magnesium secondary to increased permeability of the cell membranes. The back-leak of hydrogen ions in the collecting duct leads to distal renal tubular acidosis (dRTA).<sup>[3, 4]</sup>

Lipid-based preparations of amphotericin B decrease but do not eliminate the nephrotoxicity compared with traditional amphotericin B.<sup>[5]</sup> This may be due to a direct nephrotoxic effect of the conventional preparation.

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Contrast-Induced Nephropathy

Although the pathogenesis of contrast-induced nephropathy (CIN) remains incompletely understood, it is most likely the result of renal vasoconstriction and direct renal tubular epithelial cell toxicity. Current theories regarding CIN toxicity include a combination of direct cytotoxicity with postischemic reperfusion injury resulting in oxygen free radical production leading to endothelial damage.<sup>[6, 7]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Calcineurin Inhibitor Nephrotoxicity

[Cyclosporine](#) and [tacrolimus](#) cause acute kidney injury (AKI) by inducing afferent and efferent arteriolar vasoconstriction. Persistent injury can lead to interstitial fibrosis. Tacrolimus has been shown to cause thrombotic microangiopathy as a result of endothelial injury.<sup>[8, 9]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Cisplatin Nephrotoxicity

[Cisplatin](#) usually affects the proximal tubules primarily with some secondary effect on the glomeruli and distal tubules. Cisplatin is excreted primarily in the urine, resulting in concentrated drug levels, which encourage uptake into the cells by passive diffusion or active uptake. Cisplatin is stable in the blood stream but becomes hydrolyzed in the chloride-poor cellular environment. It is the hydrolyzed metabolite that binds DNA, RNA, proteins, and phospholipids, causing cytotoxicity.<sup>[10]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Ifosfamide Nephrotoxicity

[Ifosfamide](#) is a known analog of [cyclophosphamide](#). Although cyclophosphamide is not nephrotoxic, ifosfamide, by virtue of its metabolite chloroacetaldehyde, is toxic to the tubular cells, with preferential involvement of the proximal tubule leading to Fanconi syndrome.<sup>[11, 12]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Foscarnet Nephrotoxicity

[Foscarnet](#), which is used to treat resistant cytomegalovirus (CMV) infections, causes acute interstitial nephritis and intratubular crystal formation. In addition to crystal formation, which can be made up of calcium salts or sodium salts, chelation of calcium by foscarnet leads to hypocalcemia.<sup>[13, 14]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Crystal-Forming Drug Nephrotoxicity

Sulfa drugs, [acyclovir](#), methotrexate, ethylene glycol, and protease inhibitors like [indinavir](#) cause acute kidney injury (AKI) by tubular obstruction due to crystal formation in the tubular urine.

Acyclovir may lead to the formation of intratubular crystals, which appear as birefringent needle-shaped crystals and can elicit an acute interstitial nephritis.<sup>[15, 16]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Rhabdomyolysis

Rhabdomyolysis refers to the breakdown of skeletal muscle fibers, which leads to the release of potentially nephrotoxic intracellular contents into the circulation. Acute kidney injury (AKI) develops in this setting via the following 3 mechanisms:

- Renal vasoconstriction
- Heme-mediated proximal tubular cell toxicity
- Intratubular cast formation

Heme proteins are believed to be involved in the generation of reactive oxygen species (ROS), which are known to cause tubular injury through peroxidation of membrane lipids and intracellular enzymes.<sup>[17]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

## Multiple Myeloma

Multiple myeloma causes renal failure by several mechanisms. The extra protein can be deposited in the kidney as amyloidosis or monoclonal immunoglobulin deposition disease affecting the glomeruli. Light-chain cast nephropathy occurs when light chains become concentrated in the tubular lumen. Plasma cells can infiltrate the kidney directly, causing kidney dysfunction. Hypercalcemia can independently cause renal vasoconstriction. Volume depletion and medications used to treat multiple myeloma can also contribute to renal disease.<sup>[18, 19]</sup>

For further information, go to [Acute Renal Failure](#) and [Acute Tubular Necrosis](#).

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